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REVIEW ARTICLE

Three Decades of Valproate: A Current Model for Studying Autism Spectrum Disorder

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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with increased prevalence and incidence in recent decades. Its etiology remains largely unclear, but it seems to involve a strong genetic component and environmental factors that, in turn, induce epigenetic changes during embryonic and postnatal brain development. In recent decades, clinical studies have shown that in-utero exposure to valproic acid (VPA), a commonly prescribed antiepileptic drug, is an environmental factor associated with an increased risk of ASD. Subsequently, prenatal VPA exposure in rodents has been established as a reliable translational model to study the pathophysiology of ASD, which has helped demonstrate neurobiological changes in rodents, non-human primates, and brain organoids from human pluripotent stem cells. This evidence supports the notion that prenatal VPA exposure is a valid and current model to replicate an idiopathic ASD-like disorder in experimental animals. This review summarizes and describes the current features reported with this animal model of autism and the main neurobiological findings and correlates that help elucidate the pathophysiology of ASD. Finally, we discuss the general framework of the VPA model in comparison to other environmental and genetic ASD models.

Keywords: Autism spectrum disorder, valproic acid, HDAC inhibition, neurodevelopment, prenatal exposure, pathophysiology.

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that affects communication, social interaction, and behavior [1]. In the past few decades, the incidence and prevalence of ASD have been increasing, making it a major public health concern worldwide [2, 3]. Despite extensive research, the etiology of ASD remains largely unknown, but it is widely accepted that genetic and environmental factors play a significant role in its pathogenesis [4, 5].

One such environmental factor that has been linked to ASD is in-utero exposure to valproic acid (VPA), a commonly prescribed antiepileptic drug [6], also used for the treatment of bipolar disorder, migraine, neuropathic pain, and headaches [7, 8]. Studies have shown that children exposed to VPA during pregnancy are more likely to develop ASD [9]. This association has been established through clinical studies where prenatal VPA exposure in rodents has been developed as a reliable translational model to study the pathophysiology of ASD [10]. However, the procedures used to replicate behavioral phenotypes have consistently differed in dosages, concentrations, the gestational development period of exposure to VPA, and the molecular and biological mechanisms proposed to explain the physiopathology associated with ASD. Several experimental models have been conducted on different species, including rodents, zebrafish, and non-human primates. Furthermore, recent advances have been made by using organoids from human induced pluripotent stem cells, which report gene expression patterns affected by VPA exposure and allow for correlation with the biological mechanisms proposed by animal studies [11-13]. Thus, increasing evidence suggests that VPA impacts the growth, migration, and differentiation of neurons and certain types of glia, as well as the development of functional synapses. This study aims to review the potential mechanisms by which prenatal exposure to VPA can result in changes to brain development in contrast to findings from other animal models and postmortem evidence from individuals diagnosed with ASD.

2. VALPROATE (VPA)

Valproic acid, also known as 2-propyl pentanoic acid, is a branched and short-chain fatty acid chemically produced

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by different synthetic pathways [14], one of them as a product derivate from valeric acid [8] (Fig. **1**). After oral administration, VPA is absorbed from the gut and metabolized in the liver by three routes, mainly glucuronidation, β oxidation in the mitochondria, and, in less proportion, by cytochrome P450-mediated oxidation [15, 16]. VPA has a high protein bound mainly to albumin and low clearance [15].

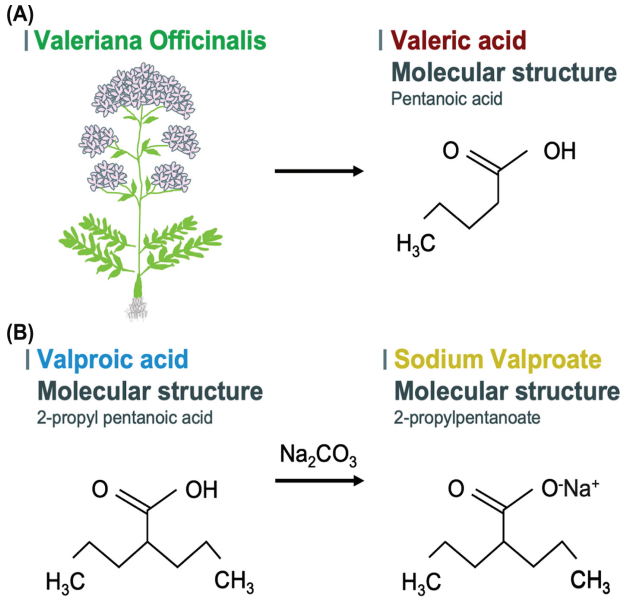


Fig. (1). Molecular structure of Valproate (VPA). (**A**) Valproic acid can be chemically synthesized from valeric acid, a natural substance from *Valeriana officinalis.* (**B**) Valproic acid by addition of sodium hydroxide to obtain sodium valproate. Both are the most common forms of valproate in the clinical. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

VPA was first introduced in the clinical as a broad-spectrum antiepileptic drug [17], which is currently used for the treatment of multiple seizure disorders [18], bipolar disorder as a mood stabilizer [19], migraine [20, 21], and schizophrenia [22]. VPA is also used for the treatment of pediatric diseases such as epilepsy, conduct disorder and for symptoms of irritability, aggression, and impulsivity [8]. VPA can cross through the placenta and accumulate in the fetal circulation with a higher concentration than maternal blood [23, 24], conferring a major risk to the fetus by exposure to VPA. On the other hand, VPA metabolites, such as 4-ene VPA, cannot cross through the placenta, and fewer concentrations are observed in comparison to VPA [24, 25].

3. STUDIES RELATED TO FETAL VPA SYNDROME AND ASD

Gestational exposure to VPA has been extensively associated with an increased risk of major congenital malformations, delayed cognitive development, and ASD [26-31]. Currently, its clinical recommendation for pregnant women is controversial [6, 32, 33].

Fetal valproate syndrome (FVS) was first reported in 1993 to describe a group of major congenital malformations associated with exposure to VPA during the first trimester [34]. Currently, there is a long list of congenital disturbances associated with FVS, including neural tube defects and skin, musculoskeletal, cardiovascular, genital, and pulmonary abnormalities [35-38]. Furthermore, fetal exposure to VPA is related to cognitive impairments and developmental delays [6, 39-44]. However, there is no clear linear relationship between VPA dose, exposure time window, and risk of major congenital or developmental delays arising from prenatal exposure to VPA. In general, the first trimester of pregnancy could be a period of susceptibility to the teratogenic effects of VPA during development [43-48]. However, this susceptibility may be explained by developmental processes during the first trimester of pregnancy. During this period, the processes of organogenesis and neural tube closure occur [49, 50], which are especially vulnerable to external factors such as infections, medications, and environmental toxins, which can interfere with the normal development of organs and structures and lead to congenital malformations [47, 51-53].

In addition, the first studies describing FVS also reported an increase in the incidence of autism diagnosis in children [27, 54-56]. Further studies support VPA during gestation as a risk factor for increased ASD diagnosis in children [28, 57-59]. In a longitudinal study with 528 children exploring the relationship between prenatal exposure to antiepileptic drugs and the prevalence of neurodevelopmental disorders, ASD was the most frequent diagnosis for the offspring of pregnant women taking monotherapy or polytherapy of VPA [60]. One of the largest studies, conducted from 1996 to 2006, with a sample of 655, 615 children, reported a two-fold increased risk of a diagnosis of ASD in children exposed to VPA in utero [31]. Further studies with large cohorts found similar results [39, 61, 62]. Curiously, fetal VPA exposure in any trimester of gestation had an increased risk of ASD diagnosis in children [9], which supports the importance of elucidating the mechanism of VPA in the cellular and molecular processes underlying ASD.

4. PRENATAL VPA EXPOSURE AS A MODEL OF ASD

According to clinical evidence, there is a link between maternal treatment with VPA and an increased risk of ASD diagnosis in their children. As a result, prenatal VPA exposure has been suggested as an experimental animal model for autism-like behaviors. The study of animal models that mimic some of the pathogenic mechanisms and clinical phenotypes observed in human disease can be valuable for developing new therapies that can be extrapolated to humans [63-65]. Currently, no medical test is available for diagnosing ASD, nor are there specific neurobiological markers associated with the disorder. Instead, clinicians rely on evidence from behavioral criteria described in DSM-V-TR [66], which limits the face validity criteria considered to model clinical phenotypes in animals. This also highlights the relevance of understanding the physiopathology of human disorders. Therefore, the face validity of prenatal VPA exposure is based on detecting behavioral impairments that resemble ASD in humans [67]. Also, this model partially achieves construct validity by using VPA, a widely described risk factor associated with ASD. The etiological and pathological mechanisms involved are not fully understood, but they are complex and heterogeneous conditions involving genetic and epigenetic

interactions during early brain development. According to this, the prenatal VPA exposure model represents a form of idiopathic ASD that involves environmental factors.

Since the first study reporting prenatal exposure to VPA in rats as a model linked to autism [68], it has been extensively reported across multiple studies that reproduce the behavioral features associated with ASD. These features include lower sociability, deficits in communication, increased repetitive behavior and stereotypies, deficits in prepulse inhibition, lowered sensitivity to pain, increased anxiety, and hyperlocomotor activity [69-72]. Despite the promising results, there is considerable variability in the methods used to induce the VPA model. The first study reporting the critical method to induce autism-like behaviors in rats involved injecting pregnant rats with a single dose of VPA around the time of fetal neural tube closure, which occurs at approximately gestational day 12 [73]. One common source of variability is the gestational day of exposure to VPA. Studies choose to expose embryos earlier or later than day 12. Indeed, social deficits and sensory abnormalities have also been observed in rodents following early postnatal exposure to VPA [74-76]. This finding supports the notion that short gestational development in rodents is comparable to the early postnatal period in humans [77]. However, the effects of VPA on gene expression were different during the postnatal period [78]. Additionally, the dose of administration and sex-specific studies are common sources of variability between studies, especially in rats and mice, which are the most commonly used species for modelling purposes, as previously discussed [69, 79]. Despite the differences reported to induce an autism-like behavioral model, behavioral features and the pathophysiological mechanisms involved appear to be conserved across species. Several studies support the role of VPA in ASD in nonhuman primates, rats, mice, chicks, and fish (Table **1**). This makes it a valuable model for further research into the complex gene-environment interactions involved in ASD. In humans, maternal VPA is a risk factor because it affects fetal brain development but seems not to be associated with a specific trimester of gestation [9]. A systematic analysis conducted in rodents recapitulates the differences in dose and time of administration for the two major core symptoms of ASD. These symptoms are characterized by deficits in social interaction and communication, and an increase in restricted or repetitive/stereotyped behavior [66]. Moreover, there is an additional sub-category described as cognitive rigidity or inflexibility, concluding that despite methodological differences, a dose between 400-600 mg/kg and a time window around E11.5-12.5 consistently induce core behavioral impairments related to ASD. This holds true even across different rodent strains and routes of administration [80]. In addition, there is consistent evidence that a dose between 300-600 mg/kg administered around E10-E13 can induce autism-like behaviors.

Herein, we have compiled a summary of studies that have investigated the effects of prenatal exposure to VPA in rodents. We have focused on studies that used a consistent dosage range (400-600 mg) and administered the VPA around E11.5-E12.5. Additionally, we have included studies conducted in nonhuman primates, chicks, and fish that have reported behavioral impairments related to the two major core symptoms of ASD (Table **1**). In addition, the studies are classified according to the developmental period of the species during which the behavioral test was performed. In this sense, although the evaluation period has introduced additional variation into the model, the results have been conclusive.

5. VPA AND DISRUPTION OF BRAIN DEVELOPMENT

The mechanisms by which VPA disrupts development have not yet been fully explained. However, several reports have shown that prenatal exposure to VPA alters the processes of cell growth, neurogenesis, migration, differentiation, and apoptosis during gestational or early postnatal development [81, 82]. Multiple mechanisms have been proposed to explain how a single exposure to VPA in the period near the closure of the neural tube impacts the course of neural development and reproduces the morphological and functional changes found in ASD patients.

Children with ASD commonly display a range of alterations of brain networks [199-201], which are considered a brain connectivity disorder that modifies excitatory/inhibitory balance [202]. However, several processes during brain development can affect this balance and the connectivity of several structures. Postmortem brain analysis of ASD patients reported alterations in cellular distribution, brain volume, and abnormal neuronal morphologies that affect their connectivity and functioning [82, 203-206]. In this section, we focus on how prenatal exposure to VPA in experimental animals replicates the clinical evidence reported in patients with ASD (Fig. **2**), which helps to understand the physiopathology of this disease.

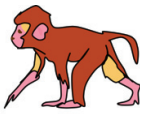
5.1. Neurogenesis and Cell Growth

Neurogenesis is the process of generating new neurons by neural stem cells (NSCs) and neural progenitor cells (NPCs), which are regulated by epigenetic and genetic factors. Neurogenesis and cell growth are coordinated events during brain development and are essential to developing functional structures and neural circuits [207]. Therefore, neurodevelopmental disorders such as ASD are linked to alterations in this process.

It was proposed that abnormal growth patterns during brain development in the physiopathology of ASD [208, 209], which manifest as differences in head circumference or brain size [210-215], are even related to higher co-morbidity with macrocephaly and microcephaly [213, 216]. These macro anatomical changes could be related to the disruption of neurogenesis and cell migration during brain development. Postmortem brain tissue from young ASD patients has shown an increased neuronal population in the cortex [217-219], abnormal cortical lamination [219], and cerebral dysplasia in several regions of the brain [220]. However, evidence from brain postmortem or imaging in ASD patients is limited, hence the relevance of animal models.

Based on the evidence from ASD patients, several reports have indicated that prenatal exposure to VPA alters the processes of neurogenesis by affecting the population of NSCs and NPCs [185, 221, 222] that, in turn, reduces the number

Table 1. Autism-like behaviors by prenatal VPA exposure model across different species.

-			Behavioral Trait Evaluated	
VPA Dose and Time Exposure	**Specie**	**Developmental Stage Tested**	**Cluster A: Social & Communication Deficits (References)**	**Cluster B: Restrictive and Perseverative Behaviors (References)**
Between 400-600 mg/kg Around E11.5-12.5	**Rodent** (Rat/Mouse) 	Newborn-Infant Rat/Mouse P0 > P19	• Ultrasonic vocalizations [83-92] • Free social interaction [93]	• Open-field repetitive behaviors [93]
		Juvenile Rat P20 >P39 Mouse P20 > P29	• Social preference [73, 85, 87, 89, 94-120] • Social Novelty [73, 85, 87, 89, 90, 94-113, 115-123] • Free social interaction [84, 86, 87, 89, 90, 93, 101, 106, 111, 114, 116, 120, 124-137] 22/10/23 3:49 PM	• Open-field repetitive behaviors [87, 89, 94, 95, 99, 103, 106-112, 116, 117, 119, 122-125, 127, 128, 130, 131, 133, 134, 137-141] • Marble Burying [104, 116, 142] • Inflexibility by T or Y maze [84, 101, 111, 129, 132]
		Pubertal Rat P40 > P69 Mouse P30 > P59	• Social preference [83, 85, 95, 97, 98, 102, 104, 104, 105, 107, 108, 110, 111, 113, 115-117, 119-122, 143-159] • Social Novelty [85, 95, 97, 98, 102, 104, 107, 110, 111, 113, 117, 119-122, 145, 150-153, 155-160] • Free social interaction [86, 111, 116, 120, 124, 125, 128-130, 134, 135, 137, 161-170]	• Open-field repetitive behaviors [85, 95, 107, 108, 111, 116, 117, 119, 122, 124, 125, 128, 130, 134, 137, 140, 143, 146, 147, 150-152, 152-155, 157-161, 169-174] • Marble Burying [104, 116, 148, 158, 170] • Inflexibility by T or Y maze [111, 129, 145, 150-152, 155, 156, 159, 163, 168]
		Adult Rat P70 > Mouse P60 >	• Social preference [83, 89, 101, 104, 114, 115, 120, 145, 149, 154, 175-179] • Social Novelty [89, 104, 120, 145, 154, 175, 179] • Free social interaction [89, 90, 101, 114, 120, 124, 134, 135, 167, 180, 181]	• Open-field repetitive behaviors [89, 124, 134, 138, 140, 154, 180-183] • Marble Burying [104] • Inflexibility by T or Y maze [101, 104, 145]
Between 200-300 mg/kg Daily E60-68 [184] Double: E26 & 29 [185] Daily E60-66 [186]	**Nonhuman Primate** 	Infant 3 months^{+}	• Vocalizations [184]	-
		Juvenile 17-21 months^{++}	• Social visual preference [185] • Free social interaction [185]	• Stereotypic circling behavior [185]
		Adult 1.4-2.2 years^{+}	• Third-party social reciprocity [186]	-
35 µmol p/egg Embryo egg day 14	**Domestic Chick** 	Newborn to 1st week of age	• Social preference [187, 188] • Social visual preference [189] • Social attachment [190] • Free social interaction [191] • Vocalizations [191, 192]	-
		2nd to 3rd week of age	• Social (familiar) preference [192]	-

(Table 1) Contd…

-			Behavioral Trait Evaluated	
VPA Dose and Time Exposure	**Specie**	**Developmental Stage Tested**	**Cluster A: Social & Communication Deficits (References)**	**Cluster B: Restrictive and Perseverative Behaviors (References)**
Between 5-75 µM Long exposure 8-108 hpf [193] 4-120 hpf [194] 0-48 hpf [195] 10-24hpf [196]	**Zebrafish** 	Young 5-21 dpf	• Social preference [194] • Social visual preference [193] • Free social interaction [193] • Shoaling behavior [193]	• Stereotypic circling behavior [194]
		Adult 70 & 120 dpf [195] 6 mpf [196]	• Social preference [195, 196]	-

Note: Studies conducted are classified according to three criteria: **1)** Group of species tested, such as rodents, including mice and rats from different strains; **2)** Developmental stage when the behavioral test was conducted for each species. Rodent developmental stages were considered based on sexual development and typical gonadal hormone-sensitive social behavior in comparison to humans [197]. Studies involving nonhuman primates, domestic chicks, and zebrafish examined the stage of development relevant to each study; **3)** Autism-like behaviors were grouped and categorized based on the two diagnostic criteria outlined in DSM-V-TR [66]. Variations on behavioral tests were grouped based on the common core of impairments reported. From **Cluster A:** Social preference: The preference to choose social stimuli, usually an animal from the same species, over neutral or nonsocial stimuli like an empty space or object. Social novelty: The preference to choose novel social stimuli over familiar ones. In domestic chicks, social familiarity is expected, which leads to opposing behavior. Free social interaction: This behavioral test measures typical social behaviors in each species, allowing animals to interact freely. Vocalizations: An analysis of the pattern and frequency of vocal calls to communicate with each other, or with its mother. Social visual preference: The tendency to choose an image or object with typical social characteristics of each species, such as faces or shapes. Third-party social reciprocity: Individuals discriminated between human actors who reciprocated in social exchanges and those who did not. Social attachment: The adaptive or learned formation of social bonds with specific individuals. Shoaling behavior: The tendency of fish to form groups or schools and swim together in a coordinated manner. From **Cluster B:** Open-field repetitive behavior: Frequency of behaviors, typically in an open field [198], which allows measuring behaviors outside of a familiar home cage arena and includes repetitive movements, rearing, self-grooming, locomotion, or hyperactivity. Marble burying: Frequency of behaviors exhibited in a familiar home cage environment (with bedding material) and unfamiliar objects that elicit digging behavior toward the novel object. Common behaviors reported: The number of marbles buried, time and frequency of burying, digging, or self-grooming. Inflexibility in the T or Y maze: The test requires the animals to switch to a new reward location between trials, thus assessing their behavioral flexibility. Stereotypic circling behavior: Repetitive and circular movement patterns exhibited by animals, including primates, mice, and zebrafish. *Terminology:* E, embryo, or gestational day (E11.5); P, postnatal day (P3); hpf, hours post-fertilization; dpf, days post-fertilization; mfp, months post-fertilization. [+]Marmoset monkey (*Callithrix jacchus*), [++]Cynomologus monkey (*Macaca fascicularis*).

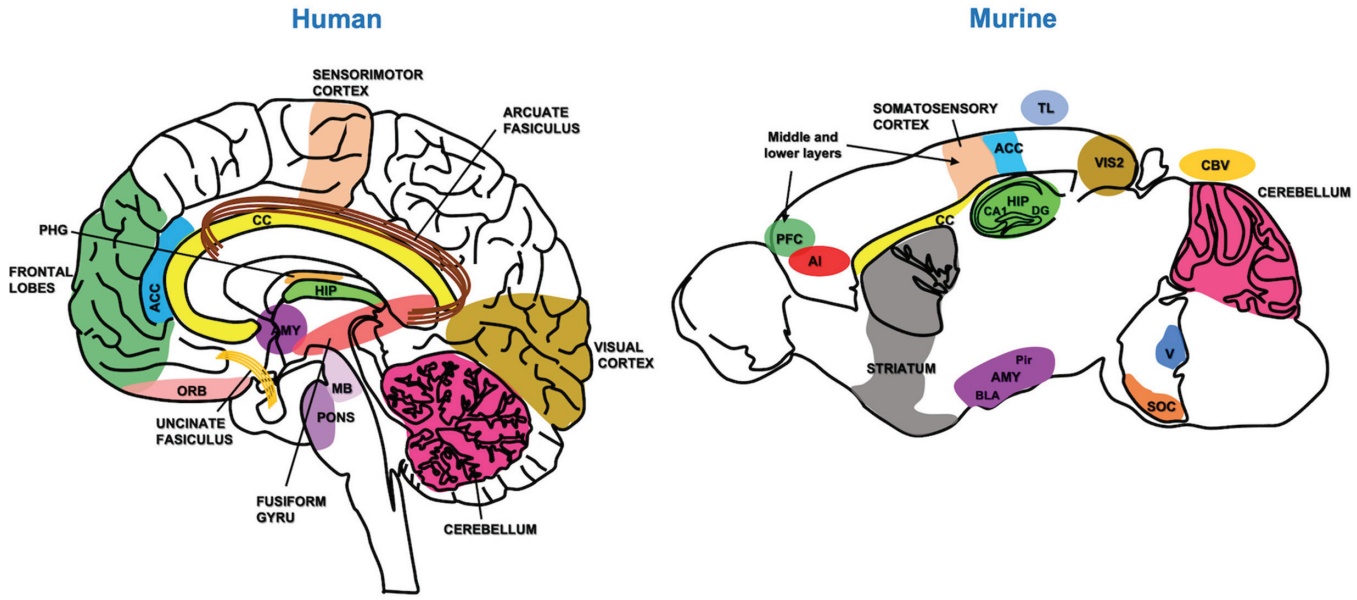


Fig. (2). Anatomical and cellular disorganization in neuronal distribution and white matter circuits observed in the human brain of ASD subjects and the autism-like model of VPA exposure. **Abbreviations**: CC Corpus callosum, HIP Hippocampus, PHG Parahippocampal gyrus, AMY Amygdala, CBV Cerebellar vermis, ACC Anterior cingulate cortex, PFC Prefrontal cortex, V Motor nuclei, SOC Superior olivary complex, VIS2 Secondary visual area, DG Dentate gyrus, CA1 Hippocampal field CA1, AI Agranular insular area, TL Temporal lobe, Pir Piriform cortex, BLA Basolateral amygdala, MB Midbrain, ORB Orbitofrontal area. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

of neuroblasts and modifies their cell fate during embryo development [82, 223, 224]. Prenatal exposure to VPA in a window from embryonic day (E) 10.5 to E12.5 alters the neuronal distribution and density in the postnatal brain hippocampus, cerebellum, brainstem motor nuclei, superior olivary complex, and cerebellar vermis [129, 225-228]. Some studies even suggest differences in cortical layers affecting the neuronal distribution in the upper layers of the prefrontal, somatosensory, and secondary visual cortex [88, 229] and middle and lower layers of the prefrontal and somatosensory cortex [130, 230]. Consistent with this, hippocampal neurogenesis in the adult brain was found to be reduced after prenatal exposure to VPA [81], and cell density impairments were reported in the dentate gyrus and CA regions. Similarly, acute exposure to VPA during the entire gestational period inhibits the cell cycle exit of NPCs and increases the production of projecting neurons in superficial neocortical layers [231].

Interestingly, non-murine models of prenatal exposure to VPA, such as non-human primates and zebrafish, show a consistent neurogenesis impairment. Prenatal exposure to VPA in cynomolgus monkey at gestational day 26, which is an equivalent period in murine models, found a decreased neurogenesis and fewer cells in the cerebellar external granular layer and layers II and IV of the prefrontal cortex (PFC) [185]. Zebrafish embryos exposed to VPA after eight hours post fertilization showed an increased proliferation rate [193] and reported on this model delayed neurogenesis NeuroD1 disruption on the optic tectum, a brain region with homology to the superior colliculus in humans [232, 233]. In addition, studies *in vitro* have helped us understand VPA's effects on neurogenesis and cell growth. Exposure to 1mM VPA decreases the proliferation of human NPCs in culture, followed by mitochondrial dysfunction and increased differentiation to an excitatory neuronal phenotype [234]. Interestingly, NPCs from rat embryos exposed to 0.5 mM VPA increase proliferation and differentiation to a neuronal phenotype [222], suggesting different effects according to the VPA concentration. Lastly, novel techniques such as three-dimensional cultures, called brain organoids, have become especially relevant for modeling brain development and neurodevelopmental disorders directly from human-derived cells [235, 236]. Single VPA exposure in brain organoids from human embryonic stem cells (hESCs) alters the neurogenesis and NPC population, which contributes to dysregulated neuronal fate toward upper-layer neurons, causing abnormal neocortical expansion [12]. The effects of the exposure to VPA appear to be time-dependent, as observed when a five-day exposure to 0.5 mM VPA in human-brain organoids shows an increase in the proliferation of neural precursors, but not after 10 days of VPA exposure [11]. This event seems to be dependent on Wingless (Wnt) signaling and Pax6 transcription factor expression [122, 222] that, in turn, can lead to differential outcomes in the total number of mature neurons. Overall, these results suggest a dysregulation in the early processes of neurogenesis and cell growth arising from prenatal exposure to VPA, similar to what occurs during neurodevelopment in patients with ASD.

5.2. Migration

Neural migration is a crucial event in the development of brain circuits (Pan *et al.*, 2019). In this process, nascent neurons undergo cellular migration from the ventricular-subventricular zone [237] in a programmed pattern to align radially into columnar structures, providing a functional unit in the neocortex [224, 238]. Disruption in the number of newborn cells or the migration process could lead to the abnormal neuronal distribution discussed in the previous section. Interestingly, abnormalities in cortical lamination have been previously reported in ASD patients [239-242]. Thus, prenatal VPA exposure disrupts granule cell number during the migratory period of cerebellar development, causing abnormal Purkinje cell layer [243], and exotopic Purkinje cells have been identified [82]. A study comparing migration patterns of BrdU+ cells from mice embryos exposed to VPA on days 12.5, 13.5, or 14.5 found less number of cells incorporated in cortical layers on postnatal day 7 by prenatal exposure on day E12.5. Interestingly, prenatal exposure on day 13.5 slightly reduces the number of BrdU+ cells, and no differences were reported in migration patterns by prenatal exposure on day 14.5 [130]. Previous studies reported that prenatal exposure to VPA alters the migration of NPCs in the adult hippocampal neurogenesis and decreases the expression of Cxcr4 [244], a chemokine related to proper migratory patterns of granule newborn neurons in neurogenesis [245, 246], suggesting a mechanism implicated in seizure susceptibility [244]. These disturbances of the migration pattern of new neurons in the adult hippocampus caused by prenatal VPA exposure are related to increased seizure susceptibility [244]. However, changes in CXCR4 transcription have been directly linked to the inhibition of histone deacetylase activity (HDACi) by VPA, thus increasing Histone H3 acetylation at the promoter site for *Cxcr4* in cultured mesenchymal cells, increasing their ability to migrate [247]. In addition, several genes involved in cell adhesion and migration processes are differentially expressed after prenatal VPA exposure [244], including *Cntnap2*, a gene recently associated with ASD [248]. Therefore, transcriptome dysregulation of genes regulating cell migration could be a mechanism related to the pathophysiology of ASD.

5.3. Cellular and Molecular Impairments in Neuronal Organization

During brain development, neurons exhibit unique morphological and molecular changes that give rise to broad neuronal phenotypes and complex neural circuits. These structural and functional changes include a long axonal process to connect with target neurons, complex dendritic arborization, the establishment of functional synapses, specific molecular profiles such as neurotransmitters, and properties of neural firing reflecting functional phenotypes [249, 250]. Furthermore, the neuronal arrangements lead to complex connectivity and brain function [251]; therefore, disrupting these processes could lead to dysfunctional networks [224]. In addition, ASD was previously suggested as a heterogeneous group of disorders emphasizing differences in brain growth and molecular phenotypes [208].

Postmortem brain analysis of ASD patients showed an increased number of 5-HT+ ascending fibers from serotonergic neurons of the medial/lateral forebrain bundles, including increased innervation density into the amygdala, piriform, superior temporal, and parahippocampal cortices [252, 253]. Furthermore, small soma in neurons and increased cell density per area were reported in the hippocampus, cerebellum, and frontal and temporal lobes of ASD patients [206, 254]. In addition, decreased density of dendritic spines was reported in the prefrontal cortex and hippocampal neurons [255-258]. According to these findings, prenatal VPA exposure generates large soma in neurons from cerebellar nuclei [227] and altered dendritic arborization patterns by higher complexity in the proximal dendritic segment, but fewer branches at distal sites of cerebellar Purkinje cells [228]. Besides, decreased dendritic density or spine density has been reported in the hippocampus, amygdala, prefrontal and somatosensory cortex [81, 82, 259, 260]. Previous studies have reported abnormal neuron compartmentation of cells in the striatum, which leads to decreased corticostriatal synapses and impaired circuits with the prefrontal, granular insular, and somatosensory cortices because of prenatal VPA exposure [88].

In addition, studies *in vitro* and on zebrafish have been helpful in understanding the mechanisms implicated in cellular and molecular impairments arising from prenatal exposure to VPA. Axonal ectopic branches and excessive abnormal branching increased in a VPA concentration-dependent pattern during the gestational development of zebrafish [261]. In contrast, at higher doses, VPA induces delayed neuropil formation and axogenesis [232]. Interestingly, VPA induces abnormal differentiation of serotoninergic neurons by downregulating the proneural ascl1b gene, a mechanism mediated by HDAC1 inhibition [262]. The effect on neuronal differentiation could be dependent on the period of development. In culture neurons from mice, embryos exposed to VPA at day 12.5 but not E14.5 had reduced dendritic morphology and expression of synaptic proteins such as *Nlgn1*, *Cntnap2*, and *Shank3*, all of which are associated with ASD [263].

5.4. Excitatory/Inhibitory Imbalance

The excitatory and inhibitory (E/I) neural activities are highly regulated at molecular, cellular, and circuitry levels in the nervous system. These changes maintain a relatively stable relationship through multidimensional and time-scaled neural circuits in the brain. Otherwise, structural alterations, especially during the brain development of cortical layers and synapse formation, could lead to dysregulated synaptic transmission, plasticity, and intrinsic neuronal excitability. These factors may contribute to an imbalance in E/I signaling, which could explain the etiology of ASD [202, 264]. The term was first introduced to explain sensory, social, and emotional behaviors in individuals with ASD [265]. Binocular rivalry is a perceptual process that emphasizes the importance of reciprocal inhibition [266, 267], which is dependent on E/I dynamics and is reduced in individuals with ASD [268, 269]. The distribution of neurons in the neocortex is arranged in mini-columns, which modulates the microcircuitry of glutamatergic and GABAergic signaling. This arrangement is altered in ASD subjects, leading to impaired integration [254, 270-272] and processing of signals [273]. In addition, lower GABA concentrations in the sensorimotor cortex correlate positively with increased sensitivity to tactile stimuli in ASD adult subjects [274]. However, differences in neurotransmitter concentrations may not be the only factor that explains these differences in sensory processing. A study found no variations in GABA levels in adults with ASD of similar age [275]. In addition, human postmortem studies have reported decreased levels of $GABA_A$ and $GABA_B$ receptors in the anterior cingulate cortex [276, 277] and dysregulated expression of glutamate decarboxylase enzymes *GAD65* and *GAD67* in the cerebellum [278-280]. Also, several genetic variants in GABA receptor subunits have been reported in individuals with ASD [281]. Both increased and decreased ratios of E/I activity have been suggested in ASD subjects. This could be attributed to various compensatory mechanisms that underlie the heterogeneity of the ASD population [282].

Prenatal exposure to VPA induces a decrease in the excitability of glutamatergic neurons and an increase in local connectivity of the prefrontal cortex in adult rats but not in adolescence [283]. This could be explained as an impaired compensatory mechanism or the result of delayed prefrontal cortex maturation. In addition, altered expression of glutamatergic (vGluT1, GluN1-2, PSD-95) and GABAergic (vGAT, GAD65, GAD67) proteins, as well as changes in the number of synapses, were reported in adolescent and adult mice exposed to VPA [284]. The same increased imbalance in E/I proteins was reported in the prefrontal cortex [95, 285]. Additionally, pharmacological blockage of the glutamatergic transmission reverses the impairments in social behavior [285]. Selectively inhibiting D2R+ pyramidal neurons in the medial PFC ameliorates social deficits, whereas non-specific inhibition does not improve social behavior [286]. In the somatosensory cortex, an overexpression of NMDA receptor subunits and enhanced mediated transmission and LTP were reported in rats prenatally exposed to VPA [287]. Moreover, local hyperconnectivity and reduced excitability of pyramidal neurons have been reported in this region, specifically the PFC [288, 289], which contribute to the altered microcircuitry of glutamatergic and GABAergic signaling. In addition to this E/I imbalance, the number of PV+ GABAergic interneurons was reduced in the neocortex [229], and inhibitory post-synaptic currents were reduced in the temporal cortex [290]. Consistently, studies have reported abnormal amygdala synaptic E/I imbalance and hyper-excitability [131]. In the anterior cingulate cortex, there was a significant decrease in the E/I imbalance during the postnatal development of mice from P7 to P30. This imbalance resulted in altered transmission and synaptic plasticity, which were associated with decreased BDNF expression during the developmental period [291]. Abnormal development of synaptic transmission was also reported in the cerebellum of VPA-treated mice [228]. In addition, nonhuman primates exposed to VPA during gestation showed impaired levels of proteins related to glutamatergic (vGluT2, mGluR5, GluN2) and GABAergic (vGAT) systems [185]. Also, a study reported a differential effect on expressed genes in E/I neurons in human forebrain-derived organoids exposed to VPA [13]. Overall, these results support the hypothesis that prenatal

exposure to VPA exposure leads to an E/I imbalance, which is associated with the physiopathology of ASD.

5.5. Oligodendroglia and Myelination Impairments

Oligodendrocytes (OLs) and myelination play critical roles in shaping the functional and structural connectivity of the central nervous system. OLs are glial cells responsible for the production and maintenance of myelin sheaths around axons. They facilitate neuronal transmission and provide trophic and metabolic factors [292]. Oligodendrocyte precursor cells (OPCs) have been identified since E12-E14 in rodents and gestational weeks 6-10 in humans. However, myelination begins late in gestational development in humans and postnatally in rodents [293-295].

Abnormalities in the development of myelination and white matter integrity have been reported in ASD subjects, which disrupt the connectivity of inter-hemispheric, short-local, and long-range association fibers, resulting in abnormal brain growth patterns [296-299]. Enlargement of white matter structures during the first years of life is described in individuals with ASD, but it tends to decrease in size as they age [300]. A study conducted with ASD adolescents revealed a low density of white matter tracts in the corpus callosum and long-range association fibers, such as the uncinate and arcuate fasciculus [301]. Also, a combination of decreased and increased white matter across brain structures has been reported, emphasizing age-related differences [302]. Thus, pathological changes in the cytoarchitecture of the white matter in the cerebral cortex and abnormal myelination in the corpus callosum may explain the dysfunctional connectivity found in several regions of ASD subjects. In addition, the presence of white matter abnormalities or their resolution is associated with the severity of symptoms [303-310]. Abnormalities in the population of OLs and axon myelination could explain these differences.

Prenatal exposure to VPA resulted in a decrease in myelin basic protein (MBP) immunoreactivity in the basolateral amygdala and piriform cortex of adult mice, which correlates with impaired social behavior. Additionally, the basolateral amygdala and piriform cortex exhibited an increase in myelin sheath thickness and a decrease in the number of Olig2+ and CC1+ cells. Olig2 is a transcription factor for the OL lineage, while CC1 is a common marker of mature OLs. These changes were observed in both the PFC and piriform cortex [299]. However, differences in age, brain structures, and the process of oligodendroglia maturation have been reported. In rats prenatally exposed to VPA, variations in *Olig2* messenger RNA (mRNA) and protein levels, as well as the number of Olig2+ cells, were observed in the hippocampus, PFC, and cerebellum [83, 311]. Also, differences were reported between early, juvenile, and adult development, with both increased and decreased patterns of Olig2 marker or positive cell numbers [311]. In contrast, a study reported a decrease in myelin content but a preserved population of OL cells in the corpus callosum at PND15. However, there was a consistent disruption observed in myelin content, number of myelinated axons, and OL population from PND15 to PND36 [312]. These stages in rats are similar to the infant and juvenile stages of human development [197]. Overall, these results suggest a significant reduction in the postnatal development of OLs and myelination in the corpus callosum. Additionally, prenatal exposure to VPA appears to affect the trajectories of OL and myelination in the gray matter differently. According to this, there is a consistent finding of reduced white matter density and structural integrity of the corpus callosum in ASD subjects, regardless of age. However, there are different patterns observed in gray matter structures and long-range association fibers [302]. In addition, downregulated expression was reported in *Olig2*, *Mbp*, and *Chd7*, while upregulated expression of *Lingo1* was observed in the PFC of prenatally exposed rats [313]. In this sense, CHD7 is a chromodomain helicase DNA-binding protein that promotes OL differentiation [314], and LINGO1 is a transmembrane signaling protein that inhibits OL differentiation and myelin production [315]. Overall, a few studies have addressed the impairments in OLs and myelination caused by prenatal exposure to VPA. Nevertheless, further studies are needed to clarify the mechanisms involved during gestational development and their relationship with ASD.

5.6. Immune and Oxidative Stress Impairments

Prenatal insults, such as infections, toxins, and maternal stress, as well as subsequent immunological activation, can increase the risk of neurodevelopmental disorders [316]. The mechanism by which maternal immune activation (MIA) leads to ASD has not been fully understood. This includes several pathological processes, such as the upregulation of cytokine and chemokine expression, oxidative stress, mitochondrial dysfunction, early glial activation, and maternal autoantibodies that cross to the fetus [317-321]. These processes result in long-lasting changes in the expression of other immune molecules, such as major histocompatibility complex I and molecules that regulate synapse formation and brain development [317].

MIA plays a significant role in the heterogeneous and biological etiology of ASD [322]. In individuals with ASD, decreased mononuclear cells, T lymphocytes CD4+, low responsiveness to mitogen stimulation [323, 324], and increased levels of pro-inflammatory cytokines [325-327] have been reported. Postmortem studies have reported increased activated microglia and reactive astrocytes in the cerebellum, fronto-insular cortex, prefrontal cortex, and visual cortex [328-330]. Noninvasive neuroimaging studies with (^{11}C)(R)-PK11195, a selective radioligand for microglia, have shown an increased activated phenotype in several brain regions, including the cerebellum, midbrain, pons, fusiform gyri, anterior cingulate, and orbitofrontal cortex [331]. In addition, MIA involves oxidative stress and mitochondrial dysfunction [332, 333]. Moreover, in individuals with ASD, impaired production of oxidative markers such as reactive oxygen species (ROS) and nitrogen free radicals [317, 318, 334] has been reported. Additionally, decreased levels of glutathione (GSH), oxidized glutathione (GSSG), and glutathione redox/antioxidant capacity (GSH/GSSG) [318] suggest increased oxidative stress and reduced antioxidant capacity.

Although VPA exposure is not an infectious factor, prenatal exposure has been shown to induce immune activation in the brain. In murine models, an increased density of astrocytes and microglia was reported in the prefrontal cortex, hippocampus, and cerebellum [154, 311, 335]. In the hippo-

campus, prenatal exposure to VPA increased the expression of anti-inflammatory microglial M2 phenotype markers. Otherwise, in the cerebral cortex, both M2 and pro-inflammatory M1 phenotype markers are increased, which is consistent with the increased expression of pro-inflammatory cytokines only in the cerebral cortex [336]. An increase in ROS and a limited antioxidant capacity have also been demonstrated in both regions [336]. This could potentially trigger immune activation. Also, TREM2 downregulation, a transmembrane immune receptor expressed exclusively in microglial cells, has been proposed as a mechanism related to the activation of a pro-inflammatory phenotype and its role in synaptic pruning [337]. In contrast, a reduction in Iba1+ microglia was observed in the motor cortex, which may be attributed to the early postnatal age [338]. In addition, studies have reported increased responses to inflammatory stimuli and elevated basal levels of corticosterone [149, 154, 180], which have both suppressive and enhancing effects on immune function [339]. According to this, prenatal exposure to VPA induces atrophy of the thymus [135, 180]. It also leads to lower levels of IFN-γ/IL10 and increased production of nitric oxide (NO) in peritoneal macrophages [180]. In fact, the levels of both IFN-γ and NO were positively correlated in individuals with ASD [340]. In contrast, several studies have reported the anti-inflammatory properties of histone deacetylase (HDAC) inhibition with VPA [341-343]. However, increased pro-inflammatory cytokines TNFα, NO, and IL-1β were reported after acute exposure to VPA in macrophages, but only in response to an inflammatory stimulus [344]. Blood-brain barrier (BBB) impairment during the gestational period was also suggested as a pivotal event to increase immune activation [345]. Accordingly, prenatal exposure to VPA causes impaired BBB permeability and aquaporin expression in the choroid plexus, prefrontal cortex, and somatosensory cortex [346]. Overall, this evidence supports immune alterations caused by prenatal exposure to VPA during postnatal brain development or in adult mice.

6. VPA MECHANISM OF ACTION DURING GESTATION

The long-term behavioral and neurobiological impairments associated with ASD in human patients caused by VPA are not completely elucidated in terms of how they begin after a single VPA exposure. However, we summarize these neurobiological alterations in the postnatal brain in Table **2**. Several studies have suggested a set of intersecting pathways and multiple chemical interactions with VPA [69]. Some of these interactions have been experimentally demonstrated, such as HDAC [347, 348], while others have been suggested theoretically or *in silico*, such as GSK3β, PKCβII, JARID1A, and EZH2 [349-351]. Furthermore, it is not clearly understood how HDAC inhibition leads to several dysregulated processes during gestational development, which we will discuss in the following section. Additionally, it is unclear how these disturbances converge with other ASD-related animal models, suggesting a complex genetic-epigenetic interplay associated with the etiology of ASD [352].

6.1. Epigenetics: HDAC Inhibition and Chromatin Remodeling

VPA can regulate gene expression due to its mechanism as a histone deacetylase inhibitor (HDACi). HDAC is an enzyme responsible for removing acetyl groups from histone proteins, which can result in the tightening of chromatin structure and the repression of gene expression [353]. Conversely, HDACi, such as VPA, increase the level of histone hyperacetylation associated with a more open chromatin structure, allowing for increased accessibility of DNA to transcription factors and other regulatory proteins [353].

VPA and its analogs inhibit multiple HDACs from Classes I and II (excluding Class IIb, which is composed of HDAC6 and 10). This inhibition leads to an increase in histone H3 and H4 acetylation [347, 348, 354], specifically at lysine (K) residues [355]. The acetylation levels of H3/H4 were transiently increased after embryonic exposure to VPA in mice, which also exhibited autism-like behaviors [130]. H3K9ac was increased after VPA exposure in mouse embryonic stem cells starting on day 14 [356]. This is a critical histone modification that helps regulate embryonic stem cell pluripotency and neural differentiation [357, 358]. In addition, H3K9 is deacetylated by HDACs from Class I [359], which are highly expressed during mid-late embryonic development [360]. Additionally, the hyperacetylation pattern of Histones induced by VPA HDACi resulted in an increase in gene expression at promoter sites, including the *CDKN1A* promoter region ($p21^{Cip/WAF1}$). In this sense, VPA increases hematopoietic cell differentiation in a p21-dependent manner through increased HDAC inhibition [347]. Interestingly, deficient HDAC1 activity during mid-late embryonic development was directly related to the up-regulation of p21 [360]. Also, lysine acetylation at the core histone domain, such as H3K56, was increased by VPA exposure [371]. H3K56 is located at the entry-exit sites of the DNA wrapped around the nucleosome. Acetylation of these sites modulates the unfolding of nucleosome-chromatin [372, 373], and it has been previously suggested that this process of chromatin remodeling relocates developmental genes, allowing the recruitment of transcription factors to promote cellular differentiation while downregulating genes that maintain pluripotency [374]. Mouse ESCs exposed to VPA undergo a significant change in chromatin accessibility. Specifically, there is a shift from pluripotency factors such as *Pou5f1*, *Nanog*, and *Sox2* to specific loci associated with chromatin remodeling and neuronal differentiation. One of the loci affected by this switch is *Pax6* [371].

In addition to the relationship between HDAC inhibition by VPA and ASD, several compounds analogous to VPA in chemical structure, such as valpromide (VPD), which lack the effect of HDAC inhibition, did not induce autism-like behaviors in murine models or cause abnormalities in brain development [130]. Also, the epigenetic effect of VPA on other pathways was not observed with non-HDACi analogs. The inhibition of NPC proliferation mediated by Wnt signaling in brain organoids exposed to VPA was not replicated with VPD [12].

Consequently, prenatal exposure to VPA induces a sequential chain of events, starting with HDAC inhibition and leading to changes in developmental transcriptional profiles.

Table 2. Neurobiological and molecular impairments caused by VPA exposure through *in vivo* and *in vitro* studies.

Category	Rodent	Nonhuman Primate	Zebrafish	*In Vitro* Studies (2D Culture & Brain Organoids)
Histone acetylation/methylation and Chromatin remodeling	• ↑ H3Kac and H4Kac [122, 130, 361] • ↑ H3Kme and H4Kme [362] • ↓ H3Kme and H4Kme [362] • Chromatin remodeling [363]	-	• ↑ H3Kac and H4Kac [233, 364]	• ↑ H3Kac and H4Kac [365] • ↑ H3Kme and H4Kme [366] • Chromatin remodeling [365]
ASD-associated genes expression	• *Chd7* [313], *Shank2*, *Shank3*, *Nlgn3* [336, 367], *Mecp2* [368]	• *SHANK3*, *SHANK1* [185]	• *shank3*, *nrxn1*, *nlgn3* [194]	• *Shank2-3*, *Nlgn1* [263], *Cntnap2* [244, 263], *FOXP1*, *RELN*, *CHD7*, *CHD8*, *NLGN2-3*, *TSC1-2, SHANK1-3* [365]
Neurogenesis and cell density	• ↑ Proliferation [122, 222] • ↑ Cortical cell density [88] • ↓ Proliferation [130, 230] • ↓ Cortical cell density [88, 130, 230] • ↑ Neuronal phenotype differentiation [122, 222]	• ↓ Proliferation [185] • ↓ Cortical cell density [185] 22/10/23 3:49 PM	• ↑ Proliferation [262] • ↓ Proliferation [233] • ↑Neuronal phenotype differentiation [194] • ↓Neuronal phenotype differentiation [232, 262] 22/10/23 3:49 PM	• ↑ Proliferation [222] • ↓ Proliferation [12, 221, 234, 369] • ↓ Cortical cell density [11, 12, 234] • ↑ Neuronal phenotype differentiation [221, 234, 369]
Excitatory/ Inhibitory Imbalance	• ↑ Glutamatergic neuronal excitability [131, 284, 285, 288, 289] • ↓ Glutamatergic neuronal excitability [283, 286, 291] • ↑ Glutamatergic neuronal density [122] • Altered synaptic protein expression [95, 122, 284, 291, 336, 337, 361] • ↓ GABAergic neuronal density [229]	• Altered synaptic protein expression [185]	-	• ↑ Glutamatergic neuronal density [234] • Altered synaptic protein expression [11, 361]
Oligodendroglia and Myelination impairments	• ↓ OL density or associated gene/protein expression [83, 299, 311-313] • ↓ Myelin density or gene/protein expression [83, 299, 311, 312]	-	-	-
Immune and Oxidative stress impairments	• ↑ Oxidative stress [336] • ↑ Microglia density [149, 154, 311, 335] • ↓ Microglia density [338] • ↓ Pro-inflammatory cytokines [154, 336]	-	-	-

Note: Studies conducted *in vivo* considered prenatal VPA exposure in a single dose during embryonic development (rodent and non-human primate) and the first five days postfertilization (zebrafish), reporting impairments during the gestational or postnatal period. Studies conducted *in vitro* considered VPA exposure over embryonic progenitor cells (EPCs), neural progenitor cells (NPCs), or induced pluripotent stem cells (iPSCs) under neural differentiation in 2D cultures and brain organoids. ASD-associated genes were considered according to the top ranking in the Autism Informatics Portal (AutDB) [370].

As a result, this leads to increased activity of transcription factors and, indirectly, abnormal neural proliferation and differentiation that may arise from these early epigenetic modifications. Chromatin immunoprecipitation demonstrated increased binding of acetylated histones to the *Pax6* promoter region, which leads to transient up-regulation of Pax6 expression and increased glutamatergic differentiation in the prefrontal cortex in VPA-treated embryos [122]. The same results were reported in mouse ESCs exposed to VPA, which led to an increase in H3K56ac locus-specific gain of function within the *Pax6* promoter [371]. This transcription factor regulates the balance between neural stem cell (NSC) proliferation and their differentiation into neurons [375, 376]. It specifically affects the development of glutamatergic phenotypes derived from the ventricular zone of the dorsal telencephalon that migrates into the cortex [377]. Interestingly, the outcome of neural differentiation could vary depending on the timing and level of Pax6 expression. This is due to the gain-of-function or loss-of-function effects caused by the transcriptional regulation of Pax6 on self-renewal, neurogenesis, and the cohort of genes that determine cell fate [378]. Also, a predicted increase in occupancy of the *Gabpa* transcription factor was reported after VPA exposure in mouse ESCs [371], which binds to the *Tert* promoter to enhance its expression [379]. In addition, VPA exposure increased histone acetylation at the *Tert* promoter region, as demonstrated *in vitro* in NPCs and *in vivo* by E14 embryo brains from rats prenatally exposed to VPA at E12 [361]. This increase also led to enhanced Pax6 and Brg1 immunoprecipitation, which subsequently recruited transcription factors that determined glutamatergic neuronal differentiation. In contrast, H3K56ac locus-specific loss of function within *Asf1a* was reported after VPA exposure in mouse ESCs [371]. The downregulation of their expression was associated with a decrease in pluripotency markers (Nanog, Sox2, Oct4) and an increase in differentiation markers (Sox17, FoxA2, Pax6) [380]. Consistently, VPA and MS-275, both HDAC inhibitors, increased the expression of the pre-synaptic glutamatergic

vGluT1 vesicle transporter and decreased the expression of GABAergic markers such as vGAT, GAD65, and GAD67 in cultured cortical neurons [284]. In contrast to this gain-of-function in glutamatergic neuronal differentiation, *Chd7* binds strongly to H3K27ac and *Sox10*/*Olig2* chromatin enhancers in OPCs to promote oligodendroglial lineage differentiation [314]. However, *Chd7* expression is downregulated in the PFC of rats exposed to VPA prenatally [313]. Although these differences were reported in the postnatal brain, OPCs have been identified as early as E12 in mice, which is a common timeframe for VPA prenatal exposure. In a similar way to how VPA inhibits HDAC function, a mouse model of HDAC1 or HDAC2 loss-of-function by conditional knockout (cKO) promotes β-catenin translocation into the nucleus and its stabilization with transcription factors to repress OL differentiation [381]. In addition, Chd7 loss-of-function decreased GABAergic differentiation during embryonic development [382], which can also contribute to an imbalance between E/I signaling in ASD.

Although VPA is a well-recognized HDAC inhibitor, the complex epigenetic interactions resulting from the hyperacetylation state are not fully elucidated. In this sense, HDACi allows for an open chromatin state while also facilitating access to other modulatory enzymes. Previously, it was suggested that the longer open state of chromatin observed after VPA treatment could be attributed to DNA and histone methylation [383]. Prenatal exposure to VPA increases the demethylation and expression of Wnt1 and Wnt2 ligands. It also upregulates mRNA levels of the downstream target genes *En1* and *Ccnd1* in the prefrontal cortex and hippocampus [363]. In addition, VPA increases both DNA demethylation of the *Reln* and *Gad67* promoters and acetylated H3 binding to the promoter regions of these genes [384, 385]. This effect of VPA was previously suggested to depend on DNA demethylase activity [386]. Accordingly, a passive mechanism was proposed that involves the decreased expression of DNA methyltransferase 1 (DNMT1) [387-389]. Additionally, an active mechanism was identified involving the activation of a DNA demethylase [390, 391], which acts on methylated CpG sites in gene promoters [392]. However, multiple mechanisms could interact in a dependent manner with histone acetylation changes. Previously, it was reported that VPA increases the expression of fat mass and obesity-associated protein (FTO). This protein suppresses the posttranscriptional processing of *Mbd2* mRNA, thereby affecting its function as a CpG demethylase over the *Scn3a* promoter region [393]. These results in indirect downregulated expression by methylation of *Scn3a* are evoked by HDAC inhibition.

Class I HDACs are contained in multiprotein complexes that commonly repress transcription [394]. Previously, it was demonstrated that VPA inhibits HDAC, thereby relieving transcriptional co-repression of PPARδ. According to this, VPA does not directly increase the expression of the PPARδ transcription factor. Instead, it downregulates the corepressor complex, which allows PPARδ to bind co-activators and enhance its transcriptional activity [395]. In addition, the interaction between PPARδ and VPA was ruled out. Therefore, it is more likely that HDAC3 inhibition, which is a core component of the nuclear corepressor complex, is responsible. Instead, acetyl groups are preserved, which partially facilitates the recruitment of co-activators [396]. According to this, VPA has the lowest IC_{50} for class I HDACs (HDAC 1-3) [347].

These corepressor complexes also include specific histone demethylases (HDMs), which are commonly involved in the combination of histone modifications [397]. According to this, both histone lysine methylation and demethylation were reported after exposure to VPA [398]. In contrast to histone acetylation, which promotes gene expression, methylation can either stimulate or suppress gene expression, depending on specific residues. In this regard, histone 3 at lysine 4 (H3K4) dimethyl and trimethylation (H3K4me2/me3) promote gene expression, and lysine 9 methylation (H3k9me) promotes gene repression [394]. Both H3K4 histone modifications were increased after VPA exposure in mouse embryonic stem cells [366], in rats exposed prenatally by E9 [362], and in cultured astrocytes and postnatal cortical neurons [399]. In contrast, prenatal exposure in rats decreased H3K9 monomethylation. However, the mechanism by which VPA induces both increased and decreased histone methylation is not fully understood. Previous studies suggest that crosstalk between histone modifications is facilitated by a complex that induces both regulatory enzymes. This crosstalk involves methylase activity-dependent substrate acetylation as well as the direct effects of VPA on EZH2 methyltransferase and JARID1A demethylase [350, 387, 400]. Moreover, histone methylation is more stable and can last for several days [383]. Increased H3K4me2 persisted for five days after exposure to VPA in cultured cortical neurons [399].

Lastly, in addition to the complex epigenetic effects of VPA, there has been a recent review of the emerging role of histone modifications and HDAC enzymes in the alternative splicing transcription of mRNAs. In general, chromatin remodeling not only enables the recruitment of regulatory enzymes and transcription factors but also can influence the timing of spliceosome complex coupling to exonic and intronic splicing sites of DNA, as well as the recruitment of chromatin-splicing adaptor proteins [401]. According to this, HDACis such as Trichostatin A (TSA) or VPA can promote H4 acetylation around splicing sites instead of promoter regions, which affects the sequential events and leads to an increase in alternative splicing of mRNAs [402]. Moreover, differentiated excitatory neurons from hiPSCs treated for 24 hours with VPA showed an increase in splicing transcriptional profiles from several genes related to ASD, as well as chromatin and transcriptional regulatory genes [365]. Given the significant importance of spatiotemporal expression patterns of alternative splicing during brain development [403] and the growing evidence of abnormal splicing variants in ASD [404], future studies should prioritize the identification of this emerging *in vitro* evidence from splice variants in brain development following prenatal exposure to VPA.

Overall, the mechanism of the VPA by HDACi could be strongly related to the heterogeneity of ASD, which is associated with genetic changes. Recently, a study was conducted using 45 postmortem brain samples from ASD subjects. The study demonstrated a shared histone-acetylome pattern in 68% of individuals, including both syndromic and idiopathic forms of ASD [405]. Interestingly, common pathways were associated with these epigenetic modifications, such as

synaptic transmission, histone deacetylation, and immunity. The genes associated with ASD primarily encode synaptic proteins, transcriptional regulators, and chromatin remodeling factors, suggesting that synapse formation and the establishment of neuronal circuits during brain development play a crucial role in ASD [367].

6.2. Signaling Pathways

Previous studies suggest several signaling processes as mechanisms of action of VPA, including Wnt/β-catenin, PI3K/Akt, and MAPK/ERK pathways [69, 349, 406]. However, it is still unclear how many of these processes are dysregulated as a direct result of a VPA mechanism of action. Otherwise, it has even been suggested that dysregulation of Wnt/β-catenin may be a downstream event in the mechanism of action of VPA on HDAC [369]. Therefore, this section focuses on the direct evidence from VPA as a mechanism of action during gestation on signaling processes and their role in cellular processes that may alter neuronal and network development related to ASD etiology.

The Wnt signaling pathway plays a key role in embryonic development, regulating processes such as cellular growth and proliferation, migration, maintenance of stem cells, and neuronal polarity [407, 408]. The canonical Wnt signaling pathway leads to increased levels of β-catenin, which translocate to the nucleus, promoting the transcription of Wnt-dependent genes. β-catenin is regulated by the phosphorylation of glycogen synthase kinase-3β (GSK-3β), which leads to its degradation and the stabilization of cytoplasmic β-catenin [349, 409]. Some studies suggest that VPA stimulates the canonical Wnt signaling pathway through the modulation of HDAC and GSK-3β [406, 409]. VPA is proposed to activate Wnt-dependent gene expression through its HDACi activity [349, 410-412]. Prenatal exposure to VPA leads to the upregulation of the Wnt/β-catenin signaling pathway through increased degradation of GSK-3β and subsequent elevation of β-catenin levels [342, 363]. Also, VPA upregulates the Wnt/β-catenin pathway by increasing the phosphorylation of GSK-3β and decreasing the phosphorylation of β-catenin. This leads to a decrease in the expression of the redox proteins Trx1 and Trx2 and an increase in the expression of the oxidative stress marker 4-HNE in the prefrontal cortex and hippocampus [174]. Wnt ligands are glycoproteins secreted in an autocrine or paracrine fashion, interacting with the Wnt inhibitory factor and the Fzd receptor to transmit the signal downstream [413]. Prenatal exposure to VPA increases the expression of Wnt1 and Wnt2 ligands and upregulates mRNA levels of the downstream target genes *En1* and *Ccnd1* in the prefrontal cortex and hippocampus [363].

In addition, altered signaling of the Wnt/β-catenin pathway has been reported in ASD [409, 414], including variants of Wnt ligands [415-419]. Also, the chromodomain helicase DNA binding protein 8 (CDH8) has been identified as a significant candidate gene for ASD [420, 421]. One of the pathways regulated by CHD8 is the Wnt signaling pathway [422]. The Phosphatase and tensin homolog (PTEN) is another major candidate gene for ASD that interacts with the Wnt pathway [423]. This signaling protein is known to be an important regulator of neural circuit formation [408, 424], indicating that these pathways play a role in neural proliferation, migration, and differentiation during embryonic brain development. It is possible that Wnt/β-catenin signaling is dysregulated in ASD [406, 425].

Overall, this evidence suggests a strong modulation of Wnt signaling following exposure to VPA. Although it has been previously suggested that there is crosstalk between multiple signaling processes, few studies have been conducted during the gestational period or under similar *in vitro* conditions to explain these interactions. In this sense, the effect of VPA on β-catenin stabilizes Ras, promoting ERK-$p21^{Cip/WAF1}$ signaling. This signaling pathway then promotes the differentiation and inhibits the proliferation of embryonic E14 NPCs [369]. Lastly, mTOR signaling through PI3K/Akt or PTEN modulation can contribute to the differentiation-induced process by VPA [426-428].

6.3. Oxidative Stress and Immune Response

The epigenetic effects and downstream signaling pathways altered by VPA exposure can partially explain an early oxidative stress environment contributing to impairments during embryogenesis and immune activation. Previously, an upregulated transcription of immune system pathways was reported to change across postnatal amygdala development in dams prenatally exposed to VPA [429]. In addition, exposure to gestational VPA before neural tube closure (E9) in mice increases ROS production and the occurrence of neural tube defects [430]. In contrast, the postnatal brain of prenatally exposed VPA showed a continued decrease in the expression of redox proteins and an increase in the expression of oxidative markers and pro-inflammatory cytokines [174, 336]. Although some of these changes could be partly explained by the epigenetic effect of VPA on transcriptional profiles, as previously suggested [429], further studies must elucidate their role through direct or indirect modulation, such as Wnt/β-catenin [174].

7. CONVERGENCE OF PRENATAL VPA EXPOSURE COMPARED TO OTHER MODELS OF AUTISM-LIKE BEHAVIOR: IDIOPATHIC AND SYNDROMIC FORMS OF ASD

ASD is frequently described as syndromic when its etiology is related to a single gene mutation or chromosome abnormality that explains a syndrome with a high prevalence of ASD diagnosis. Examples of such syndromes include Phelan-McDermid's syndrome, which is often associated with a *SHANK3* mutation; Rett's syndrome and MecP2 duplication syndrome, which are associated with *MECP2* mutations; Fragile-X syndrome, which is associated with *FMR1* mutations, Tuberous sclerosis complex, which is associated with *TSC1/2* mutations, Angelman's syndrome, which is associated with *UBE3A* mutations, Prader-Willi's syndrome, which is associated with chromosome 15q11-q13 deletion, and *CACNA1C* mutations [431]. On the other hand, non-syndromic ASD cases, which do not have identified etiological factors, are often referred to as idiopathic [432]. Both concepts are frequently applied to animal models, including prenatal exposure to VPA as an idiopathic model.

Also, risk factors associated with the incidence of ASD can be classified into environmental factors, epigenetic

changes, and genetic variants [433]. Nevertheless, boundaries between this classification can be diffuse, given that environmental factors can cause epigenetic modifications. However, it is important to note that not all of the epigenome results from an environmental insult. It also depends on the interaction with specific genetic patterns and the predisposition of genetic variants [434]. Moreover, ASD-related genetic variants could lead to epigenetic modifications, such as MecP2 variants [435]. Instead, the etiology of ASD could be better conceptualized as an interplay of genetic-epigenetic interactions that affect specific pathways in brain development. This supports the observed complex heterogeneity in ASD [436]. According to this view, environmental risk factors such as VPA primarily increase the epigenetic load for ASD. On the other hand, single, well-identified mutations mainly increase the genetic load. Each case contributes to compromising shared pathways during brain development. Interestingly, a novel histone methyltransferase (EHMT1) loss-of-function syndrome in mice results in reduced levels of H3K9me3 in the embryonic brain at E11.5. This syndrome also leads to differential gene expression, including enrichment in Wnt signaling. Furthermore, mice with this syndrome exhibit behavioral inflexibility and social deficits during the postnatal period [437, 438]. Also, the knockdown of *EHMT1* in NSCs promotes a differentiated state [439]. A novel inbred strain BTBR/R idiopathic ASD model gains copy number variants (CNVs) in HDAC1, contributing to epigenetic reprogramming and immune dysfunction during embryogenesis at E11.5 [440, 441]. In addition, impairments in HDAC are involved in *SHANK3* mutations in Phelan-McDermid syndrome [442]. Prenatal HDAC inhibition by VPA transiently reduces the expression of *Shank3* 14 days after culturing embryonic neurons [263], which suggests the presence of a compensatory mechanism that reduces the genetic load for ASD, in contrast to the strong impact of Shank3 mutations in Phelan-McDermid syndrome. Interestingly, Shank3 expression and protein levels are lower during postnatal development of the cerebellum in mice exposed to prenatal VPA [367]. This indicates that differences could be established in specific structures in the postnatal brain. Moreover, *MECP2* mutations in Rett syndrome and ASD models highlight the importance of genetic variants that result in impairments in dependence on the epigenetic background. MecP2 binds to methyl CpG sites in the promoter region of several genes, which mainly leads to gene repression but can also result in gene expression depending on its interaction with co-factors [435]. In contrast, prenatal exposure to VPA at E12.5, but not E14.5, downregulated the expression of *Mecp2* and increased the expression of *Bdnf* and miR132 after exposure but not at birth [368]. Interestingly, this study suggests that MecP2 expression would not be directly regulated by HDACi. Instead, it was reported that HDACi increased *Bdnf* expression, increasing miR132 expression through a downstream transcription factor. As previously reported, increased miR132 expression leads to the downregulation of *Mecp2* expression [443]. This explains the immediate BDNF expression one hour after VPA until six hours, but only mir-132 shows sustained expression 24 hours later [368]. Moreover, the MecP2-BDNF-miR132 regulatory feedback loop was found to be altered in postmortem brain tissue from individuals with Rett syndrome [444]. In addition, exposure to VPA increased CpG promoter demethylation of *Reln* and *Gad67*, as well as H3ac binding. This could be attributed to the activity of HDACi and demethylation [384, 385, 392], which contribute to the epigenetic load caused by VPA exposure. Overall, these monogenic and environmental ASD models recapitulate several points of convergence with prenatal exposure to VPA and the interplay of genetic-epigenetic interactions during brain development.

As summarized in Table **2**, prenatal exposure to the VPA model has been shown to explain certain aspects of ASD etiology, especially the regulation of epigenomics through histone acetylation. This model also involves downstream pathways, such as Wnt signaling, during gestation, which affect various brain developmental processes, including the proliferation of NPCs, differentiation, and cellular organization in the cerebral cortex. Some of these impairments in differentiation could be triggered after exposure to VPA, leading to a reprogramming of transcriptional profiles. This reprogramming may result in increased glutamatergic differentiation and impairments in GABAergic and oligodendroglial lineages. Epigenetic modifications, such as histone acetylation, induce immediate and transient differential gene expression, while DNA and histone methylation could later sustain it. Also, it has been suggested that VPA, through Wnt signaling, could regulate the expression of redox proteins such as Trx1/2, leading to an increase in oxidative stress. Overall, these early events during gestational development could later result in an imbalance between E/I signals as well as impaired immune function and connectivity. Still, it is unclear how these early gestational events selectively impact certain structures that contribute to the core ASD symptoms in the postnatal brain. However, both gestational and postnatal impairments reported by prenatal exposure to VPA align with common pathological processes observed in ASD subjects. Interestingly, other environmental and monogenic-induced models of ASD converge on several mechanisms that could explain a common physiopathology [10, 202, 264, 409, 445].

8. PERSPECTIVES AND LIMITATIONS

The prenatal VPA exposure model has consistently recapitulated core ASD symptoms and neurobiological impairments that have been reported in multiple studies involving human and animal models. The significant variability reported in the model should be carefully considered to establish more reproducible results. The *in vivo* studies would consider the period of embryonic development, which may affect the outcome after VPA administration. This includes the effect on neural progenitor differentiation processes and the reported behavioral disturbances. Some of these changes appear to be temporary, so the timing of the evaluation should also be taken into consideration. In summary of the articles discussed here, a dose of 400-600 mg/kg and embryonic exposure time between E11.5 and E12.5 seem to be reasonable thresholds, as previously suggested [80]. Interestingly, when considering this VPA threshold, consistent impairments in two core behaviors of ASD were reported across postnatal developmental stages. Given the limited number of studies reporting autism-like behaviors resulting from prolonged prenatal or early postnatal exposure, these models should not be discarded. Instead, they should be further classified as single or sustained prenatal and postnatal

exposures to VPA, and the neurobiological correlates should be carefully compared. In general, for VPA and other ASD models, behavioral evidence can be enhanced by standardizing current protocols and expanding specific domains. These domains include semi-natural habitat social behavior, decision-making, cognitive flexibility, perseverative behavior, and sensory processing and integration [80, 446-448]. Furthermore, animal models of ASD should increase their focus on endophenotypes, which are characteristics that may have a genetic relationship to a disorder without necessarily predicting a diagnosis. Identifying the points of convergence and divergence between monogenic and environmental models will help us better understand the complex and heterogeneous etiology of ASD. For example, seizure susceptibility, anxiety-like behaviors, abnormalities in sensory processing, and sleep disturbances are frequently reported endophenotypes in ASD animal models. Prenatal exposure to VPA exposure is a common factor that converges with monogenic and other environmental models [449, 450].

The *in vitro* studies would consider the standardized dose and time of administration of VPA, as well as the days after exposure. This is because concentration and time dependence in transcriptional profiles by HDACi, including VPA, have been previously reported [451]. Interestingly, this study demonstrated an adaptive response to epigenomic disruption by HDACi, including the downregulation of lysine acetyltransferases (KATs) in a dose-dependent manner. Considering that most *in vitro* studies have been conducted using cells of embryonic origin, iPSCs, or NPCs to assess the level of neuronal differentiation, it seems that the dosage is the least significant variation factor. Commonly used concentrations include 0.2, 0.5, 1, and 2 mM, with similar results observed in the 0.5-1 mM range. On the other hand, the duration of exposure and the number of days after exposure have been identified as the primary sources of variation across different studies, with both ranging from hours to days. Cell genomic programs during pluripotency and the proliferative state are different compared to differentiated cells, which are compromised by VPA HDACi and should be taken into consideration. Many of the *in vitro* studies considered in this review focus on the effect of VPA on neural development and ASD. These studies primarily use proliferative cells, such as embryonic progenitors or iPCs, that have been reprogrammed to exhibit a neural phenotype. To mechanistically explain the epigenetic regulation of VPA, several studies were conducted on cell lines, including tumor-derived cell lines with proliferative capacity.

It is important to note that the VPA model has limitations, and it is unclear if the variation between the VPA models represents a wide spectrum of ASD or more technical differences in approach among different laboratories. The specific causes of autism are still largely unknown, and it is reasonable to assume that most patients were not exposed to VPA during gestation. This raises questions about the validity of the VPA model in relation to human autism. On the other hand, highly penetrant ASD-related gene variants have not been identified in the majority of cases, accounting for only about 5-15% of ASD cases [270, 452]. Also, some of these gene variants are related to specific clinical features unrelated to ASD. Interestingly, these monogenic disorders share comorbidities with idiopathic ASD cases, which may be attributed to epigenomic reprogramming and impairments during embryonic development, both of which are associated with exposure to VPA.

CONCLUSION

The prenatal exposure to the VPA model has been a valuable tool for studying the etiology and physiopathology related to ASD over the past three decades. This model has garnered research support, demonstrating both construct validity and face validity as an animal model. Since the first studies suggested multiple targets and interactions of VPA, there has been a better understanding of a complex series of events during embryonic development. These events begin with epigenetic modifications and later involve the reprogramming of transcriptional profiles following HDAC inhibition. This conceptualizes the framework in which this model fits into the epigenetic-genetic interplay in brain development. It contributes to the understanding of the etiology of ASD and subsequent disturbances in the postnatal brain, including neuronal organization and architecture, immune dysregulation, and imbalances in the functioning of excitatory/inhibitory systems. These disturbances are mainly caused by synapse signaling and interact with other environmental and genetic models. Thus, combining human and animal studies has helped us better understand the molecular and neurobiological mechanisms associated with the behavioral phenotypes of ASD.

LIST OF ABBREVIATIONS

ASD	=	Autism Spectrum Disorder
BBB	=	Blood-brain Barrier
BTBR/R	=	Inbred Mouse Strain BTBR TF/ArtRbrc
cKO	=	Conditional Knock-out
CNV	=	Copy Number Variant
CpG	=	Cytosine Guanine Dinucleotide
DMNT1	=	DNA Methyltransferase 1
dpf	=	Days Post-fertilization
E,DSM-V-TR	=	Diagnostic Statistics and Mental Health Disorders V-Text Revised Embryonal day
E/I	=	Excitatory/Inhibitory Imbalance
EHMT1	=	Histone Methyltransferase
FVS	=	Fetal Valproate Syndrome
GSK-3β	=	Glycogen Synthase Kinase-3β
H3/H4Kac	=	Histone Lysine Acetylation
H4/H4Kme	=	Histone Lysine Methylation
HDACi	=	Histone Deacetylase Inhibition
HDM	=	Histone Demethylase
hiPSC	=	Human Induced Pluripotent Stem Cell
HPF	=	Hours Post-fertilization
MFP	=	Months Post-fertilization

MIA	=	Maternal Immune Activation
mRNA	=	Messenger RNA
NO	=	Nitric Oxide
NPC	=	Neural Progenitor Cells
NSC	=	Neural Stem Cells
P	=	Postnatal Day
PFC	=	Prefrontal Cortex
ROS	=	Reactive Oxygen Species
TSA	=	Trichostatin A
VPA	=	Valproate
VPD	=	Valpromide

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Lord, C.; Elsabbagh, M.; Baird, G.; Veenstra-Vanderweele, J. Autism spectrum disorder. *Lancet,* **2018**, *392*(10146), 508-520. http://dx.doi.org/10.1016/S0140-6736(18)31129-2 PMID: 30078460

[2] Li, Y.A.; Chen, Z.J.; Li, X.D.; Gu, M.H.; Xia, N.; Gong, C.; Zhou, Z.W.; Yasin, G.; Xie, H.Y.; Wei, X.P.; Liu, Y.L.; Han, X.H.; Lu, M.; Xu, J.; Huang, X.L. Epidemiology of autism spectrum disorders: Global burden of disease 2019 and bibliometric analysis of risk factors. *Front Pediatr.,* **2022**, *10*, 972809. http://dx.doi.org/10.3389/fped.2022.972809 PMID: 36545666

[3] Sharma, S.R.; Gonda, X.; Tarazi, F.I. Autism spectrum disorder: Classification, diagnosis and therapy. *Pharmacol. Ther.,* **2018**, *190*, 91-104. http://dx.doi.org/10.1016/j.pharmthera.2018.05.007 PMID: 29763648

[4] Bölte, S.; Girdler, S.; Marschik, P.B. The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cell. Mol. Life Sci.,* **2019**, *76*(7), 1275-1297. http://dx.doi.org/10.1007/s00018-018-2988-4 PMID: 30570672

[5] Lord, C.; Brugha, T.S.; Charman, T.; Cusack, J.; Dumas, G.; Frazier, T.; Jones, E.J.H.; Jones, R.M.; Pickles, A.; State, M.W.; Taylor, J.L.; Veenstra-VanderWeele, J. Autism spectrum disorder. *Nat. Rev. Dis. Primers,* **2020**, *6*(1), 5. http://dx.doi.org/10.1038/s41572-019-0138-4 PMID: 31949163

[6] Tomson, T.; Battino, D.; Perucca, E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. *Lancet Neurol.,* **2016**, *15*(2), 210-218. http://dx.doi.org/10.1016/S1474-4422(15)00314-2 PMID: 26655849

[7] Johannessen, C.U.; Johannessen, S.I. Valproate: Past, present, and future. *CNS Drug Rev.,* **2003**, *9*(2), 199-216. http://dx.doi.org/10.1111/j.1527-3458.2003.tb00249.x PMID: 12847559

[8] Rahman, M.; Nguyen, H. Valproic Acid. **2022**. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559112/

[9] Mohamed, Z.A.; Thokerunga, E.; Jimale, A.O.; Liu, Z.; Fan, J. Risk of autism spectrum disorder according to the dose and trimester of exposure to antiseizure medications: A systematic review and meta-analysis. *Open J. Psychiatr.,* **2023**, *13*(2), 106-121. http://dx.doi.org/10.4236/ojpsych.2023.132011

[10] Sato, A.; Kotajima-Murakami, H.; Tanaka, M.; Katoh, Y.; Ikeda, K. Influence of prenatal drug exposure, maternal inflammation, and parental aging on the development of autism spectrum disorder. *Front. Psychiatry,* **2022**, *13*, 821455. http://dx.doi.org/10.3389/fpsyt.2022.821455 PMID: 35222122

[11] Cui, K.; Wang, Y.; Zhu, Y.; Tao, T.; Yin, F.; Guo, Y.; Liu, H.; Li, F.; Wang, P.; Chen, Y.; Qin, J. Neurodevelopmental impairment induced by prenatal valproic acid exposure shown with the human cortical organoid-on-a-chip model. *Microsyst. Nanoeng.,* **2020**, *6*(1), 49. http://dx.doi.org/10.1038/s41378-020-0165-z PMID: 34567661

[12] Zang, Z.; Yin, H.; Du, Z.; Xie, R.; Yang, L.; Cai, Y.; Wang, L.; Zhang, D.; Li, X.; Liu, T.; Gong, H.; Gao, J.; Yang, H.; Warner, M.; Gustafsson, J.A.; Xu, H.; Fan, X. Valproic acid exposure decreases neurogenic potential of outer radial glia in human brain organoids. *Front. Mol. Neurosci.,* **2022**, *15*, 1023765. http://dx.doi.org/10.3389/fnmol.2022.1023765 PMID: 36523605

[13] Meng, Q.; Zhang, W.; Wang, X.; Jiao, C.; Xu, S.; Liu, C.; Tang, B.; Chen, C. Human forebrain organoids reveal connections between valproic acid exposure and autism risk. *Transl. Psychiatry,* **2022**, *12*(1), 130. http://dx.doi.org/10.1038/s41398-022-01898-x PMID: 35351869

[14] Chang, Z.L. Sodium valproate and valproic acid. In: *Analytical Profiles of Drug Substances*; Elsevier, **1979**; pp. 529-556.

[15] Ghodke-Puranik, Y.; Thorn, C.F.; Lamba, J.K.; Leeder, J.S.; Song, W.; Birnbaum, A.K.; Altman, R.B.; Klein, T.E. Valproic acid pathway. *Pharmacogenet. Genomics,* **2013**, *23*(4), 236-241. http://dx.doi.org/10.1097/FPC.0b013e32835ea0b2 PMID: 23407051

[16] Methaneethorn, J. A systematic review of population pharmacokinetics of valproic acid. *Br. J. Clin. Pharmacol.,* **2018**, *84*(5), 816-834. http://dx.doi.org/10.1111/bcp.13510 PMID: 29328514

[17] Henry, T.R. The history of valproate in clinical neuroscience. *Psychopharmacol. Bull.,* **2003**, *37*(S2), 5-16. PMID: 14624229

[18] Romoli, M.; Mazzocchetti, P.; D'Alonzo, R.; Siliquini, S.; Rinaldi, V.E.; Verrotti, A.; Calabresi, P.; Costa, C. Valproic acid and epilepsy: From molecular mechanisms to clinical evidences. *Curr. Neuropharmacol.,* **2019**, *17*(10), 926-946. http://dx.doi.org/10.2174/1570159X17666181227165722 PMID: 30592252

[19] Carli, M.; Weiss, F.; Grenno, G.; Ponzini, S.; Kolachalam, S.; Vaglini, F.; Viaggi, C.; Pardini, C.; Tidona, S.; Longoni, B.; Maggio, R.; Scarselli, M. Pharmacological strategies for bipolar disorders in acute phases and chronic management with a special focus on lithium, valproic acid, and atypical antipsychotics. *Curr. Neuropharmacol.,* **2023**, *21*(4), 935-950. http://dx.doi.org/10.2174/1570159X21666230224102318 PMID: 36825703

[20] Yurekli, V.A.; Akhan, G.; Kutluhan, S.; Uzar, E.; Koyuncuoglu, H.R.; Gultekin, F. The effect of sodium valproate on chronic daily headache and its subgroups. *J. Headache Pain,* **2008**, *9*(1), 37-41. http://dx.doi.org/10.1007/s10194-008-0002-5 PMID: 18231713

[21] Wang, F.; Zhang, H.; Wang, L.; Cao, Y.; He, Q. Intravenous sodium valproate for acute migraine in the emergency department: A meta-analysis. *Acta Neurol. Scand.,* **2020**, *142*(6), 521-530. http://dx.doi.org/10.1111/ane.13325 PMID: 32740903

[22] Wang, Y.; Xia, J.; Helfer, B.; Li, C.; Leucht, S. Valproate for schizophrenia. *Cochrane Database Syst. Rev.,* **2016**, *11*(11), CD004028. PMID: 27884042

[23] Nau, H.; Rating, D.; Koch, S.; Häuser, I.; Helge, H. Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics,

transfer *via* mother's milk and clinical status in neonates of epileptic mothers. *J. Pharmacol. Exp. Ther.,* **1981**, *219*(3), 768-777. PMID: 6795343

[24] Jeong, E.J.; Yu, W.J.; Kim, C.Y.; Chung, M.K. Placenta transfer and toxicokinetics of valproic acid in pregnant cynomolgus monkeys. *Toxicol. Res.,* **2010**, *26*(4), 275-283. http://dx.doi.org/10.5487/TR.2010.26.4.275 PMID: 24278535

[25] Lee, J.H.; Yu, W.J.; Jeong, E.J.; Chung, M.K. Milk transfer and toxicokinetics of valproic Acid in lactating cynomolgus monkeys. *Toxicol. Res.,* **2013**, *29*(1), 53-60. http://dx.doi.org/10.5487/TR.2013.29.1.053 PMID: 24278629

[26] Genton, P.; Semah, F.; Trinka, E. Valproic acid in epilepsy : Pregnancy-related issues. *Drug Saf.,* **2006**, *29*(1), 1-21. http://dx.doi.org/10.2165/00002018-200629010-00001 PMID: 16454531

[27] Williams, G.; King, J.; Cunningham, M.; Stephan, M.; Kerr, B.; Hersh, J.H. Fetal valproate syndrome and autism: Additional evidence of an association. *Dev. Med. Child Neurol.,* **2001**, *43*(3), 202-206. http://dx.doi.org/10.1111/j.1469-8749.2001.tb00188.x PMID: 11263692

[28] Rasalam, A.D.; Hailey, H.; Williams, J.H.G.; Moore, S.J.; Turnpenny, P.D.; Lloyd, D.J.; Dean, J.C.S. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev. Med. Child Neurol.,* **2005**, *47*(8), 551-555. http://dx.doi.org/10.1017/S0012162205001076 PMID: 16108456

[29] Ornoy, A. Valproic acid in pregnancy: How much are we endangering the embryo and fetus? *Reprod. Toxicol.,* **2009**, *28*(1), 1-10. http://dx.doi.org/10.1016/j.reprotox.2009.02.014 PMID: 19490988

[30] Harden, C.L. In utero valproate exposure and autism: Long suspected, finally proven. *Epilepsy Curr.,* **2013**, *13*(6), 282-284. http://dx.doi.org/10.5698/1535-7597-13.6.282 PMID: 24348128

[31] Christensen, J.; Grønborg, T.K.; Sørensen, M.J.; Schendel, D.; Parner, E.T.; Pedersen, L.H.; Vestergaard, M. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA,* **2013**, *309*(16), 1696-1703. http://dx.doi.org/10.1001/jama.2013.2270 PMID: 23613074

[32] Elger, C.E. Is valproate contraindicated in young women with epilepsy? No. *Epileptology,* **2013**, *1*(1), 43-45. http://dx.doi.org/10.1016/j.epilep.2013.01.002

[33] Macfarlane, A.; Greenhalgh, T. Sodium valproate in pregnancy: What are the risks and should we use a shared decision-making approach? *BMC Pregnancy Childbirth,* **2018**, *18*(1), 200. http://dx.doi.org/10.1186/s12884-018-1842-x PMID: 29859057

[34] Thisted, E; Ebbesen, F Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child.,* **1993**, *69*, 288-291. http://dx.doi.org/10.1136/adc.69.3_Spec_No.288

[35] Wiedemann, K.; Stüber, T.; Rehn, M.; Frieauff, E. Fetal valproate syndrome - still a problem today! *Z. Geburtshilfe Neonatol.,* **2017**, *221*(5), 243-246. http://dx.doi.org/10.1055/s-0043-107619 PMID: 29073690

[36] Kulkarni, M.L.; Zaheeruddin, M.; Shenoy, N.; Vani, H.N. Fetal valproate syndrome. *Indian J. Pediatr.,* **2006**, *73*(10), 937-939. http://dx.doi.org/10.1007/BF02859291 PMID: 17090909

[37] Chandane, P.; Shah, I. Fetal valproate syndrome. *Indian J. Hum. Genet.,* **2014**, *20*(2), 187-188. http://dx.doi.org/10.4103/0971-6866.142898 PMID: 25400349

[38] Zaki, S.A.; Phulsundar, A.; Shanbag, P.; Mauskar, A. Fetal valproate syndrome in a 2-month-old male infant. *Ann. Saudi Med.,* **2010**, *30*(3), 233-235. http://dx.doi.org/10.4103/0256-4947.62839 PMID: 20427941

[39] Wood, A.G.; Nadebaum, C.; Anderson, V.; Reutens, D.; Barton, S.; O'Brien, T.J.; Vajda, F. Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia,* **2015**, *56*(7), 1047-1055. http://dx.doi.org/10.1111/epi.13007 PMID: 25963613

[40] Cummings, C.; Stewart, M.; Stevenson, M.; Morrow, J.; Nelson, J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch. Dis. Child.,* **2011**, *96*(7), 643-647. http://dx.doi.org/10.1136/adc.2009.176990 PMID: 21415043

[41] Shallcross, R.; Bromley, R.L.; Irwin, B.; Bonnett, L.J.; Morrow, J.; Baker, G.A. Child development following in utero exposure: Levetiracetam *vs* sodium valproate. *Neurology,* **2011**, *76*(4), 383-389. http://dx.doi.org/10.1212/WNL.0b013e3182088297 PMID: 21263139

[42] Meador, K.J.; Baker, G.A.; Browning, N.; Clayton-Smith, J.; Combs-Cantrell, D.T.; Cohen, M.; Kalayjian, L.A.; Kanner, A.; Liporace, J.D.; Pennell, P.B.; Privitera, M.; Loring, D.W. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N. Engl. J. Med.,* **2009**, *360*(16), 1597-1605. http://dx.doi.org/10.1056/NEJMoa0803531 PMID: 19369666

[43] Nadebaum, C.; Anderson, V.; Vajda, F.; Reutens, D.; Barton, S.; Wood, A. The Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. *J. Int. Neuropsychol. Soc.,* **2011**, *17*(1), 133-142. http://dx.doi.org/10.1017/S1355617710001359 PMID: 21092354

[44] Nadebaum, C.; Anderson, V.A.; Vajda, F.; Reutens, D.C.; Barton, S.; Wood, A.G. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology,* **2011**, *76*(8), 719-726. http://dx.doi.org/10.1212/WNL.0b013e31820d62c7 PMID: 21339499

[45] Goyal, M.; Gupta, A.; Sharma, M.; Mathur, P.; Bansal, N. Fetal valproate syndrome with limb defects: An Indian case report. *Case Rep. Pediatr.,* **2016**, *2016*, 1-4. http://dx.doi.org/10.1155/2016/3495910 PMID: 28003925

[46] Tomson, T.; Battino, D.; Bonizzoni, E.; Craig, J.; Lindhout, D.; Sabers, A.; Perucca, E.; Vajda, F. Dose-dependent risk of malformations with antiepileptic drugs: An analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol.,* **2011**, *10*(7), 609-617. http://dx.doi.org/10.1016/S1474-4422(11)70107-7 PMID: 21652013

[47] Jentink, J; Dolk, H; Loane, MA; Morris, JK; Wellesley, D; Garne, E Intrauterine exposure to carbamazepine and specific congenital malformations: Systematic review and case-control study. *BMJ.,* **2010**, *341*, c6581-c6581. http://dx.doi.org/10.1136/bmj.c6581

[48] Stadelmaier, R.; Nasri, H.; Deutsch, C.K.; Bauman, M.; Hunt, A.; Stodgell, C.J.; Adams, J.; Holmes, L.B. Exposure to sodium valproate during pregnancy: Facial Features and Signs of Autism. *Birth Defects Res.,* **2017**, *109*(14), 1134-1143. http://dx.doi.org/10.1002/bdr2.1052 PMID: 28635121

[49] Donovan, M.F.; Cascella, M. Embryology, Weeks 6-8.*StatPearls*; StatPearls Publishing: Treasure Island, FL, **2023**.

[50] O'Rahilly, R.; Müller, F. Developmental stages in human embryos: Revised and new measurements. *Cells Tissues Organs,* **2010**, *192*(2), 73-84. http://dx.doi.org/10.1159/000289817 PMID: 20185898

[51] Sass, L.; Urhoj, S.K.; Kjærgaard, J.; Dreier, J.W.; Strandberg-Larsen, K.; Nybo Andersen, A.M. Fever in pregnancy and the risk of congenital malformations: A cohort study. *BMC Pregnancy Childbirth,* **2017**, *17*(1), 413. http://dx.doi.org/10.1186/s12884-017-1585-0 PMID: 29221468

[52] Romøren, M.; Lindbaek, M.; Nordeng, H. Pregnancy outcome after gestational exposure to erythromycin - a population-based register study from Norway. *Br. J. Clin. Pharmacol.,* **2012**, *74*(6), 1053-1062. http://dx.doi.org/10.1111/j.1365-2125.2012.04286.x PMID: 22463376

[53] Sun, L.; Xi, Y.; Wen, X.; Zou, W. Use of metoclopramide in the first trimester and risk of major congenital malformations: A systematic review and meta-analysis. *PLoS One.,* **2021**, *16*(9), e0257584. http://dx.doi.org/10.1371/journal.pone.0257584

[54] Christianson, A.L.; Chester, N.; Kromberg, J.G.R. Fetal valproate syndrome: Clinical and neuro-developmental features in two sibling pairs. *Dev. Med. Child Neurol.,* **1994**, *36*(4), 361-369. http://dx.doi.org/10.1111/j.1469-8749.1994.tb11858.x PMID: 7512516

[55] Laegreid, L.; Kyllerman, M.; Hedner, T.; Hagberg, B.; Viggedahl, G. Benzodiazepine amplification of valproate teratogenic effects in children of mothers with absence epilepsy. *Neuropediatrics,* **1993**, *24*(2), 88-92.

http://dx.doi.org/10.1055/s-2008-1071520 PMID: 7687042

[56] Williams, P.G.; Hersh, J.H. A male with fetal valproate syndrome and autism. *Dev. Med. Child Neurol.,* **1997**, *39*(9), 632-634. http://dx.doi.org/10.1111/j.1469-8749.1997.tb07500.x PMID: 9344057

[57] Bromley, R.L.; Mawer, G.; Clayton-Smith, J.; Baker, G.A. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology,* **2008**, *71*(23), 1923-1924. http://dx.doi.org/10.1212/01.wnl.0000339399.64213.1a PMID: 19047565

[58] Moore, S.J.; Turnpenny, P.; Quinn, A.; Glover, S.; Lloyd, D.J.; Montgomery, T.; Dean, J.C. A clinical study of 57 children with fetal anticonvulsant syndromes. *J. Med. Genet.,* **2000**, *37*(7), 489-497. http://dx.doi.org/10.1136/jmg.37.7.489 PMID: 10882750

[59] Dean, J.C.S.; Hailey, H.; Moore, S.J.; Lloyd, D.J.; Turnpenny, P.D.; Little, J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J. Med. Genet.,* **2002**, *39*(4), 251-259. http://dx.doi.org/10.1136/jmg.39.4.251 PMID: 11950853

[60] Bromley, R.L.; Mawer, G.E.; Briggs, M.; Cheyne, C.; Clayton-Smith, J.; García-Fiñana, M.; Kneen, R.; Lucas, S.B.; Shallcross, R.; Baker, G.A.; Baker, G.; Briggs, M.; Bromley, R.; Clayton-Smith, J.; Dixon, P.; Fryer, A.; Gummery, A.; Kneen, R.; Kerr, L.; Lucas, S.; Mawer, G.; Shallcross, R. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J. Neurol. Neurosurg. Psychiatry,* **2013**, *84*(6), 637-643. http://dx.doi.org/10.1136/jnnp-2012-304270 PMID: 23370617

[61] Petersen, I.; Collings, S.L.; McCrea, R.L.; Nazareth, I.; Osborn, D.P.; Cowen, P.J.; Sammon, C.J. Antiepileptic drugs prescribed in pregnancy and prevalence of major congenital malformations: Comparative prevalence studies. *Clin. Epidemiol.,* **2017**, *9*, 95-103. http://dx.doi.org/10.2147/CLEP.S118336 PMID: 28243149

[62] Hisle-Gorman, E.; Susi, A.; Stokes, T.; Gorman, G.; Erdie-Lalena, C.; Nylund, C.M. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. *Pediatr. Res.,* **2018**, *84*(2), 190-198. http://dx.doi.org/10.1038/pr.2018.23 PMID: 29538366

[63] Crawley, J.N. Translational animal models of autism and neurodevelopmental disorders. *Dialogues Clin. Neurosci.,* **2012**, *14*(3), 293-305. http://dx.doi.org/10.31887/DCNS.2012.14.3/jcrawley PMID: 23226954

[64] Bauman, M.D.; Crawley, J.N.; Berman, R.F. *Autism: Animal Models,* 1st ed.; John Wiley & Sons, Ltd., **2010**.

[65] Belzung, C.; Lemoine, M. Criteria of validity for animal models of psychiatric disorders: Focus on anxiety disorders and depression. *Biol. Mood Anxiety Disord.,* **2011**, *1*(1), 9. http://dx.doi.org/10.1186/2045-5380-1-9 PMID: 22738250

[66] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, Text Revision; American Psychiatric Association: Washington, DC, **2022**.

[67] Mabunga, D.F.N.; Gonzales, E.L.T.; Kim, J.; Kim, K.C.; Shin, C.Y. Exploring the validity of valproic acid animal model of autism. *Exp. Neurobiol.,* **2015**, *24*(4), 285-300. http://dx.doi.org/10.5607/en.2015.24.4.285 PMID: 26713077

[68] Rodier, P.M.; Ingram, J.L.; Tisdale, B.; Nelson, S.; Romano, J. Embryological origin for autism: Developmental anomalies of the cranial nerve motor nuclei. *J. Comp. Neurol.,* **1996**, *370*(2), 247-261. http://dx.doi.org/10.1002/(SICI)1096-9861(19960624)370:2<247::AID-CNE8>3.0.CO;2-2 PMID: 8808733

[69] Tartaglione, A.M.; Schiavi, S.; Calamandrei, G.; Trezza, V. Prenatal valproate in rodents as a tool to understand the neural underpinnings of social dysfunctions in autism spectrum disorder. *Neuropharmacology,* **2019**, *159*, 107477. http://dx.doi.org/10.1016/j.neuropharm.2018.12.024 PMID: 30639388

[70] Nicolini, C.; Fahnestock, M. The valproic acid-induced rodent model of autism. *Exp. Neurol.,* **2018**, *299*(Pt A), 217-227. http://dx.doi.org/10.1016/j.expneurol.2017.04.017 PMID: 28472621

[71] Ranger, P.; Ellenbroek, B.A. Perinatal influences of valproate on brain and behaviour: An animal model for autism. In: *Neurotoxin Modeling of Brain Disorders—Life-long Outcomes in Behavioral Teratology*; Kostrzewa, RM; Archer, A., Eds.; Springer International Publishing: Cham, **2015**; pp. 363-386.

[72] Roullet, F.I.; Lai, J.K.Y.; Foster, J.A. In utero exposure to valproic acid and autism — A current review of clinical and animal studies. *Neurotoxicol. Teratol.,* **2013**, *36*, 47-56. http://dx.doi.org/10.1016/j.ntt.2013.01.004 PMID: 23395807

[73] Kim, K.C.; Kim, P.; Go, H.S.; Choi, C.S.; Yang, S.I.; Cheong, J.H.; Shin, C.Y.; Ko, K.H. The critical period of valproate exposure to induce autistic symptoms in Sprague–Dawley rats. *Toxicol. Lett.,* **2011**, *201*(2), 137-142. http://dx.doi.org/10.1016/j.toxlet.2010.12.018 PMID: 21195144

[74] Yochum, C.L.; Dowling, P.; Reuhl, K.R.; Wagner, G.C.; Ming, X. VPA-induced apoptosis and behavioral deficits in neonatal mice. *Brain Res.,* **2008**, *1203*, 126-132. http://dx.doi.org/10.1016/j.brainres.2008.01.055 PMID: 18316065

[75] Chomiak, T.; Karnik, V.; Block, E.; Hu, B. Altering the trajectory of early postnatal cortical development can lead to structural and behavioural features of autism. *BMC Neurosci.,* **2010**, *11*(1), 102. http://dx.doi.org/10.1186/1471-2202-11-102 PMID: 20723245

[76] Reynolds, S.; Millette, A.; Devine, D.P. Sensory and motor characterization in the postnatal valproate rat model of autism. *Dev. Neurosci.,* **2012**, *34*(2-3), 258-267. http://dx.doi.org/10.1159/000336646 PMID: 22627078

[77] Wagner, G.C.; Reuhl, K.R.; Cheh, M.; McRae, P.; Halladay, A.K. A new neurobehavioral model of autism in mice: Pre- and postnatal exposure to sodium valproate. *J. Autism Dev. Disord.,* **2006**, *36*(6), 779-793. http://dx.doi.org/10.1007/s10803-006-0117-y PMID: 16609825

[78] Oguchi-Katayama, A.; Monma, A.; Sekino, Y.; Moriguchi, T.; Sato, K. Comparative gene expression analysis of the amygdala in autistic rat models produced by pre- and post-natal exposures to valproic acid. *J. Toxicol. Sci.,* **2013**, *38*(3), 391-402. http://dx.doi.org/10.2131/jts.38.391 PMID: 23665938

[79] Larner, O.; Roberts, J.; Twiss, J.; Freeman, L. A Need for consistency in behavioral phenotyping for ASD: Analysis of the valproic acid model. Rossignol D; Treat, A.R., Ed.; , **2021**, pp. 1-10.

[80] Chaliha, D.; Albrecht, M.; Vaccarezza, M.; Takechi, R.; Lam, V.; Al-Salami, H.; Mamo, J. A systematic review of the valproic-acid-induced rodent model of autism. *Dev. Neurosci.,* **2020**, *42*(1), 12-48. http://dx.doi.org/10.1159/000509109 PMID: 32810856

[81] Juliandi, B.; Tanemura, K.; Igarashi, K.; Tominaga, T.; Furukawa, Y.; Otsuka, M.; Moriyama, N.; Ikegami, D.; Abematsu, M.; Sanosaka, T.; Tsujimura, K.; Narita, M.; Kanno, J.; Nakashima, K. Reduced adult hippocampal neurogenesis and cognitive impairments following prenatal treatment of the antiepileptic drug valproic acid. *Stem Cell Reports,* **2015**, *5*(6), 996-1009. http://dx.doi.org/10.1016/j.stemcr.2015.10.012 PMID: 26677766

[82] Main, S.L.; Kulesza, R.J. Repeated prenatal exposure to valproic acid results in cerebellar hypoplasia and ataxia. *Neuroscience,* **2017**, *340*, 34-47. http://dx.doi.org/10.1016/j.neuroscience.2016.10.052 PMID: 27984183

[83] Cartocci, V.; Catallo, M.; Tempestilli, M.; Segatto, M.; Pfrieger, F.W.; Bronzuoli, M.R.; Scuderi, C.; Servadio, M.; Trezza, V.; Pallottini, V. Altered brain cholesterol/isoprenoid metabolism in a rat model of autism spectrum disorders. *Neuroscience,* **2018**, *372*, 27-37. http://dx.doi.org/10.1016/j.neuroscience.2017.12.053 PMID: 29309878

[84] Cezar, LC; Kirsten, TB; da Fonseca, CCN; de Lima, APN; Bernardi, MM; Felicio, LF Zinc as a therapy in a rat model of autism prenatally induced by valproic acid. *Prog. Neuropsychopharmacol. Biol. Psychiatry.,* **2018**, *84*(Pt A), 173-180. http://dx.doi.org/10.1016/j.pnpbp.2018.02.008

[85] Dai, Y.C.; Zhang, H.F.; Schön, M.; Böckers, T.M.; Han, S.P.; Han, J.S.; Zhang, R. Neonatal oxytocin treatment ameliorates autistic-like behaviors and oxytocin deficiency in valproic acid-induced rat model of autism. *Front. Cell. Neurosci.,* **2018**, *12*, 355. http://dx.doi.org/10.3389/fncel.2018.00355 PMID: 30356897

[86] Felix-Ortiz, A.C.; Febo, M. Gestational valproate alters BOLD activation in response to complex social and primary sensory stimuli. *PLoS One,* **2012**, *7*(5), e37313.

http://dx.doi.org/10.1371/journal.pone.0037313 PMID: 22615973

[87] Moldrich, R.X.; Leanage, G.; She, D.; Dolan-Evans, E.; Nelson, M.; Reza, N.; Reutens, D.C. Inhibition of histone deacetylase in utero causes sociability deficits in postnatal mice. *Behav. Brain Res.,* **2013**, *257*, 253-264. http://dx.doi.org/10.1016/j.bbr.2013.09.049 PMID: 24103642

[88] Kuo, H.Y.; Liu, F.C. Valproic acid induces aberrant development of striatal compartments and corticostriatal pathways in a mouse model of autism spectrum disorder. *FASEB J.,* **2017**, *31*(10), 4458-4471. http://dx.doi.org/10.1096/fj.201700054R PMID: 28687613

[89] Melancia, F.; Schiavi, S.; Servadio, M.; Cartocci, V.; Campolongo, P.; Palmery, M.; Pallottini, V.; Trezza, V. Sex-specific autistic endophenotypes induced by prenatal exposure to valproic acid involve anandamide signalling. *Br. J. Pharmacol.,* **2018**, *175*(18), 3699-3712. http://dx.doi.org/10.1111/bph.14435 PMID: 29968249

[90] Servadio, M.; Manduca, A.; Melancia, F.; Leboffe, L.; Schiavi, S.; Campolongo, P.; Palmery, M.; Ascenzi, P.; di Masi, A.; Trezza, V. Impaired repair of DNA damage is associated with autistic-like traits in rats prenatally exposed to valproic acid. *Eur. Neuropsychopharmacol.,* **2018**, *28*(1), 85-96. http://dx.doi.org/10.1016/j.euroneuro.2017.11.014 PMID: 29174949

[91] Tsuji, C.; Fujisaku, T.; Tsuji, T. Oxytocin ameliorates maternal separation-induced ultrasonic vocalisation calls in mouse pups prenatally exposed to valproic acid. *J. Neuroendocrinol.,* **2020**, *32*(4), e12850. http://dx.doi.org/10.1111/jne.12850 PMID: 32321197

[92] Tyzio, R.; Nardou, R.; Ferrari, D.C.; Tsintsadze, T.; Shahrokhi, A.; Eftekhari, S.; Khalilov, I.; Tsintsadze, V.; Brouchoud, C.; Chazal, G.; Lemonnier, E.; Lozovaya, N.; Burnashev, N.; Ben-Ari, Y. Oxytocin-mediated GABA inhibition during delivery attenuates autism pathogenesis in rodent offspring. *Science,* **2014**, *343*(6171), 675-679. http://dx.doi.org/10.1126/science.1247190 PMID: 24503856

[93] Zhang, J.; Liu, L.M.; Ni, J.F. Rapamycin modulated brain-derived neurotrophic factor and B-cell lymphoma 2 to mitigate autism spectrum disorder in rats. *Neuropsychiatr. Dis. Treat.,* **2017**, *13*, 835-842. http://dx.doi.org/10.2147/NDT.S125088 PMID: 28360521

[94] Kim, P.; Park, J.H.; Kwon, K.J.; Kim, K.C.; Kim, H.J.; Lee, J.M.; Kim, H.Y.; Han, S.H.; Shin, C.Y. Effects of Korean red ginseng extracts on neural tube defects and impairment of social interaction induced by prenatal exposure to valproic acid. *Food Chem. Toxicol.,* **2013**, *51*, 288-296. http://dx.doi.org/10.1016/j.fct.2012.10.011 PMID: 23104247

[95] Kim, K.C.; Kim, P.; Go, H.S.; Choi, C.S.; Park, J.H.; Kim, H.J.; Jeon, S.J.; dela Pena, I.C.; Han, S.H.; Cheong, J.H.; Ryu, J.H.; Shin, C.Y. Male-specific alteration in excitatory post-synaptic development and social interaction in pre-natal valproic acid exposure model of autism spectrum disorder. *J. Neurochem.,* **2013**, *124*(6), 832-843. http://dx.doi.org/10.1111/jnc.12147 PMID: 23311691

[96] Zhao, G.; Gao, J.; Liang, S.; Wang, X.; Sun, C.; Xia, W.; Hao, Y.; Li, X.; Cao, Y.; Wu, L. Study of the serum levels of polyunsaturated fatty acids and the expression of related liver metabolic enzymes in a rat valproate-induced autism model. *Int. J. Dev. Neurosci.,* **2015**, *44*(1), 14-21. http://dx.doi.org/10.1016/j.ijdevneu.2015.04.350 PMID: 25916973

[97] Cho, H.; Kim, C.H.; Knight, E.Q.; Oh, H.W.; Park, B.; Kim, D.G.; Park, H.J. Changes in brain metabolic connectivity underlie autistic-like social deficits in a rat model of autism spectrum disorder. *Sci. Rep.,* **2017**, *7*(1), 13213. http://dx.doi.org/10.1038/s41598-017-13642-3 PMID: 29038507

[98] Wu, H.; Wang, X.; Gao, J.; Liang, S.; Hao, Y.; Sun, C.; Xia, W.; Cao, Y.; Wu, L. Fingolimod (FTY720) attenuates social deficits, learning and memory impairments, neuronal loss and neuroinflammation in the rat model of autism. *Life Sci.,* **2017**, *173*, 43-54. http://dx.doi.org/10.1016/j.lfs.2017.01.012 PMID: 28161158

[99] Al-Amin, M.M.; Rahman, M.M.; Khan, F.R.; Zaman, F.; Mahmud Reza, H. Astaxanthin improves behavioral disorder and oxidative stress in prenatal valproic acid-induced mice model of autism. *Behav. Brain Res.,* **2015**, *286*, 112-121. http://dx.doi.org/10.1016/j.bbr.2015.02.041 PMID: 25732953

[100] Bambini-Junior, V.; Zanatta, G.; Della, F.N.G.; Mueller de Melo, G.; Michels, M.; Fontes-Dutra, M.; Nogueira Freire, V.; Riesgo, R.; Gottfried, C. Resveratrol prevents social deficits in animal model of autism induced by valproic acid. *Neurosci. Lett.,* **2014**, *583*, 176-181. http://dx.doi.org/10.1016/j.neulet.2014.09.039 PMID: 25263788

[101] Campolongo, M.; Kazlauskas, N.; Falasco, G.; Urrutia, L.; Salgueiro, N.; Höcht, C.; Depino, A.M. Sociability deficits after prenatal exposure to valproic acid are rescued by early social enrichment. *Mol. Autism,* **2018**, *9*(1), 36. http://dx.doi.org/10.1186/s13229-018-0221-9 PMID: 29946415

[102] Chau, D.K.F.; Choi, A.Y.T.; Yang, W.; Leung, W.N.; Chan, C.W. Downregulation of glutamatergic and GABAergic proteins in valproric acid associated social impairment during adolescence in mice. *Behav. Brain Res.,* **2017**, *316*, 255-260. http://dx.doi.org/10.1016/j.bbr.2016.09.003 PMID: 27614006

[103] Dai, X.; Yin, Y.; Qin, L. Valproic acid exposure decreases the mRNA stability of Bcl-2 *via* up-regulating miR-34a in the cerebellum of rat. *Neurosci. Lett.,* **2017**, *657*, 159-165. http://dx.doi.org/10.1016/j.neulet.2017.08.018 PMID: 28803955

[104] Eissa, N.; Jayaprakash, P.; Azimullah, S.; Ojha, S.K.; Al-Houqani, M.; Jalal, F.Y.; Łażewska, D.; Kieć-Kononowicz, K.; Sadek, B. The histamine H3R antagonist DL77 attenuates autistic behaviors in a prenatal valproic acid-induced mouse model of autism. *Sci. Rep.,* **2018**, *8*(1), 13077. http://dx.doi.org/10.1038/s41598-018-31385-7 PMID: 30166610

[105] Gao, J.; Wu, H.; Cao, Y.; Liang, S.; Sun, C.; Wang, P.; Wang, J.; Sun, H.; Wu, L. Maternal DHA supplementation protects rat offspring against impairment of learning and memory following prenatal exposure to valproic acid. *J. Nutr. Biochem.,* **2016**, *35*, 87-95. http://dx.doi.org/10.1016/j.jnutbio.2016.07.003 PMID: 27469996

[106] Hirsch, M.M.; Deckmann, I.; Santos-Terra, J.; Staevie, G.Z.; Fontes-Dutra, M.; Carello-Collar, G.; Körbes-Rockenbach, M.; Brum Schwingel, G.; Bauer-Negrini, G.; Rabelo, B.; Gonçalves, M.C.B.; Corrêa-Velloso, J.; Naaldijk, Y.; Castillo, A.R.G.; Schneider, T.; Bambini-Junior, V.; Ulrich, H.; Gottfried, C. Effects of single-dose antipurinergic therapy on behavioral and molecular alterations in the valproic acid-induced animal model of autism. *Neuropharmacology,* **2020**, *167*, 107930. http://dx.doi.org/10.1016/j.neuropharm.2019.107930 PMID: 31904357

[107] Hou, Q.; Wang, Y.; Li, Y.; Chen, D.; Yang, F.; Wang, S. A developmental study of abnormal behaviors and altered gabaergic signaling in the vpa-treated rat model of autism. *Front. Behav. Neurosci.,* **2018**, *12*, 182. http://dx.doi.org/10.3389/fnbeh.2018.00182 PMID: 30186123

[108] Kerr, D.M.; Downey, L.; Conboy, M.; Finn, D.P.; Roche, M. Alterations in the endocannabinoid system in the rat valproic acid model of autism. *Behav. Brain Res.,* **2013**, *249*, 124-132. http://dx.doi.org/10.1016/j.bbr.2013.04.043 PMID: 23643692

[109] Khalaj, R.; Hajizadeh Moghaddam, A.; Zare, M. Hesperetin and it nanocrystals ameliorate social behavior deficits and oxido-inflammatory stress in rat model of autism. *Int. J. Dev. Neurosci.,* **2018**, *69*(1), 80-87. http://dx.doi.org/10.1016/j.ijdevneu.2018.06.009 PMID: 29966739

[110] Kim, J.W.; Seung, H.; Kim, K.C.; Gonzales, E.L.T.; Oh, H.A.; Yang, S.M.; Ko, M.J.; Han, S.H.; Banerjee, S.; Shin, C.Y. Agmatine rescues autistic behaviors in the valproic acid-induced animal model of autism. *Neuropharmacology,* **2017**, *113*(Pt A), 71-81. http://dx.doi.org/10.1016/j.neuropharm.2016.09.014 PMID: 27638451

[111] Matsuo, K.; Yabuki, Y.; Fukunaga, K. 5-aminolevulinic acid inhibits oxidative stress and ameliorates autistic-like behaviors in prenatal valproic acid-exposed rats. *Neuropharmacology,* **2020**, *168*, 107975. http://dx.doi.org/10.1016/j.neuropharm.2020.107975 PMID: 31991146

[112] Qin, L.; Dai, X.; Yin, Y. Valproic acid exposure sequentially activates Wnt and mTOR pathways in rats. *Mol. Cell. Neurosci.,* **2016**, *75*, 27-35. http://dx.doi.org/10.1016/j.mcn.2016.06.004 PMID: 27343825

[113] Rajizadeh, M.A.; Afarinesh, M.R.; Zarif, M.; Mirasadi, A.; Esmaeilpour, K. Does caffeine therapy improve cognitive impair-

ments in valproic acid rat model of autism? *Toxin Rev.,* **2021**, *40*(4), 654-664.
http://dx.doi.org/10.1080/15569543.2019.1680563

[114] Servadio, M.; Melancia, F.; Cartocci, V.; Pallottini, V.; Trezza, V. Role of the endocannabinoid system in the altered social behavior observed in the rat valproic acid model of autism. *Eur. Neuropsychopharmacol.,* **2016**, *26*, S269-S270.
http://dx.doi.org/10.1016/S0924-977X(16)31152-X

[115] Štefánik, P.; Olexová, L.; Kršková, L. Increased sociability and gene expression of oxytocin and its receptor in the brains of rats affected prenatally by valproic acid. *Pharmacol. Biochem. Behav.,* **2015**, *131*, 42-50.
http://dx.doi.org/10.1016/j.pbb.2015.01.021 PMID: 25662821

[116] Wu, H.F.; Chen, P.S.; Chen, Y.J.; Lee, C.W.; Chen, I.T.; Lin, H.C. Alleviation of N-Methyl-d-aspartate receptor-dependent long-term depression *via* regulation of the glycogen synthase kinase-3β pathway in the amygdala of a valproic acid-induced animal model of autism. *Mol. Neurobiol.,* **2017**, *54*(7), 5264-5276.
http://dx.doi.org/10.1007/s12035-016-0074-1 PMID: 27578017

[117] Zamberletti, E.; Gabaglio, M.; Woolley-Roberts, M.; Bingham, S.; Rubino, T.; Parolaro, D. Cannabidivarin treatment ameliorates autism-like behaviors and restores hippocampal endocannabinoid system and glia alterations induced by prenatal valproic acid exposure in rats. *Front. Cell. Neurosci.,* **2019**, *13*, 367.
http://dx.doi.org/10.3389/fncel.2019.00367 PMID: 31447649

[118] Zhang, R.; Zhou, J.; Ren, J.; Sun, S.; Di, Y.; Wang, H.; An, X.; Zhang, K.; Zhang, J.; Qian, Z.; Shi, M.; Qiao, Y.; Ren, W.; Tian, Y. Transcriptional and splicing dysregulation in the prefrontal cortex in valproic acid rat model of autism. *Reprod. Toxicol.,* **2018**, *77*, 53-61.
http://dx.doi.org/10.1016/j.reprotox.2018.01.008 PMID: 29427782

[119] Zhang, Y.; Xiang, Z.; Jia, Y.; He, X.; Wang, L.; Cui, W. The notch signaling pathway inhibitor dapt alleviates autism-like behavior, autophagy and dendritic spine density abnormalities in a valproic acid-induced animal model of autism. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2019**, *94*, 109644.
http://dx.doi.org/10.1016/j.pnpbp.2019.109644 PMID: 31075347

[120] Schiavi, S.; Iezzi, D.; Manduca, A.; Leone, S.; Melancia, F.; Carbone, C.; Petrella, M.; Mannaioni, G.; Masi, A.; Trezza, V. Reward-related behavioral, neurochemical and electrophysiological changes in a rat model of autism based on prenatal exposure to valproic acid. *Front. Cell. Neurosci.,* **2019**, *13*, 479.
http://dx.doi.org/10.3389/fncel.2019.00479 PMID: 31708750

[121] Hajisoltani, R.; Karimi, S.A.; Rahdar, M.; Davoudi, S.; Borjkhani, M.; Hosseinmardi, N.; Behzadi, G.; Janahmadi, M. Hyperexcitability of hippocampal CA1 pyramidal neurons in male offspring of a rat model of autism spectrum disorder (ASD) induced by prenatal exposure to valproic acid: A possible involvement of Ih channel current. *Brain Res.,* **2019**, *1708*, 188-199.
http://dx.doi.org/10.1016/j.brainres.2018.12.011 PMID: 30537517

[122] Kim, K.C.; Lee, D.K.; Go, H.S.; Kim, P.; Choi, C.S.; Kim, J.W.; Jeon, S.J.; Song, M.R.; Shin, C.Y. Pax6-dependent cortical glutamatergic neuronal differentiation regulates autism-like behavior in prenatally valproic acid-exposed rat offspring. *Mol. Neurobiol.,* **2014**, *49*(1), 512-528.
http://dx.doi.org/10.1007/s12035-013-8535-2 PMID: 24030726

[123] Wu, H.F.; Chen, Y.J.; Chu, M.C.; Hsu, Y.T.; Lu, T.Y.; Chen, I.T.; Chen, P.; Lin, H.C. Deep brain stimulation modified autism-like deficits *via* the serotonin system in a valproic acid-induced rat model. *Int. J. Mol. Sci.,* **2018**, *19*(9), 2840.
http://dx.doi.org/10.3390/ijms19092840 PMID: 30235871

[124] Schneider, T.; Turczak, J.; Przewłocki, R. Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: Issues for a therapeutic approach in autism. *Neuropsychopharmacology,* **2006**, *31*(1), 36-46.
http://dx.doi.org/10.1038/sj.npp.1300767 PMID: 15920505

[125] Degroote, S.; Hunting, D.; Sébire, G.; Takser, L. Autistic-like traits in Lewis rats exposed perinatally to a mixture of common endocrine disruptors. *Endocr. Disruptors,* **2014**, *2*(1), e976123.
http://dx.doi.org/10.4161/23273747.2014.976123

[126] Ahn, Y.; Narous, M.; Tobias, R.; Rho, J.M.; Mychasiuk, R. The ketogenic diet modifies social and metabolic alterations identified in the prenatal valproic acid model of autism spectrum disorder. *Dev. Neurosci.,* **2014**, *36*(5), 371-380.
http://dx.doi.org/10.1159/000362645 PMID: 25011527

[127] Codagnone, M.G.; Podestá, M.F.; Uccelli, N.A.; Reinés, A. Differential local connectivity and neuroinflammation profiles in the medial prefrontal cortex and hippocampus in the valproic acid rat model of autism. *Dev. Neurosci.,* **2015**, *37*(3), 215-231.
http://dx.doi.org/10.1159/000375489 PMID: 25895486

[128] Du, L.; Zhao, G.; Duan, Z.; Li, F. Behavioral improvements in a valproic acid rat model of autism following vitamin D supplementation. *Psychiatry Res.,* **2017**, *253*, 28-32.
http://dx.doi.org/10.1016/j.psychres.2017.03.003 PMID: 28324861

[129] Edalatmanesh, M.A.; Nikfarjam, H.; Vafaee, F.; Moghadas, M. Increased hippocampal cell density and enhanced spatial memory in the valproic acid rat model of autism. *Brain Res.,* **2013**, *1526*, 15-25.
http://dx.doi.org/10.1016/j.brainres.2013.06.024 PMID: 23806776

[130] Kataoka, S.; Takuma, K.; Hara, Y.; Maeda, Y.; Ago, Y.; Matsuda, T. Autism-like behaviours with transient histone hyperacetylation in mice treated prenatally with valproic acid. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(1), 91-103.
http://dx.doi.org/10.1017/S1461145711001714 PMID: 22093185

[131] Lin, H.C.; Gean, P.W.; Wang, C.C.; Chan, Y.H.; Chen, P.S. The amygdala excitatory/inhibitory balance in a valproate-induced rat autism model. *PLoS ONE.,* **2013**, *8*(1), e55248.

[132] Markram, K.; Rinaldi, T.; Mendola, D.L.; Sandi, C.; Markram, H. Abnormal fear conditioning and amygdala processing in an animal model of autism. *Neuropsychopharmacology,* **2008**, *33*(4), 901-912.
http://dx.doi.org/10.1038/sj.npp.1301453 PMID: 17507914

[133] Olde Loohuis, N.F.M.; Martens, G.J.M.; van Bokhoven, H.; Kaplan, B.B.; Homberg, J.R.; Aschrafi, A. Altered expression of circadian rhythm and extracellular matrix genes in the medial prefrontal cortex of a valproic acid rat model of autism. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2017**, *77*, 128-132.
http://dx.doi.org/10.1016/j.pnpbp.2017.04.009 PMID: 28408291

[134] Sandhya, T.; Sowjanya, J.; Veeresh, B. *Bacopa monniera* (L.) Wettst ameliorates behavioral alterations and oxidative markers in sodium valproate induced autism in rats. *Neurochem. Res.,* **2012**, *37*(5), 1121-1131.
http://dx.doi.org/10.1007/s11064-012-0717-1 PMID: 22322665

[135] Schneider, T.; Przewłocki, R. Behavioral alterations in rats prenatally exposed to valproic acid: Animal model of autism. *Neuropsychopharmacology,* **2005**, *30*(1), 80-89.
http://dx.doi.org/10.1038/sj.npp.1300518 PMID: 15238991

[136] Wang, C.C.; Lin, H.C.; Chan, Y.H.; Gean, P.W.; Yang, Y.K.; Chen, P.S. 5-HT1A-receptor agonist modified amygdala activity and amygdala-associated social behavior in a valproate-induced rat autism model. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(9), 2027-2039.
http://dx.doi.org/10.1017/S1461145713000473 PMID: 23823694

[137] Yamaguchi, H.; Hara, Y.; Ago, Y.; Takano, E.; Hasebe, S.; Nakazawa, T.; Hashimoto, H.; Matsuda, T.; Takuma, K. Environmental enrichment attenuates behavioral abnormalities in valproic acid-exposed autism model mice. *Behav. Brain Res.,* **2017**, *333*, 67-73.
http://dx.doi.org/10.1016/j.bbr.2017.06.035 PMID: 28655565

[138] Bringas, M.E.; Carvajal-Flores, F.N.; López-Ramírez, T.A.; Atzori, M.; Flores, G. Rearrangement of the dendritic morphology in limbic regions and altered exploratory behavior in a rat model of autism spectrum disorder. *Neuroscience,* **2013**, *241*, 170-187.
http://dx.doi.org/10.1016/j.neuroscience.2013.03.030 PMID: 23535253

[139] Choi, C.S.; Hong, M.; Kim, K.C.; Kim, J.W.; Yang, S.M.; Seung, H.; Ko, M.J.; Choi, D.H.; You, J.S.; Shin, C.Y.; Bahn, G.H. Effects of atomoxetine on hyper-locomotive activity of the prenatally valproate-exposed rat offspring. *Biomol. Ther.,* **2014**, *22*(5), 406-413.
http://dx.doi.org/10.4062/biomolther.2014.027 PMID: 25414770

[140] Olexová, L.; Štefánik, P.; Kršková, L. Increased anxiety-like behaviour and altered GABAergic system in the amygdala and cerebellum of VPA rats — An animal model of autism. *Neurosci. Lett.,* **2016**, *629*, 9-14.
http://dx.doi.org/10.1016/j.neulet.2016.06.035 PMID: 27353514

[141] Zhang, Y.; Cui, W.; Zhai, Q.; Zhang, T.; Wen, X. N-acetylcysteine ameliorates repetitive/stereotypic behavior due to its antioxidant properties without activation of the canonical Wnt pathway in a

valproic acid-induced rat model of autism. *Mol. Med. Rep.,* **2017**, *16*(2), 2233-2240. http://dx.doi.org/10.3892/mmr.2017.6787 PMID: 28627665

[142] Wu, H.F.; Chen, P.S.; Hsu, Y.T.; Lee, C.W.; Wang, T.F.; Chen, Y.J.; Lin, H.C. D-cycloserine ameliorates autism-like deficits by removing glua2-containing AMPA receptors in a valproic acid-induced rat model. *Mol. Neurobiol.,* **2018**, *55*(6), 4811-4824. http://dx.doi.org/10.1007/s12035-017-0685-1 PMID: 28733898

[143] Al Sagheer, T.; Haida, O.; Balbous, A.; Francheteau, M.; Matas, E.; Fernagut, P.O.; Jaber, M. Motor impairments correlate with social deficits and restricted neuronal loss in an environmental model of autism. *Int. J. Neuropsychopharmacol.,* **2018**, *21*(9), 871-882. http://dx.doi.org/10.1093/ijnp/pyy043 PMID: 29762671

[144] Kerr, DM; Gilmartin, A; Roche, M Pharmacological inhibition of fatty acid amide hydrolase attenuates social behavioural deficits in male rats prenatally exposed to valproic acid. *Pharmacol. Res.,* **2016**, *113*(Pt A), 228-235. http://dx.doi.org/10.1016/j.phrs.2016.08.033

[145] Bambini-Junior, V.; Rodrigues, L.; Behr, G.A.; Moreira, J.C.F.; Riesgo, R.; Gottfried, C. Animal model of autism induced by prenatal exposure to valproate: Behavioral changes and liver parameters. *Brain Res.,* **2011**, *1408*, 8-16. http://dx.doi.org/10.1016/j.brainres.2011.06.015 PMID: 21767826

[146] Gobshtis, N.; Tfilin, M.; Wolfson, M.; Fraifeld, V.E.; Turgeman, G. Transplantation of mesenchymal stem cells reverses behavioural deficits and impaired neurogenesis caused by prenatal exposure to valproic acid. *Oncotarget,* **2017**, *8*(11), 17443-17452. http://dx.doi.org/10.18632/oncotarget.15245 PMID: 28407680

[147] Guo, Q.; Yin, X.; Qiao, M.; Jia, Y.; Chen, D.; Shao, J.; Lebaron, T.W.; Gao, Y.; Shi, H.; Jia, B. Hydrogen-rich water ameliorates autistic-like behavioral abnormalities in valproic acid-treated adolescent mice offspring. *Front. Behav. Neurosci.,* **2018**, *12*, 170. http://dx.doi.org/10.3389/fnbeh.2018.00170 PMID: 30127728

[148] Huang, F.; Chen, X.; Jiang, X.; Niu, J.; Cui, C.; Chen, Z.; Sun, J. Betaine ameliorates prenatal valproic-acid-induced autism-like behavioral abnormalities in mice by promoting homocysteine metabolism. *Psychiatry Clin. Neurosci.,* **2019**, *73*(6), 317-322. http://dx.doi.org/10.1111/pcn.12833 PMID: 30821067

[149] Kazlauskas, N.; Seiffe, A.; Campolongo, M.; Zappala, C.; Depino, A.M. Sex-specific effects of prenatal valproic acid exposure on sociability and neuroinflammation: Relevance for susceptibility and resilience in autism. *Psychoneuroendocrinology,* **2019**, *110*, 104441. http://dx.doi.org/10.1016/j.psyneuen.2019.104441 PMID: 31541913

[150] Kumar, H.; Sharma, B. Memantine ameliorates autistic behavior, biochemistry & blood brain barrier impairments in rats. *Brain Res. Bull.,* **2016**, *124*, 27-39. http://dx.doi.org/10.1016/j.brainresbull.2016.03.013 PMID: 27034117

[151] Kumar, H.; Sharma, B. Minocycline ameliorates prenatal valproic acid induced autistic behaviour, biochemistry and blood brain barrier impairments in rats. *Brain Res.,* **2016**, *1630*, 83-97. http://dx.doi.org/10.1016/j.brainres.2015.10.052 PMID: 26551768

[152] Kumar, H.; Sharma, B.M.; Sharma, B. Benefits of agomelatine in behavioral, neurochemical and blood brain barrier alterations in prenatal valproic acid induced autism spectrum disorder. *Neurochem. Int.,* **2015**, *91*, 34-45. http://dx.doi.org/10.1016/j.neuint.2015.10.007 PMID: 26498253

[153] Lim, J.S.; Lim, M.Y.; Choi, Y.; Ko, G. Modeling environmental risk factors of autism in mice induces IBD-related gut microbial dysbiosis and hyperserotonemia. *Mol. Brain,* **2017**, *10*(1), 14. http://dx.doi.org/10.1186/s13041-017-0292-0 PMID: 28427452

[154] Lucchina, L.; Depino, A.M. Altered peripheral and central inflammatory responses in a mouse model of autism. *Autism Res.,* **2014**, *7*(2), 273-289. http://dx.doi.org/10.1002/aur.1338 PMID: 24124122

[155] Mirza, R.; Sharma, B. Beneficial effects of pioglitazone, a selective peroxisome proliferator-activated receptor-γ agonist in prenatal valproic acid-induced behavioral and biochemical autistic like features in Wistar rats. *Int. J. Dev. Neurosci.,* **2019**, *76*(1), 6-16. http://dx.doi.org/10.1016/j.ijdevneu.2019.05.006 PMID: 31128204

[156] Mirza, R.; Sharma, B. Benefits of Fenofibrate in prenatal valproic acid-induced autism spectrum disorder related phenotype in rats. *Brain Res. Bull.,* **2019**, *147*, 36-46. http://dx.doi.org/10.1016/j.brainresbull.2019.02.003 PMID: 30769127

[157] Mohammadi, S.; Asadi-Shekaari, M.; Basiri, M.; Parvan, M.; Shabani, M.; Nozari, M. Improvement of autistic-like behaviors in adult rats prenatally exposed to valproic acid through early suppression of NMDA receptor function. *Psychopharmacology.,* **2020**, *237*(1), 199-208. http://dx.doi.org/10.1007/s00213-019-05357-2 PMID: 31595334

[158] Wang, Y.; Zhao, S.; Liu, X.; Zheng, Y.; Li, L.; Meng, S. Oxytocin improves animal behaviors and ameliorates oxidative stress and inflammation in autistic mice. *Biomed. Pharmacother.,* **2018**, *107*, 262-269. http://dx.doi.org/10.1016/j.biopha.2018.07.148 PMID: 30098544

[159] Wang, J.; Feng, S.; Li, M.; Liu, Y.; Yan, J.; Tang, Y.; Du, D.; Chen, F. Increased expression of Kv10.2 in the hippocampus attenuates valproic acid-induced autism-like behaviors in rats. *Neurochem. Res.,* **2019**, *44*(12), 2796-2808. http://dx.doi.org/10.1007/s11064-019-02903-4 PMID: 31728858

[160] Tian, Y.; Yabuki, Y.; Moriguchi, S.; Fukunaga, K.; Mao, P.J.; Hong, L.J.; Lu, Y.M.; Wang, R.; Ahmed, M.M.; Liao, M.H.; Huang, J.Y.; Zhang, R.T.; Zhou, T.Y.; Long, S.; Han, F. Melatonin reverses the decreases in hippocampal protein serine/threonine kinases observed in an animal model of autism. *J. Pineal Res.,* **2014**, *56*(1), 1-11. http://dx.doi.org/10.1111/jpi.12081 PMID: 23952810

[161] Hirsch, M.M.; Deckmann, I.; Fontes-Dutra, M.; Bauer-Negrini, G.; Nunes, G.D.F.; Nunes, W.; Rabelo, B.; Riesgo, R.; Margis, R.; Bambini-Junior, V.; Gottfried, C. Data on social transmission of food preference in a model of autism induced by valproic acid and translational analysis of circulating microRNA. *Data Brief,* **2018**, *18*, 1433-1440. http://dx.doi.org/10.1016/j.dib.2018.04.047 PMID: 29904648

[162] Hara, Y.; Ago, Y.; Taruta, A.; Hasebe, S.; Kawase, H.; Tanabe, W.; Tsukada, S.; Nakazawa, T.; Hashimoto, H.; Matsuda, T.; Takuma, K. Risperidone and aripiprazole alleviate prenatal valproic acid-induced abnormalities in behaviors and dendritic spine density in mice. *Psychopharmacology.,* **2017**, *234*(21), 3217-3228. http://dx.doi.org/10.1007/s00213-017-4703-9 PMID: 28798977

[163] Cuevas-Olguin, R.; Roychowdhury, S.; Banerjee, A.; Garcia-Oscos, F.; Esquivel-Rendon, E.; Bringas, M.E.; Kilgard, M.P.; Flores, G.; Atzori, M. Cerebrolysin prevents deficits in social behavior, repetitive conduct, and synaptic inhibition in a rat model of autism. *J. Neurosci. Res.,* **2017**, *95*(12), 2456-2468. http://dx.doi.org/10.1002/jnr.24072 PMID: 28609577

[164] Hara, Y.; Ago, Y.; Higuchi, M.; Hasebe, S.; Nakazawa, T.; Hashimoto, H.; Matsuda, T.; Takuma, K. Oxytocin attenuates deficits in social interaction but not recognition memory in a prenatal valproic acid-induced mouse model of autism. *Horm. Behav.,* **2017**, *96*, 130-136. http://dx.doi.org/10.1016/j.yhbeh.2017.09.013 PMID: 28942000

[165] Hara, Y.; Ago, Y.; Taruta, A.; Katashiba, K.; Hasebe, S.; Takano, E.; Onaka, Y.; Hashimoto, H.; Matsuda, T.; Takuma, K. Improvement by methylphenidate and atomoxetine of social interaction deficits and recognition memory impairment in a mouse model of valproic acid-induced autism. *Autism Res.,* **2016**, *9*(9), 926-939. http://dx.doi.org/10.1002/aur.1596 PMID: 26714434

[166] Kawase, H.; Ago, Y.; Naito, M.; Higuchi, M.; Hara, Y.; Hasebe, S.; Tsukada, S.; Kasai, A.; Nakazawa, T.; Mishina, T.; Kouji, H.; Takuma, K.; Hashimoto, H. mS-11, a mimetic of the mSin3-binding helix in NRSF, ameliorates social interaction deficits in a prenatal valproic acid-induced autism mouse model. *Pharmacol. Biochem. Behav.,* **2019**, *176*, 1-5. http://dx.doi.org/10.1016/j.pbb.2018.11.003 PMID: 30419271

[167] Kotajima-Murakami, H.; Kobayashi, T.; Kashii, H.; Sato, A.; Hagino, Y.; Tanaka, M.; Nishito, Y.; Takamatsu, Y.; Uchino, S.; Ikeda, K. Effects of rapamycin on social interaction deficits and gene expression in mice exposed to valproic acid in utero. *Mol. Brain,* **2019**, *12*(1), 3. http://dx.doi.org/10.1186/s13041-018-0423-2 PMID: 30621732

[168] Matsuo, K.; Yabuki, Y.; Fukunaga, K. 493. Improvement of social interaction and cognition by oxytocin for autism-like behaviors in

valproic acid-exposed rats. *Biol. Psychiatry,* **2017**, *81*(10), S200-S201.
http://dx.doi.org/10.1016/j.biopsych.2017.02.1101

[169] Olde Loohuis, N.F.M.; Kole, K.; Glennon, J.C.; Karel, P.; Van der Borg, G.; Van Gemert, Y.; Van den Bosch, D.; Meinhardt, J.; Kos, A.; Shahabipour, F.; Tiesinga, P.; van Bokhoven, H.; Martens, G.J.M.; Kaplan, B.B.; Homberg, J.R.; Aschrafi, A. Elevated microRNA-181c and microRNA-30d levels in the enlarged amygdala of the valproic acid rat model of autism. *Neurobiol. Dis.,* **2015**, *80*, 42-53.
http://dx.doi.org/10.1016/j.nbd.2015.05.006 PMID: 25986729

[170] Wang, X.; Tao, J.; Qiao, Y.; Luo, S.; Zhao, Z.; Gao, Y.; Guo, J.; Kong, J.; Chen, C.; Ge, L.; Zhang, B.; Guo, P.; Liu, L.; Song, Y. Gastrodin rescues autistic-like phenotypes in valproic acid-induced animal model. *Front. Neurol.,* **2018**, *9*, 1052.
http://dx.doi.org/10.3389/fneur.2018.01052 PMID: 30581411

[171] Zhang, Y.; Yang, C.; Yuan, G.; Wang, Z.; Cui, W.; Li, R. Sulindac attenuates valproic acid-induced oxidative stress levels in primary cultured cortical neurons and ameliorates repetitive/stereotypic-like movement disorders in Wistar rats prenatally exposed to valproic acid. *Int. J. Mol. Med.,* **2015**, *35*(1), 263-270.
http://dx.doi.org/10.3892/ijmm.2014.1996 PMID: 25384498

[172] Eissa, N.; Azimullah, S.; Jayaprakash, P.; Jayaraj, R.L.; Reiner, D.; Ojha, S.K.; Beiram, R.; Stark, H.; Łażewska, D.; Kieć-Kononowicz, K.; Sadek, B. The dual-active histamine H3 receptor antagonist and acetylcholine esterase inhibitor E100 ameliorates stereotyped repetitive behavior and neuroinflammmation in sodium valproate induced autism in mice. *Chem. Biol. Interact.,* **2019**, *312*, 108775.
http://dx.doi.org/10.1016/j.cbi.2019.108775 PMID: 31369746

[173] Hara, Y.; Takuma, K.; Takano, E.; Katashiba, K.; Taruta, A.; Higashino, K.; Hashimoto, H.; Ago, Y.; Matsuda, T. Reduced prefrontal dopaminergic activity in valproic acid-treated mouse autism model. *Behav. Brain Res.,* **2015**, *289*, 39-47.
http://dx.doi.org/10.1016/j.bbr.2015.04.022 PMID: 25907743

[174] Zhang, Y.; Sun, Y.; Wang, F.; Wang, Z.; Peng, Y.; Li, R. Down-regulating the canonical Wnt/β-catenin signaling pathway attenuates the susceptibility to autism-like phenotypes by decreasing oxidative stress. *Neurochem. Res.,* **2012**, *37*(7), 1409-1419.
http://dx.doi.org/10.1007/s11064-012-0724-2 PMID: 22374471

[175] Anshu, K.; Nair, A.K.; Kumaresan, U.D.; Kutty, B.M.; Srinath, S.; Laxmi, T.R. Altered attentional processing in male and female rats in a prenatal valproic acid exposure model of autism spectrum disorder. *Autism Res.,* **2017**, *10*(12), 1929-1944.
http://dx.doi.org/10.1002/aur.1852 PMID: 28851114

[176] Favre, M.Ã´.R.; La Mendola, D.; Meystre, J.; Christodoulou, D.; Cochrane, M.J.; Markram, H.; Markram, K. Predictable enriched environment prevents development of hyper-emotionality in the VPA rat model of autism. *Front. Neurosci.,* **2015**, *9*(MAR), 127.
http://dx.doi.org/10.3389/fnins.2015.00127 PMID: 26089770

[177] Foley, A.G.; Gannon, S.; Rombach-Mullan, N.; Prendergast, A.; Barry, C.; Cassidy, A.W.; Regan, C.M. Class I histone deacetylase inhibition ameliorates social cognition and cell adhesion molecule plasticity deficits in a rodent model of autism spectrum disorder. *Neuropharmacology,* **2012**, *63*(4), 750-760.
http://dx.doi.org/10.1016/j.neuropharm.2012.05.042 PMID: 22683514

[178] Foley, A.G.; Cassidy, A.W.; Regan, C.M. Pentyl-4-yn-VPA, a histone deacetylase inhibitor, ameliorates deficits in social behavior and cognition in a rodent model of autism spectrum disorders. *Eur. J. Pharmacol.,* **2014**, *727*(1), 80-86.
http://dx.doi.org/10.1016/j.ejphar.2014.01.050 PMID: 24486700

[179] Win-Shwe, T.T.; Nway, N.C.; Imai, M.; Lwin, T.T.; Mar, O.; Watanabe, H. Social behavior, neuroimmune markers and glutamic acid decarboxylase levels in a rat model of valproic acid-induced autism. *J. Toxicol. Sci.,* **2018**, *43*(11), 631-643.
http://dx.doi.org/10.2131/jts.43.631 PMID: 30404997

[180] Schneider, T.; Roman, A.; Basta-Kaim, A.; Kubera, M.; Budziszewska, B.; Schneider, K.; Przewłocki, R. Gender-specific behavioral and immunological alterations in an animal model of autism induced by prenatal exposure to valproic acid. *Psychoneuroendocrinology,* **2008**, *33*(6), 728-740.
http://dx.doi.org/10.1016/j.psyneuen.2008.02.011 PMID: 18396377

[181] Banerjee, A.; Engineer, C.T.; Sauls, B.L.; Morales, A.A.; Kilgard, M.P.; Ploski, J.E. Abnormal emotional learning in a rat model of autism exposed to valproic acid in utero. *Front. Behav. Neurosci.,* **2014**, *8*(387), 387.
http://dx.doi.org/10.3389/fnbeh.2014.00387 PMID: 25429264

[182] Kumaravel, P.; Melchias, G.; Vasanth, N.; Manivasagam, T. Epigallocatechin gallate attenuates behavioral defects in sodium valproate induced autism rat model. *Res. J. Pharm. Technol.,* **2017**, *10*(5), 1477.
http://dx.doi.org/10.5958/0974-360X.2017.00260.8

[183] Song, T.J.; Lan, X.Y.; Wei, M.P.; Zhai, F.J.; Boeckers, T.M.; Wang, J.N.; Yuan, S.; Jin, M.Y.; Xie, Y.F.; Dang, W.W.; Zhang, C.; Schön, M.; Song, P.W.; Qiu, M.H.; Song, Y.Y.; Han, S.P.; Han, J.S.; Zhang, R. Altered behaviors and impaired synaptic function in a novel rat model with a complete *shank3* deletion. *Front. Cell. Neurosci.,* **2019**, *13*, 111.
http://dx.doi.org/10.3389/fncel.2019.00111 PMID: 30971895

[184] Watanabe, S.; Kurotani, T.; Oga, T.; Noguchi, J.; Isoda, R.; Nakagami, A.; Sakai, K.; Nakagaki, K.; Sumida, K.; Hoshino, K.; Saito, K.; Miyawaki, I.; Sekiguchi, M.; Wada, K.; Minamimoto, T.; Ichinohe, N. Functional and molecular characterization of a non-human primate model of autism spectrum disorder shows similarity with the human disease. *Nat. Commun.,* **2021**, *12*(1), 5388.
http://dx.doi.org/10.1038/s41467-021-25487-6 PMID: 34526497

[185] Zhao, H.; Wang, Q.; Yan, T.; Zhang, Y.; Xu, H.; Yu, H.; Tu, Z.; Guo, X.; Jiang, Y.; Li, X.; Zhou, H.; Zhang, Y.Q. Maternal valproic acid exposure leads to neurogenesis defects and autism-like behaviors in non-human primates. *Transl. Psychiatry,* **2019**, *9*(1), 267.
http://dx.doi.org/10.1038/s41398-019-0608-1 PMID: 31636273

[186] Yasue, M.; Nakagami, A.; Banno, T.; Nakagaki, K.; Ichinohe, N.; Kawai, N. Indifference of marmosets with prenatal valproate exposure to third-party non-reciprocal interactions with otherwise avoided non-reciprocal individuals. *Behav. Brain Res.,* **2015**, *292*, 323-326.
http://dx.doi.org/10.1016/j.bbr.2015.06.006 PMID: 26133500

[187] Sgadò, P.; Rosa-Salva, O.; Versace, E.; Vallortigara, G. Embryonic exposure to valproic acid impairs social predispositions of newly-hatched chicks. *Sci. Rep.,* **2018**, *8*(1), 5919.
http://dx.doi.org/10.1038/s41598-018-24202-8 PMID: 29650996

[188] Lorenzi, E.; Pross, A.; Rosa-Salva, O.; Versace, E.; Sgadò, P.; Vallortigara, G. Embryonic exposure to valproic acid affects social predispositions for dynamic cues of animate motion in newly-hatched chicks. *Front. Physiol.,* **2019**, *10*, 501.
http://dx.doi.org/10.3389/fphys.2019.00501 PMID: 31114510

[189] Adiletta, A.; Pedrana, S.; Rosa-Salva, O.; Sgadò, P. Spontaneous visual preference for face-like stimuli is impaired in newly-hatched domestic chicks exposed to valproic acid during embryogenesis. *Front. Behav. Neurosci.,* **2021**, *15*, 733140.
http://dx.doi.org/10.3389/fnbeh.2021.733140 PMID: 34858146

[190] Matsushima, T; Miura, M; Patzke, N; Toji, N; Wada, K; Ogura, Y Fetal blockade of nicotinic acetylcholine transmission causes autism-like impairment of biological motion preference in the neonatal chick. *Cereb Cortex,* **2022**, tgac041.
http://dx.doi.org/10.1093/texcom/tgac041

[191] Nishigori, H.; Kagami, K.; Takahashi, A.; Tezuka, Y.; Sanbe, A.; Nishigori, H. Impaired social behavior in chicks exposed to sodium valproate during the last week of embryogenesis. *Psychopharmacology.,* **2013**, *227*(3), 393-402.
http://dx.doi.org/10.1007/s00213-013-2979-y PMID: 23371491

[192] Zachar, G.; Tóth, A.S.; Gerecsei, L.I.; Zsebők, S.; Ádám, Á.; Csillag, A. Valproate exposure *in ovo* attenuates the acquisition of social preferences of young post-hatch domestic chicks. *Front. Physiol.,* **2019**, *10*, 881.
http://dx.doi.org/10.3389/fphys.2019.00881 PMID: 31379596

[193] Chen, J.; Lei, L.; Tian, L.; Hou, F.; Roper, C.; Ge, X.; Zhao, Y.; Chen, Y.; Dong, Q.; Tanguay, R.L.; Huang, C. Developmental and behavioral alterations in zebrafish embryonically exposed to valproic acid (VPA): An aquatic model for autism. *Neurotoxicol. Teratol.,* **2018**, *66*, 8-16.
http://dx.doi.org/10.1016/j.ntt.2018.01.002 PMID: 29309833

[194] Dwivedi, S.; Medishetti, R.; Rani, R.; Sevilimedu, A.; Kulkarni, P.; Yogeeswari, P. Larval zebrafish model for studying the effects of

valproic acid on neurodevelopment: An approach towards modeling autism. *J. Pharmacol. Toxicol. Methods,* **2019**, *95*, 56-65. http://dx.doi.org/10.1016/j.vascn.2018.11.006 PMID: 30500431

[195] Zimmermann, F.F.; Gaspary, K.V.; Leite, C.E.; De Paula, C.G.; Bonan, C.D. Embryological exposure to valproic acid induces social interaction deficits in zebrafish (*Danio rerio*): A developmental behavior analysis. *Neurotoxicol. Teratol.,* **2015**, *52*(Pt A), 36-41. http://dx.doi.org/10.1016/j.ntt.2015.10.002 PMID: 26477937

[196] Baronio, D.; Puttonen, H.A.J.; Sundvik, M.; Semenova, S.; Lehtonen, E.; Panula, P. Embryonic exposure to valproic acid affects the histaminergic system and the social behaviour of adult zebrafish (*Danio rerio*). *Br. J. Pharmacol.,* **2018**, *175*(5), 797-809. http://dx.doi.org/10.1111/bph.14124 PMID: 29235100

[197] Bell, M.R. Comparing postnatal development of gonadal hormones and associated social behaviors in rats, mice, and humans. *Endocrinology,* **2018**, *159*(7), 2596-2613. http://dx.doi.org/10.1210/en.2018-00220 PMID: 29767714

[198] Carter, M. Animal behavior. In: *Guide to Research Techniques in Neuroscience*; Elsevier, **2015**; pp. 39-71. http://dx.doi.org/10.1016/B978-0-12-800511-8.00002-2

[199] Rudie, J.D.; Brown, J.A.; Beck-Pancer, D.; Hernandez, L.M.; Dennis, E.L.; Thompson, P.M.; Bookheimer, S.Y.; Dapretto, M. Altered functional and structural brain network organization in autism. *Neuroimage Clin.,* **2013**, *2*, 79-94. http://dx.doi.org/10.1016/j.nicl.2012.11.006 PMID: 24179761

[200] Zhao, Y.; Chen, H.; Li, Y.; Lv, J.; Jiang, X.; Ge, F.; Zhang, T.; Zhang, S.; Ge, B.; Lyu, C.; Zhao, S.; Han, J.; Guo, L.; Liu, T. Connectome-scale group-wise consistent resting-state network analysis in autism spectrum disorder. *Neuroimage Clin.,* **2016**, *12*, 23-33. http://dx.doi.org/10.1016/j.nicl.2016.06.004 PMID: 27358766

[201] Guo, X.; Duan, X.; Chen, H.; He, C.; Xiao, J.; Han, S.; Fan, Y.S.; Guo, J.; Chen, H. Altered inter- and intrahemispheric functional connectivity dynamics in autistic children. *Hum. Brain Mapp.,* **2020**, *41*(2), 419-428. http://dx.doi.org/10.1002/hbm.24812 PMID: 31600014

[202] Uzunova, G.; Pallanti, S.; Hollander, E. Excitatory/inhibitory imbalance in autism spectrum disorders: Implications for interventions and therapeutics. *World J. Biol. Psychiatry,* **2016**, *17*(3), 174-186. http://dx.doi.org/10.3109/15622975.2015.1085597 PMID: 26469219

[203] Hampson, D.R.; Blatt, G.J. Autism spectrum disorders and neuropathology of the cerebellum. *Front. Neurosci.,* **2015**, *9*, 420. http://dx.doi.org/10.3389/fnins.2015.00420 PMID: 26594141

[204] D'Mello, A.M.; Crocetti, D.; Mostofsky, S.H.; Stoodley, C.J. Cerebellar gray matter and lobular volumes correlate with core autism symptoms. *Neuroimage Clin.,* **2015**, *7*, 631-639. http://dx.doi.org/10.1016/j.nicl.2015.02.007 PMID: 25844317

[205] Hanaie, R.; Mohri, I.; Kagitani-Shimono, K.; Tachibana, M.; Azuma, J.; Matsuzaki, J.; Watanabe, Y.; Fujita, N.; Taniike, M. Altered microstructural connectivity of the superior cerebellar peduncle is related to motor dysfunction in children with autistic spectrum disorders. *Cerebellum,* **2013**, *12*(5), 645-656. http://dx.doi.org/10.1007/s12311-013-0475-x PMID: 23564050

[206] Bauman, M.L.; Kemper, T.L. Neuroanatomic observations of the brain in autism: A review and future directions. *Int. J. Dev. Neurosci.,* **2005**, *23*(2-3), 183-187. http://dx.doi.org/10.1016/j.ijdevneu.2004.09.006 PMID: 15749244

[207] Pang, Y.; Fan, L-W. Dysregulation of neurogenesis by neuroinflammation: key differences in neurodevelopmental and neurological disorders. *Neural Regen. Res.,* **2017**, *12*(3), 366-371. http://dx.doi.org/10.4103/1673-5374.202926 PMID: 28469641

[208] Subramanian, M.; Timmerman, C.K.; Schwartz, J.L.; Pham, D.L.; Meffert, M.K. Characterizing autism spectrum disorders by key biochemical pathways. *Front. Neurosci.,* **2015**, *9*, 313. http://dx.doi.org/10.3389/fnins.2015.00313 PMID: 26483618

[209] Chen, O.; Tahmazian, I.; Ferrara, H.J.; Hu, B.; Chomiak, T. The early overgrowth theory of autism spectrum disorder: Insight into convergent mechanisms from valproic acid exposure and translational models. In: *Progress in Molecular Biology and Translational Science*; Elsevier, **2020**; pp. 275-300.

[210] Libero, L.E.; DeRamus, T.P.; Lahti, A.C.; Deshpande, G.; Kana, R.K. Multimodal neuroimaging based classification of autism spectrum disorder using anatomical, neurochemical, and white matter correlates. *Cortex,* **2015**, *66*, 46-59. http://dx.doi.org/10.1016/j.cortex.2015.02.008 PMID: 25797658

[211] Mraz, K.D.; Green, J.; Dumont-Mathieu, T.; Makin, S.; Fein, D. Correlates of head circumference growth in infants later diagnosed with autism spectrum disorders. *J. Child Neurol.,* **2007**, *22*(6), 700-713. http://dx.doi.org/10.1177/0883073807304005 PMID: 17641255

[212] Lainhart, J.; Piven, J.; Wzorek, M.; Landa, R.; Santangelo, S.L.; Coon, H.; Folstein, S. Macrocephaly in children and adults with autism. *J. Am. Acad. Child Adolesc. Psychiatry,* **1997**, *36*(2), 282-290. http://dx.doi.org/10.1097/00004583-199702000-00019 PMID: 9031582

[213] Sacco, R.; Gabriele, S.; Persico, A.M. Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis. *Psychiatry Res. Neuroimaging,* **2015**, *234*(2), 239-251. http://dx.doi.org/10.1016/j.pscychresns.2015.08.016 PMID: 26456415

[214] Nordahl, C.W.; Braunschweig, D.; Iosif, A.M.; Lee, A.; Rogers, S.; Ashwood, P.; Amaral, D.G.; Van de Water, J. Maternal autoantibodies are associated with abnormal brain enlargement in a subgroup of children with autism spectrum disorder. *Brain Behav. Immun.,* **2013**, *30*, 61-65. http://dx.doi.org/10.1016/j.bbi.2013.01.084 PMID: 23395715

[215] Surén, P.; Stoltenberg, C.; Bresnahan, M.; Hirtz, D.; Lie, K.K.; Lipkin, W.I.; Magnus, P.; Reichborn-Kjennerud, T.; Schjølberg, S.; Susser, E.; Øyen, A.S.; Li, L.; Hornig, M. Early growth patterns in children with autism. *Epidemiology,* **2013**, *24*(5), 660-670. http://dx.doi.org/10.1097/EDE.0b013e31829e1d45 PMID: 23867813

[216] Lainhart, J.E.; Bigler, E.D.; Bocian, M.; Coon, H.; Dinh, E.; Dawson, G.; Deutsch, C.K.; Dunn, M.; Estes, A.; Tager-Flusberg, H.; Folstein, S.; Hepburn, S.; Hyman, S.; McMahon, W.; Minshew, N.; Munson, J.; Osann, K.; Ozonoff, S.; Rodier, P.; Rogers, S.; Sigman, M.; Spence, M.A.; Stodgell, C.J.; Volkmar, F. Head circumference and height in autism: A study by the collaborative program of excellence in autism. *Am. J. Med. Genet. A.,* **2006**, *140A*(21), 2257-2274. http://dx.doi.org/10.1002/ajmg.a.31465 PMID: 17022081

[217] Courchesne, E.; Mouton, P.R.; Calhoun, M.E.; Semendeferi, K.; Ahrens-Barbeau, C.; Hallet, M.J.; Barnes, C.C.; Pierce, K. Neuron number and size in prefrontal cortex of children with autism. *JAMA,* **2011**, *306*(18), 2001-2010. http://dx.doi.org/10.1001/jama.2011.1638 PMID: 22068992

[218] Marchetto, M.C.; Belinson, H.; Tian, Y.; Freitas, B.C.; Fu, C.; Vadodaria, K.C.; Beltrao-Braga, P.C.; Trujillo, C.A.; Mendes, A.P.D.; Padmanabhan, K.; Nunez, Y.; Ou, J.; Ghosh, H.; Wright, R.; Brennand, K.J.; Pierce, K.; Eichenfield, L.; Pramparo, T.; Eyler, L.T.; Barnes, C.C.; Courchesne, E.; Geschwind, D.H.; Gage, F.H.; Wynshaw-Boris, A.; Muotri, A.R. Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. *Mol. Psychiatry,* **2017**, *22*(6), 820-835. http://dx.doi.org/10.1038/mp.2016.95 PMID: 27378147

[219] Hutsler, J.J.; Love, T.; Zhang, H. Histological and magnetic resonance imaging assessment of cortical layering and thickness in autism spectrum disorders. *Biol. Psychiatry,* **2007**, *61*(4), 449-457. http://dx.doi.org/10.1016/j.biopsych.2006.01.015 PMID: 16580643

[220] Wegiel, J.; Kuchna, I.; Nowicki, K.; Imaki, H.; Wegiel, J.; Marchi, E.; Ma, S.Y.; Chauhan, A.; Chauhan, V.; Bobrowicz, T.W.; de Leon, M.; Louis, L.A.S.; Cohen, I.L.; London, E.; Brown, W.T.; Wisniewski, T. The neuropathology of autism: Defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol.,* **2010**, *119*(6), 755-770. http://dx.doi.org/10.1007/s00401-010-0655-4 PMID: 20198484

[221] Hsieh, J.; Nakashima, K.; Kuwabara, T.; Mejia, E.; Gage, F.H. Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells. *Proc. Natl. Acad. Sci.,* **2004**, *101*(47), 16659-16664. http://dx.doi.org/10.1073/pnas.0407643101 PMID: 15537713

[222] Go, H.S.; Kim, K.C.; Choi, C.S.; Jeon, S.J.; Kwon, K.J.; Han, S.H.; Lee, J.; Cheong, J.H.; Ryu, J.H.; Kim, C.H.; Ko, K.H.; Shin, C.Y. Prenatal exposure to valproic acid increases the neural progenitor

cell pool and induces macrocephaly in rat brain *via* a mechanism involving the GSK-3β/β-catenin pathway. *Neuropharmacology,* **2012**, *63*(6), 1028-1041. http://dx.doi.org/10.1016/j.neuropharm.2012.07.028 PMID: 22841957

[223] Bicker, F.; Nardi, L.; Maier, J.; Vasic, V.; Schmeisser, M.J. Criss-crossing autism spectrum disorder and adult neurogenesis. *J. Neurochem.,* **2021**, *159*(3), 452-478. http://dx.doi.org/10.1111/jnc.15501 PMID: 34478569

[224] Gilbert, J.; Man, H.Y. Fundamental elements in autism: From neurogenesis and neurite growth to synaptic plasticity. *Front. Cell. Neurosci.,* **2017**, *11*, 359. http://dx.doi.org/10.3389/fncel.2017.00359 PMID: 29209173

[225] Watanabe, Y.; Murakami, T.; Kawashima, M.; Hasegawa-Baba, Y.; Mizukami, S.; Imatanaka, N.; Akahori, Y.; Yoshida, T.; Shibutani, M. Maternal exposure to valproic acid primarily targets interneurons followed by late effects on neurogenesis in the hippocampal dentate gyrus in rat offspring. *Neurotox. Res.,* **2017**, *31*(1), 46-62. http://dx.doi.org/10.1007/s12640-016-9660-2 PMID: 27566479

[226] Ingram, J.L.; Peckham, S.M.; Tisdale, B.; Rodier, P.M. Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. *Neurotoxicol. Teratol.,* **2000**, *22*(3), 319-324. http://dx.doi.org/10.1016/S0892-0362(99)00083-5 PMID: 10840175

[227] Mowery, T.M.; Wilson, S.M.; Kostylev, P.V.; Dina, B.; Buchholz, J.B.; Prieto, A.L.; Garraghty, P.E. Embryological exposure to valproic acid disrupts morphology of the deep cerebellar nuclei in a sexually dimorphic way. *Int. J. Dev. Neurosci.,* **2015**, *40*(1), 15-23. http://dx.doi.org/10.1016/j.ijdevneu.2014.10.003 PMID: 25447790

[228] Wang, R.; Tan, J.; Guo, J.; Zheng, Y.; Han, Q.; So, K.F.; Yu, J.; Zhang, L. Aberrant development and synaptic transmission of cerebellar cortex in a VPA induced mouse autism model. *Front. Cell. Neurosci.,* **2018**, *12*, 500. http://dx.doi.org/10.3389/fncel.2018.00500 PMID: 30622458

[229] Gogolla, N.; LeBlanc, J.J.; Quast, K.B.; Südhof, T.C.; Fagiolini, M.; Hensch, T.K. Common circuit defect of excitatory-inhibitory balance in mouse models of autism. *J. Neurodev. Disord.,* **2009**, *1*(2), 172-181. http://dx.doi.org/10.1007/s11689-009-9023-x PMID: 20664807

[230] Hara, Y.; Maeda, Y.; Kataoka, S.; Ago, Y.; Takuma, K.; Matsuda, T. Effect of prenatal valproic acid exposure on cortical morphology in female mice. *J. Pharmacol. Sci.,* **2012**, *118*(4), 543-546. http://dx.doi.org/10.1254/jphs.12025SC PMID: 22447305

[231] Fujimura, K.; Mitsuhashi, T.; Shibata, S.; Shimozato, S.; Takahashi, T. *In utero* exposure to valproic acid induces neocortical dysgenesis *via* dysregulation of neural progenitor cell proliferation/differentiation. *J. Neurosci.,* **2016**, *36*(42), 10908-10919. http://dx.doi.org/10.1523/JNEUROSCI.0229-16.2016 PMID: 27798144

[232] Dixon, S.C.; Calder, B.J.; Lilya, S.M.; Davies, B.M.; Martin, A.; Peterson, M.; Hansen, J.M.; Suli, A. Valproic acid affects neurogenesis during early optic tectum development in zebrafish. *Biol. Open,* **2023**, *12*(1), bio059567. http://dx.doi.org/10.1242/bio.059567 PMID: 36537579

[233] Dozawa, M.; Kono, H.; Sato, Y.; Ito, Y.; Tanaka, H.; Ohshima, T. Valproic acid, a histone deacetylase inhibitor, regulates cell proliferation in the adult zebrafish optic tectum. *Dev. Dyn.,* **2014**, *243*(11), 1401-1415. http://dx.doi.org/10.1002/dvdy.24173 PMID: 25091230

[234] Chen, A.; Wang, M.; Xu, C.; Zhao, Y.; Xian, P.; Li, Y.; Zheng, W.; Yi, X.; Wu, S.; Wang, Y. Glycolysis mediates neuron specific histone acetylation in valproic acid-induced human excitatory neuron differentiation. *Front. Mol. Neurosci.,* **2023**, *16*, 1151162. http://dx.doi.org/10.3389/fnmol.2023.1151162 PMID: 37089691

[235] Wang, H. Modeling neurological diseases with human brain organoids. *Front. Synaptic Neurosci.,* **2018**, *10*, 15. http://dx.doi.org/10.3389/fnsyn.2018.00015 PMID: 29937727

[236] Trujillo, C.A.; Muotri, A.R. Brain Organoids and the Study of Neurodevelopment. *Trends Mol. Med.,* **2018**, *24*(12), 982-990. http://dx.doi.org/10.1016/j.molmed.2018.09.005 PMID: 30377071

[237] Hansen, A.H.; Hippenmeyer, S. Non-cell-autonomous mechanisms in radial projection neuron migration in the developing cerebral cortex. *Front. Cell Dev. Biol.,* **2020**, *8*, 574382. http://dx.doi.org/10.3389/fcell.2020.574382 PMID: 33102480

[238] Gao, P.; Sultan, K.T.; Zhang, X.J.; Shi, S.H. Lineage-dependent circuit assembly in the neocortex. *Development,* **2013**, *140*(13), 2645-2655. http://dx.doi.org/10.1242/dev.087668 PMID: 23757410

[239] Stoner, R.; Chow, M.L.; Boyle, M.P.; Sunkin, S.M.; Mouton, P.R.; Roy, S.; Wynshaw-Boris, A.; Colamarino, S.A.; Lein, E.S.; Courchesne, E. Patches of disorganization in the neocortex of children with autism. *N. Engl. J. Med.,* **2014**, *370*(13), 1209-1219. http://dx.doi.org/10.1056/NEJMoa1307491 PMID: 24670167

[240] Bailey, A.; Luthert, P.; Dean, A.; Harding, B.; Janota, I.; Montgomery, M.; Rutter, M.; Lantos, P. A clinicopathological study of autism. *Brain,* **1998**, *121*(5), 889-905. http://dx.doi.org/10.1093/brain/121.5.889 PMID: 9619192

[241] Kemper, T.L.; Bauman, M. Neuropathology of infantile autism. *J. Neuropathol. Exp. Neurol.,* **1998**, *57*(7), 645-652. http://dx.doi.org/10.1097/00005072-199807000-00001 PMID: 9690668

[242] Simms, M.L.; Kemper, T.L.; Timbie, C.M.; Bauman, M.L.; Blatt, G.J. The anterior cingulate cortex in autism: heterogeneity of qualitative and quantitative cytoarchitectonic features suggests possible subgroups. *Acta Neuropathol.,* **2009**, *118*(5), 673-684. http://dx.doi.org/10.1007/s00401-009-0568-2 PMID: 19590881

[243] Goldowitz, D.; Hamre, K. The cells and molecules that make a cerebellum. *Trends Neurosci.,* **1998**, *21*(9), 375-382. http://dx.doi.org/10.1016/S0166-2236(98)01313-7 PMID: 9735945

[244] Sakai, A.; Matsuda, T.; Doi, H.; Nagaishi, Y.; Kato, K.; Nakashima, K. Ectopic neurogenesis induced by prenatal antiepileptic drug exposure augments seizure susceptibility in adult mice. *Proc. Natl. Acad. Sci.,* **2018**, *115*(16), 4270-4275. http://dx.doi.org/10.1073/pnas.1716479115 PMID: 29610328

[245] Choe, Y.; Pleasure, S.J. Wnt signaling regulates intermediate precursor production in the postnatal dentate gyrus by regulating CXCR4 expression. *Dev. Neurosci.,* **2012**, *34*(6), 502-514. http://dx.doi.org/10.1159/000345353 PMID: 23257686

[246] Schultheiß, C.; Abe, P.; Hoffmann, F.; Mueller, W.; Kreuder, A.E.; Schütz, D.; Haege, S.; Redecker, C.; Keiner, S.; Kannan, S.; Claasen, J.H.; Pfrieger, F.W.; Stumm, R. CXCR4 prevents dispersion of granule neuron precursors in the adult dentate gyrus. *Hippocampus,* **2013**, *23*(12), 1345-1358. http://dx.doi.org/10.1002/hipo.22180 PMID: 23929505

[247] Tsai, L.K.; Leng, Y.; Wang, Z.; Leeds, P.; Chuang, D.M. The mood stabilizers valproic acid and lithium enhance mesenchymal stem cell migration *via* distinct mechanisms. *Neuropsychopharmacology,* **2010**, *35*(11), 2225-2237. http://dx.doi.org/10.1038/npp.2010.97 PMID: 20613717

[248] Peñagarikano, O.; Geschwind, D.H. What does CNTNAP2 reveal about autism spectrum disorder? *Trends Mol. Med.,* **2012**, *18*(3), 156-163. http://dx.doi.org/10.1016/j.molmed.2012.01.003 PMID: 22365836

[249] Tahirovic, S.; Bradke, F. Neuronal polarity. *Cold Spring Harb. Perspect. Biol.,* **2009**, *1*(3), a001644-a001644. http://dx.doi.org/10.1101/cshperspect.a001644 PMID: 20066106

[250] Migliore, M.; Shepherd, G.M. An integrated approach to classifying neuronal phenotypes. *Nat. Rev. Neurosci.,* **2005**, *6*(10), 810-818. http://dx.doi.org/10.1038/nrn1769 PMID: 16276357

[251] Sporns, O. Structure and function of complex brain networks. *Dialogues Clin. Neurosci.,* **2013**, *15*(3), 247-262. http://dx.doi.org/10.31887/DCNS.2013.15.3/osporns PMID: 24174898

[252] Azmitia, E.C.; Singh, J.S.; Hou, X.P.; Wegiel, J. Dystrophic serotonin axons in postmortem brains from young autism patients. *Anat. Rec.,* **2011**, *294*(10), 1653-1662. http://dx.doi.org/10.1002/ar.21243 PMID: 21901837

[253] Azmitia, E.C.; Singh, J.S.; Whitaker-Azmitia, P.M. Increased serotonin axons (immunoreactive to 5-HT transporter) in postmortem brains from young autism donors. *Neuropharmacology,* **2011**, *60*(7-8), 1347-1354. http://dx.doi.org/10.1016/j.neuropharm.2011.02.002 PMID: 21329710

[254] Casanova, M.F.; Buxhoeveden, D.P.; Switala, A.E.; Roy, E. Minicolumnar pathology in autism. *Neurology,* **2002**, *58*(3), 428-432. http://dx.doi.org/10.1212/WNL.58.3.428 PMID: 11839843

[255] Raymond, G.V.; Bauman, M.L.; Kemper, T.L. Hippocampus in autism: A Golgi analysis. *Acta Neuropathol.,* **1995**, *91*(1), 117-119. http://dx.doi.org/10.1007/s004010050401 PMID: 8773156

[256] Mukaetova-Ladinska, E.B.; Arnold, H.; Jaros, E.; Perry, R.; Perry, E. Depletion of MAP2 expression and laminar cytoarchitectonic changes in dorsolateral prefrontal cortex in adult autistic individuals. *Neuropathol. Appl. Neurobiol.,* **2004**, *30*(6), 615-623. http://dx.doi.org/10.1111/j.1365-2990.2004.00574.x PMID: 15541002

[257] Hutsler, J.J.; Zhang, H. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Res.,* **2010**, *1309*, 83-94. http://dx.doi.org/10.1016/j.brainres.2009.09.120 PMID: 19896929

[258] Martínez-Cerdeño, V.; Camacho, J.; Fox, E.; Miller, E.; Ariza, J.; Kienzle, D.; Plank, K.; Noctor, S.C.; Van de Water, J. Prenatal exposure to autism-specific maternal autoantibodies alters proliferation of cortical neural precursor cells, enlarges brain, and increases neuronal size in adult animals. *Cereb. Cortex,* **2016**, *26*(1), 374-383. http://dx.doi.org/10.1093/cercor/bhu291 PMID: 25535268

[259] Snow, W.M.; Hartle, K.; Ivanco, T.L. Altered morphology of motor cortex neurons in the VPA rat model of autism. *Dev. Psychobiol.,* **2008**, *50*(7), 633-639. http://dx.doi.org/10.1002/dev.20337 PMID: 18985861

[260] Mychasiuk, R.; Richards, S.; Nakahashi, A.; Kolb, B.; Gibb, R. Effects of rat prenatal exposure to valproic acid on behaviour and neuro-anatomy. *Dev. Neurosci.,* **2012**, *34*(2-3), 268-276. http://dx.doi.org/10.1159/000341786 PMID: 22890088

[261] Muhsen, M.; Youngs, J.; Riu, A.; Gustafsson, J.Å.; Kondamadugu, V.S.; Garyfalidis, E.; Bondesson, M. Folic acid supplementation rescues valproic acid-induced developmental neurotoxicity and behavioral alterations in zebrafish embryos. *Epilepsia,* **2021**, *62*(7), 1689-1700. http://dx.doi.org/10.1111/epi.16915 PMID: 33997963

[262] Jacob, J; Ribes, V; Moore, S; Constable, SC; Sasai, N; Gerety, SS Valproic acid silencing of ascl1b/ascl1 results in the failure of serotonergic differentiation in a zebrafish model of fetal valproate syndrome. *Dis Model Mech,* **2013**, *7*(1), 107-117.

[263] Kawanai, T.; Ago, Y.; Watanabe, R.; Inoue, A.; Taruta, A.; Onaka, Y.; Hasebe, S.; Hashimoto, H.; Matsuda, T.; Takuma, K. Prenatal exposure to histone deacetylase inhibitors affects gene expression of autism-related molecules and delays neuronal maturation. *Neurochem. Res.,* **2016**, *41*(10), 2574-2584. http://dx.doi.org/10.1007/s11064-016-1969-y PMID: 27300699

[264] Lee, E.; Lee, J.; Kim, E. Excitation/inhibition imbalance in animal models of autism spectrum disorders. *Biol. Psychiatry,* **2017**, *81*(10), 838-847. http://dx.doi.org/10.1016/j.biopsych.2016.05.011 PMID: 27450033

[265] Rubenstein, J.L.R.; Merzenich, M.M. Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav.,* **2003**, *2*(5), 255-267. http://dx.doi.org/10.1034/j.1601-183X.2003.00037.x PMID: 14606691

[266] Tong, F.; Meng, M.; Blake, R. Neural bases of binocular rivalry. *Trends Cogn. Sci.,* **2006**, *10*(11), 502-511. http://dx.doi.org/10.1016/j.tics.2006.09.003 PMID: 16997612

[267] van Loon, A.M.; Knapen, T.; Scholte, H.S.; St John-Saaltink, E.; Donner, T.H.; Lamme, V.A.F. GABA shapes the dynamics of bistable perception. *Curr. Biol.,* **2013**, *23*(9), 823-827. http://dx.doi.org/10.1016/j.cub.2013.03.067 PMID: 23602476

[268] Choi, Y.B.; Mentch, J.; Haskins, A.J.; Van Wicklin, C.; Robertson, C.E. Visual processing in genetic conditions linked to autism: A behavioral study of binocular rivalry in individuals with 16p11.2 deletions and age-matched controls. *Autism Res.,* **2023**, *16*(4), 831-840. http://dx.doi.org/10.1002/aur.2901 PMID: 36751102

[269] Robertson, C.E.; Ratai, E.M.; Kanwisher, N. Reduced GABAergic action in the autistic brain. *Curr. Biol.,* **2016**, *26*(1), 80-85. http://dx.doi.org/10.1016/j.cub.2015.11.019 PMID: 26711497

[270] Casanova, M. Cortical organization. *Transl. Neurosci.,* **2010**, *1*(1), 62-71. http://dx.doi.org/10.2478/v10134-010-0002-2 PMID: 22754693

[271] Casanova, M.F.; El-Baz, A.; Switala, A. Laws of conservation as related to brain growth, aging, and evolution: Symmetry of the minicolumn. *Front. Neuroanat.,* **2011**, *5*, 66. http://dx.doi.org/10.3389/fnana.2011.00066 PMID: 22207838

[272] Casanova, M.F.; Van Kooten, I.A.J.; Switala, A.E.; Van Engeland, H.; Heinsen, H.; Steinbusch, H.W.M.; Hof, P.R.; Trippe, J.; Stone, J.; Schmitz, C. Minicolumnar abnormalities in autism. *Acta Neuropathol.,* **2006**, *112*(3), 287-303. http://dx.doi.org/10.1007/s00401-006-0085-5 PMID: 16819561

[273] McKavanagh, R.; Buckley, E.; Chance, S.A. Wider minicolumns in autism: A neural basis for altered processing? *Brain,* **2015**, *138*(7), 2034-2045. http://dx.doi.org/10.1093/brain/awv110 PMID: 25935724

[274] Sapey-Triomphe, L.A.; Lamberton, F.; Sonié, S.; Mattout, J.; Schmitz, C. Tactile hypersensitivity and GABA concentration in the sensorimotor cortex of adults with autism. *Autism Res.,* **2019**, *12*(4), 562-575. http://dx.doi.org/10.1002/aur.2073 PMID: 30632707

[275] Kolodny, T.; Schallmo, M.P.; Gerdts, J.; Edden, R.A.E.; Bernier, R.A.; Murray, S.O. Concentrations of cortical GABA and glutamate in young adults with autism spectrum disorder. *Autism Res.,* **2020**, *13*(7), 1111-1129. http://dx.doi.org/10.1002/aur.2300 PMID: 32297709

[276] Oblak, A.L.; Gibbs, T.T.; Blatt, G.J. Decreased GABAB receptors in the cingulate cortex and fusiform gyrus in Autism: Decreased GABAB receptors in autism. *J Neurochem.,* **2010**, *114*(5), 1414-1423.

[277] Oblak, A.; Gibbs, T.T.; Blatt, G.J. Decreased GABA $_A$ receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. *Autism Res.,* **2009**, *2*(4), 205-219. http://dx.doi.org/10.1002/aur.88 PMID: 19650112

[278] Yip, J.; Soghomonian, J.J.; Blatt, G.J. Decreased GAD65 mRNA levels in select subpopulations of neurons in the cerebellar dentate nuclei in autism: An *in situ* hybridization study. *Autism Res.,* **2009**, *2*(1), 50-59. http://dx.doi.org/10.1002/aur.62 PMID: 19358307

[279] Yip, J.; Soghomonian, J.J.; Blatt, G.J. IncreasedGAD67 mRNA expression in cerebellar interneurons in autism: Implications for Purkinje cell dysfunction. *J. Neurosci. Res.,* **2008**, *86*(3), 525-530. http://dx.doi.org/10.1002/jnr.21520 PMID: 17918742

[280] Yip, J.; Soghomonian, J.J.; Blatt, G.J. Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta Neuropathol.,* **2007**, *113*(5), 559-568. http://dx.doi.org/10.1007/s00401-006-0176-3 PMID: 17235515

[281] Zhao, H.; Mao, X.; Zhu, C.; Zou, X.; Peng, F.; Yang, W.; Li, B.; Li, G.; Ge, T.; Cui, R. GABAergic system dysfunction in autism spectrum disorders. *Front. Cell Dev. Biol.,* **2022**, *9*, 781327. http://dx.doi.org/10.3389/fcell.2021.781327 PMID: 35198562

[282] Nelson, S.B.; Valakh, V. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. *Neuron,* **2015**, *87*(4), 684-698. http://dx.doi.org/10.1016/j.neuron.2015.07.033 PMID: 26291155

[283] Martin, H.G.S.; Manzoni, O.J. Late onset deficits in synaptic plasticity in the valproic acid rat model of autism. *Front. Cell. Neurosci.,* **2014**, *8*, 23. http://dx.doi.org/10.3389/fncel.2014.00023 PMID: 24550781

[284] Iijima, Y.; Behr, K.; Iijima, T.; Biemans, B.; Bischofberger, J.; Scheiffele, P. Distinct defects in synaptic differentiation of neocortical neurons in response to prenatal valproate exposure. *Sci. Rep.,* **2016**, *6*(1), 27400. http://dx.doi.org/10.1038/srep27400 PMID: 27264355

[285] Kim, J.W.; Park, K.; Kang, R.J.; Gonzales, E.L.T.; Kim, D.G.; Oh, H.A.; Seung, H.; Ko, M.J.; Kwon, K.J.; Kim, K.C.; Lee, S.H.; Chung, C.; Shin, C.Y. Pharmacological modulation of AMPA receptor rescues social impairments in animal models of autism. *Neuropsychopharmacology,* **2019**, *44*(2), 314-323. http://dx.doi.org/10.1038/s41386-018-0098-5 PMID: 29899405

[286] Brumback, A.C.; Ellwood, I.T.; Kjaerby, C.; Iafrati, J.; Robinson, S.; Lee, A.T.; Patel, T.; Nagaraj, S.; Davatolhagh, F.; Sohal, V.S. Identifying specific prefrontal neurons that contribute to autism-associated abnormalities in physiology and social behavior. *Mol. Psychiatry,* **2018**, *23*(10), 2078-2089. http://dx.doi.org/10.1038/mp.2017.213 PMID: 29112191

[287] Rinaldi, T.; Kulangara, K.; Antoniello, K.; Markram, H. Elevated NMDA receptor levels and enhanced postsynaptic long-term potentiation induced by prenatal exposure to valproic acid. *Proc. Natl. Acad. Sci. USA,* **2007**, *104*(33), 13501-13506. http://dx.doi.org/10.1073/pnas.0704391104 PMID: 17675408

[288] Rinaldi, T.; Perrodin, C.; Markram, H. Hyper-connectivity and hyper-plasticity in the medial prefrontal cortex in the valproic acid animal model of autism. *Front. Neural Circuits,* **2008**, *2*, 4. http://dx.doi.org/10.3389/neuro.04.004.2008 PMID: 18989389

[289] Rinaldi, T.; Silberberg, G.; Markram, H. Hyperconnectivity of local neocortical microcircuitry induced by prenatal exposure to valproic acid. *Cereb. Cortex,* **2008**, *18*(4), 763-770. http://dx.doi.org/10.1093/cercor/bhm117 PMID: 17638926

[290] Banerjee, A.; García-Oscos, F.; Roychowdhury, S.; Galindo, L.C.; Hall, S.; Kilgard, M.P.; Atzori, M. Impairment of cortical GABAergic synaptic transmission in an environmental rat model of autism. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(6), 1309-1318. http://dx.doi.org/10.1017/S1461145712001216 PMID: 23228615

[291] Qi, C.; Chen, A.; Mao, H.; Hu, E.; Ge, J.; Ma, G.; Ren, K.; Xue, Q.; Wang, W.; Wu, S. Excitatory and inhibitory synaptic imbalance caused by brain-derived neurotrophic factor deficits during development in a valproic acid mouse model of autism. *Front. Mol. Neurosci.,* **2022**, *15*, 860275. http://dx.doi.org/10.3389/fnmol.2022.860275 PMID: 35465089

[292] Bradl, M.; Lassmann, H. Oligodendrocytes: Biology and pathology. *Acta Neuropathol.,* **2010**, *119*(1), 37-53. http://dx.doi.org/10.1007/s00401-009-0601-5 PMID: 19847447

[293] Kuhn, S.; Gritti, L.; Crooks, D.; Dombrowski, Y. Oligodendrocytes in development, myelin generation and beyond. *Cells,* **2019**, *8*(11), 1424. http://dx.doi.org/10.3390/cells8111424 PMID: 31726662

[294] Jakovcevski, I.; Filipovic, R.; Mo, Z.; Rakic, S.; Zecevic, N. Oligodendrocyte development and the onset of myelination in the human fetal brain. *Front. Neuroanat.,* **2009**, *3*, 5. http://dx.doi.org/10.3389/neuro.05.005.2009 PMID: 19521542

[295] Ackerman, S.D.; Monk, K.R. The scales and tales of myelination: Using zebrafish and mouse to study myelinating glia. *Brain Res.,* **2016**, *1641*(Pt A), 79-91. http://dx.doi.org/10.1016/j.brainres.2015.10.011 PMID: 26498880

[296] Travers, B.G.; Adluru, N.; Ennis, C.; Tromp, D.P.M.; Destiche, D.; Doran, S.; Bigler, E.D.; Lange, N.; Lainhart, J.E.; Alexander, A.L. Diffusion tensor imaging in autism spectrum disorder: a review. *Autism Res.,* **2012**, *5*(5), 289-313. http://dx.doi.org/10.1002/aur.1243 PMID: 22786754

[297] Chauhan, A.; Chauhan, V. Oxidative stress in autism. *Pathophysiology,* **2006**, *13*(3), 171-181. http://dx.doi.org/10.1016/j.pathophys.2006.05.007 PMID: 16766163

[298] Ameis, S.H.; Lerch, J.P.; Taylor, M.J.; Lee, W.; Viviano, J.D.; Pipitone, J.; Nazeri, A.; Croarkin, P.E.; Voineskos, A.N.; Lai, M.C.; Crosbie, J.; Brian, J.; Soreni, N.; Schachar, R.; Szatmari, P.; Arnold, P.D.; Anagnostou, E. A diffusion tensor imaging study in children with adhd, autism spectrum disorder, OCD, and matched controls: Distinct and non-distinct white matter disruption and dimensional brain-behavior relationships. *Am. J. Psychiatry,* **2016**, *173*(12), 1213-1222. http://dx.doi.org/10.1176/appi.ajp.2016.15111435 PMID: 27363509

[299] Graciarena, M.; Seiffe, A.; Nait-Oumesmar, B.; Depino, A.M. Hypomyelination and oligodendroglial alterations in a mouse model of autism spectrum disorder. *Front. Cell. Neurosci.,* **2019**, *12*, 517. http://dx.doi.org/10.3389/fncel.2018.00517 PMID: 30687009

[300] Courchesne, E.; Karns, C.M.; Davis, H.R.; Ziccardi, R.; Carper, R.A.; Tigue, Z.D.; Chisum, H.J.; Moses, P.; Pierce, K.; Lord, C.; Lincoln, A.J.; Pizzo, S.; Schreibman, L.; Haas, R.H.; Akshoomoff, N.A.; Courchesne, R.Y. Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology,* **2001**, *57*(2), 245-254. http://dx.doi.org/10.1212/WNL.57.2.245 PMID: 11468308

[301] Dimond, D.; Schuetze, M.; Smith, R.E.; Dhollander, T.; Cho, I.; Vinette, S.; Ten Eycke, K.; Lebel, C.; McCrimmon, A.; Dewey, D.; Connelly, A.; Bray, S. Reduced white matter fiber density in autism spectrum disorder. *Cereb. Cortex,* **2019**, *29*(4), 1778-1788. http://dx.doi.org/10.1093/cercor/bhy348 PMID: 30668849

[302] Galvez-Contreras, A.Y.; Zarate-Lopez, D.; Torres-Chavez, A.L.; Gonzalez-Perez, O. Role of oligodendrocytes and myelin in the pathophysiology of autism spectrum disorder. *Brain Sci.,* **2020**, *10*(12), 951. http://dx.doi.org/10.3390/brainsci10120951 PMID: 33302549

[303] Hong, S.J.; Hyung, B.; Paquola, C.; Bernhardt, B.C. The superficial white matter in autism and its role in connectivity anomalies and symptom severity. *Cereb. Cortex,* **2019**, *29*(10), 4415-4425. http://dx.doi.org/10.1093/cercor/bhy321 PMID: 30566613

[304] Carmody, D.P.; Lewis, M. Regional white matter development in children with autism spectrum disorders. *Dev. Psychobiol.,* **2010**, *52*(8), 755-763. http://dx.doi.org/10.1002/dev.20471 PMID: 20564327

[305] Noriuchi, M.; Kikuchi, Y.; Yoshiura, T.; Kira, R.; Shigeto, H.; Hara, T.; Tobimatsu, S.; Kamio, Y. Altered white matter fractional anisotropy and social impairment in children with autism spectrum disorder. *Brain Res.,* **2010**, *1362*, 141-149. http://dx.doi.org/10.1016/j.brainres.2010.09.051 PMID: 20858472

[306] Wolff, J.J.; Gerig, G.; Lewis, J.D.; Soda, T.; Styner, M.A.; Vachet, C.; Botteron, K.N.; Elison, J.T.; Dager, S.R.; Estes, A.M.; Hazlett, H.C.; Schultz, R.T.; Zwaigenbaum, L.; Piven, J. Altered corpus callosum morphology associated with autism over the first 2 years of life. *Brain,* **2015**, *138*(7), 2046-2058. http://dx.doi.org/10.1093/brain/awv118 PMID: 25937563

[307] Cheon, K.A.; Kim, Y.S.; Oh, S.H.; Park, S.Y.; Yoon, H.W.; Herrington, J.; Nair, A.; Koh, Y.J.; Jang, D.P.; Kim, Y.B.; Leventhal, B.L.; Cho, Z.H.; Castellanos, F.X.; Schultz, R.T. Involvement of the anterior thalamic radiation in boys with high functioning autism spectrum disorders: A Diffusion Tensor Imaging study. *Brain Res.,* **2011**, *1417*(12), 77-86. http://dx.doi.org/10.1016/j.brainres.2011.08.020 PMID: 21890117

[308] Kumar, A.; Sundaram, S.K.; Sivaswamy, L.; Behen, M.E.; Makki, M.I.; Ager, J.; Janisse, J.; Chugani, H.T.; Chugani, D.C. Alterations in frontal lobe tracts and corpus callosum in young children with autism spectrum disorder. *Cereb. Cortex,* **2010**, *20*(9), 2103-2113. http://dx.doi.org/10.1093/cercor/bhp278 PMID: 20019145

[309] Ikuta, T.; Shafritz, K.M.; Bregman, J.; Peters, B.D.; Gruner, P.; Malhotra, A.K.; Szeszko, P.R. Abnormal cingulum bundle development in autism: A probabilistic tractography study. *Psychiatry Res. Neuroimaging,* **2014**, *221*(1), 63-68. http://dx.doi.org/10.1016/j.pscychresns.2013.08.002 PMID: 24231056

[310] Nair, A.; Treiber, J.M.; Shukla, D.K.; Shih, P.; Müller, R.A. Impaired thalamocortical connectivity in autism spectrum disorder: A study of functional and anatomical connectivity. *Brain,* **2013**, *136*(6), 1942-1955. http://dx.doi.org/10.1093/brain/awt079 PMID: 23739917

[311] Bronzuoli, M.R.; Facchinetti, R.; Ingrassia, D.; Sarvadio, M.; Schiavi, S.; Steardo, L.; Verkhratsky, A.; Trezza, V.; Scuderi, C. Neuroglia in the autistic brain: Evidence from a preclinical model. *Mol. Autism,* **2018**, *9*(1), 66. http://dx.doi.org/10.1186/s13229-018-0254-0 PMID: 30603062

[312] Uccelli, N.A.; Codagnone, M.G.; Traetta, M.E.; Levanovich, N.; Rosato Siri, M.V.; Urrutia, L.; Falasco, G.; Vázquez, S.; Pasquini, J.M.; Reinés, A.G. Neurobiological substrates underlying corpus callosum hypoconnectivity and brain metabolic patterns in the valproic acid rat model of autism spectrum disorder. *J. Neurochem.,* **2021**, *159*(1), 128-144. http://dx.doi.org/10.1111/jnc.15444 PMID: 34081798

[313] Zhou, B.; Yan, X.; Yang, L.; Zheng, X.; Chen, Y.; Liu, Y.; Ren, Y.; Peng, J.; Zhang, Y.; Huang, J.; Tang, L.; Wen, M. Effects of arginine vasopressin on the transcriptome of prefrontal cortex in autistic rat model. *J. Cell. Mol. Med.,* **2022**, *26*(21), 5493-5505. http://dx.doi.org/10.1111/jcmm.17578 PMID: 36239083

[314] Marie, C.; Clavairoly, A.; Frah, M.; Hmidan, H.; Yan, J.; Zhao, C.; Van Steenwinckel, J.; Daveau, R.; Zalc, B.; Hassan, B.; Thomas, J.L.; Gressens, P.; Ravassard, P.; Moszer, I.; Martin, D.M.; Lu, Q.R.; Parras, C. Oligodendrocyte precursor survival and differentiation requires chromatin remodeling by Chd7 and Chd8. *Proc. Natl. Acad. Sci.,* **2018**, *115*(35), E8246-E8255. http://dx.doi.org/10.1073/pnas.1802620115 PMID: 30108144

[315] Hanafy, K.A.; Sloane, J.A. Regulation of remyelination in multiple sclerosis. *FEBS Lett.,* **2011**, *585*(23), 3821-3828.

http://dx.doi.org/10.1016/j.febslet.2011.03.048 PMID: 21443876

[316] Boulanger-Bertolus, J.; Pancaro, C.; Mashour, G.A. Increasing role of maternal immune activation in neurodevelopmental disorders. *Front. Behav. Neurosci.,* **2018**, *12*, 230. http://dx.doi.org/10.3389/fnbeh.2018.00230 PMID: 30344483

[317] Zawadzka, A.; Cieślik, M.; Adamczyk, A. The role of maternal immune activation in the pathogenesis of autism: A review of the evidence, proposed mechanisms and implications for treatment. *Int. J. Mol. Sci.,* **2021**, *22*(21), 11516. http://dx.doi.org/10.3390/ijms222111516 PMID: 34768946

[318] Rose, S.; Melnyk, S.; Pavliv, O.; Bai, S.; Nick, T.G.; Frye, R.E.; James, S.J. Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. *Transl. Psychiatry,* **2012**, *2*(7), e134-e134. http://dx.doi.org/10.1038/tp.2012.61 PMID: 22781167

[319] Yockey, L.J.; Iwasaki, A. Interferons and proinflammatory cytokines in pregnancy and fetal development. *Immunity,* **2018**, *49*(3), 397-412. http://dx.doi.org/10.1016/j.immuni.2018.07.017 PMID: 30231982

[320] Fox, E.; Amaral, D.; Van de Water, J. Maternal and fetal antibrain antibodies in development and disease. *Dev. Neurobiol.,* **2012**, *72*(10), 1327-1334. http://dx.doi.org/10.1002/dneu.22052 PMID: 22911883

[321] Heuer, L.; Braunschweig, D.; Ashwood, P.; Van de Water, J.; Campbell, D.B. Association of a MET genetic variant with autism-associated maternal autoantibodies to fetal brain proteins and cytokine expression. *Transl. Psychiatry,* **2011**, *1*(10), e48-e48. http://dx.doi.org/10.1038/tp.2011.48 PMID: 22833194

[322] Bilbo, S.D.; Block, C.L.; Bolton, J.L.; Hanamsagar, R.; Tran, P.K. Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Exp. Neurol.,* **2018**, *299*(Pt A), 241-251. http://dx.doi.org/10.1016/j.expneurol.2017.07.002 PMID: 28698032

[323] Stubbs, E.G.; Crawford, M.L.; Burger, D.R.; Vandenbark, A.A. Depressed lymphocyte responsiveness in autistic children. *J. Autism Child. Schizophr.,* **1977**, *7*(1), 49-55. http://dx.doi.org/10.1007/BF01531114 PMID: 139400

[324] Burger, R.A.; Warren, R.P. Possible immunogenetic basis for autism. *Ment. Retard. Dev. Disabil. Res. Rev.,* **1998**, *4*(2), 137-141. http://dx.doi.org/10.1002/(SICI)1098-2779(1998)4:2<137::AID-MRDD11>3.0.CO;2-W

[325] Croonenberghs, J.; Bosmans, E.; Deboutte, D.; Kenis, G.; Maes, M. Activation of the inflammatory response system in autism. *Neuropsychobiology,* **2002**, *45*(1), 1-6. http://dx.doi.org/10.1159/000048665 PMID: 11803234

[326] Molloy, C.; Morrow, A.; Meinzenderr, J.; Schleifer, K.; Dienger, K.; Manningcourtney, P.; Altaye, M.; Willskarp, M. Elevated cytokine levels in children with autism spectrum disorder. *J. Neuroimmunol.,* **2006**, *172*(1-2), 198-205. http://dx.doi.org/10.1016/j.jneuroim.2005.11.007 PMID: 16360218

[327] Jyonouchi, H.; Sun, S.; Le, H. Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. *J. Neuroimmunol.,* **2001**, *120*(1-2), 170-179. http://dx.doi.org/10.1016/S0165-5728(01)00421-0 PMID: 11694332

[328] Vargas, D.L.; Nascimbene, C.; Krishnan, C.; Zimmerman, A.W.; Pardo, C.A. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann. Neurol.,* **2005**, *57*(1), 67-81. http://dx.doi.org/10.1002/ana.20315 PMID: 15546155

[329] Morgan, J.T.; Chana, G.; Pardo, C.A.; Achim, C.; Semendeferi, K.; Buckwalter, J.; Courchesne, E.; Everall, I.P. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biol. Psychiatry,* **2010**, *68*(4), 368-376. http://dx.doi.org/10.1016/j.biopsych.2010.05.024 PMID: 20674603

[330] McDougle, C.J.; Landino, S.M.; Vahabzadeh, A.; O'Rourke, J.; Zurcher, N.R.; Finger, B.C.; Palumbo, M.L.; Helt, J.; Mullett, J.E.; Hooker, J.M.; Carlezon, W.A., Jr Toward an immune-mediated subtype of autism spectrum disorder. *Brain Res.,* **2015**, *1617*, 72-92. http://dx.doi.org/10.1016/j.brainres.2014.09.048 PMID: 25445995

[331] Suzuki, K.; Sugihara, G.; Ouchi, Y.; Nakamura, K.; Futatsubashi, M.; Takebayashi, K.; Yoshihara, Y.; Omata, K.; Matsumoto, K.; Tsuchiya, K.J.; Iwata, Y.; Tsujii, M.; Sugiyama, T.; Mori, N. Microglial activation in young adults with autism spectrum disorder. *JAMA Psychiatry,* **2013**, *70*(1), 49-58. http://dx.doi.org/10.1001/jamapsychiatry.2013.272 PMID: 23404112

[332] Oskvig, D.B.; Elkahloun, A.G.; Johnson, K.R.; Phillips, T.M.; Herkenham, M. Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. *Brain Behav. Immun.,* **2012**, *26*(4), 623-634. http://dx.doi.org/10.1016/j.bbi.2012.01.015 PMID: 22310921

[333] Shook, L.L.; Fourman, L.T.; Edlow, A.G. Immune responses to sARS-CoV-2 in pregnancy: Implications for the health of the next generation. *J. Immunol.,* **2022**, *209*(8), 1465-1473. http://dx.doi.org/10.4049/jimmunol.2200414 PMID: 36192115

[334] Pangrazzi, L.; Balasco, L.; Bozzi, Y. Oxidative stress and immune system dysfunction in autism spectrum disorders. *Int. J. Mol. Sci.,* **2020**, *21*(9), 3293. http://dx.doi.org/10.3390/ijms21093293 PMID: 32384730

[335] Kazlauskas, N.; Campolongo, M.; Lucchina, L.; Zappala, C.; Depino, A.M. Postnatal behavioral and inflammatory alterations in female pups prenatally exposed to valproic acid. *Psychoneuroendocrinology,* **2016**, *72*, 11-21. http://dx.doi.org/10.1016/j.psyneuen.2016.06.001 PMID: 27337090

[336] Gąssowska-Dobrowolska, M.; Cieślik, M.; Czapski, G.A.; Jęśko, H.; Frontczak-Baniewicz, M.; Gewartowska, M.; Dominiak, A.; Polowy, R.; Filipkowski, R.K.; Babiec, L.; Adamczyk, A. Prenatal exposure to valproic acid affects microglia and synaptic ultrastructure in a brain-region-specific manner in young-adult male rats: relevance to autism spectrum disorders. *Int. J. Mol. Sci.,* **2020**, *21*(10), 3576. http://dx.doi.org/10.3390/ijms21103576 PMID: 32443651

[337] Luo, L.; Chen, J.; Wu, Q.; Yuan, B.; Hu, C.; Yang, T.; Wei, H.; Li, T. Prenatally VPA exposure is likely to cause autistic-like behavior in the rats offspring *via* TREM2 down-regulation to affect the microglial activation and synapse alterations. *Environ. Toxicol. Pharmacol.,* **2023**, *99*, 104090. http://dx.doi.org/10.1016/j.etap.2023.104090 PMID: 36870407

[338] Triyasakorn, K.; Ubah, U.D.B.; Roan, B.; Conlin, M.; Aho, K.; Awale, P.S. The antiepileptic drug and toxic teratogen valproic acid alters microglia in an environmental mouse model of autism. *Toxics,* **2022**, *10*(7), 379. http://dx.doi.org/10.3390/toxics10070379 PMID: 35878284

[339] Dhabhar, F.S. Enhancing *versus* suppressive effects of stress on immune function: Implications for immunoprotection and immunopathology. *Neuroimmunomodulation,* **2009**, *16*(5), 300-317. http://dx.doi.org/10.1159/000216188 PMID: 19571591

[340] Sweeten, T.L.; Posey, D.J.; Shankar, S.; McDougle, C.J. High nitric oxide production in autistic disorder: A possible role for interferon-γ. *Biol. Psychiatry,* **2004**, *55*(4), 434-437. http://dx.doi.org/10.1016/j.biopsych.2003.09.001 PMID: 14960298

[341] Wu, C.; Li, A.; Leng, Y.; Li, Y.; Kang, J. Histone deacetylase inhibition by sodium valproate regulates polarization of macrophage subsets. *DNA Cell Biol.,* **2012**, *31*(4), 592-599. http://dx.doi.org/10.1089/dna.2011.1401 PMID: 22054065

[342] Zhang, Z.; Zhang, Z.Y.; Wu, Y.; Schluesener, H.J. Valproic acid ameliorates inflammation in experimental autoimmune encephalomyelitis rats. *Neuroscience,* **2012**, *221*, 140-150. http://dx.doi.org/10.1016/j.neuroscience.2012.07.013 PMID: 22800566

[343] Chen, S.; Ye, J.; Chen, X.; Shi, J.; Wu, W.; Lin, W.; Lin, W.; Li, Y.; Fu, H.; Li, S. Valproic acid attenuates traumatic spinal cord injury-induced inflammation *via* STAT1 and NF-κB pathway dependent of HDAC3. *J. Neuroinflammation,* **2018**, *15*(1), 150. http://dx.doi.org/10.1186/s12974-018-1193-6 PMID: 29776446

[344] Ubah, U.D.B.; Triyasakorn, K.; Roan, B.; Conlin, M.; Lai, J.C.K.; Awale, P.S. Pan HDACi valproic acid and trichostatin a show apparently contrasting inflammatory responses in cultured J774A.1 macrophages. *Epigenomes,* **2022**, *6*(4), 38. http://dx.doi.org/10.3390/epigenomes6040038 PMID: 36412793

[345] Noriega, D.B.; Savelkoul, H.F.J. Immune dysregulation in autism spectrum disorder. *Eur. J. Pediatr.,* **2014**, *173*(1), 33-43. http://dx.doi.org/10.1007/s00431-013-2183-4 PMID: 24297668

[346] Deckmann, I.; Santos-Terra, J.; Fontes-Dutra, M.; Körbes-Rockenbach, M.; Bauer-Negrini, G.; Schwingel, G.B.; Riesgo, R.; Bambini-Junior, V.; Gottfried, C. Resveratrol prevents brain edema, blood–brain barrier permeability, and altered aquaporin profile in autism animal model. *Int. J. Dev. Neurosci.,* **2021**, *81*(7), 579-604.
http://dx.doi.org/10.1002/jdn.10137 PMID: 34196408

[347] Gurvich, N.; Tsygankova, O.M.; Meinkoth, J.L.; Klein, P.S. Histone deacetylase is a target of valproic acid-mediated cellular differentiation. *Cancer Res.,* **2004**, *64*(3), 1079-1086.
http://dx.doi.org/10.1158/0008-5472.CAN-03-0799 PMID: 14871841

[348] Bolden, J.E.; Peart, M.J.; Johnstone, R.W. Anticancer activities of histone deacetylase inhibitors. *Nat. Rev. Drug Discov.,* **2006**, *5*(9), 769-784.
http://dx.doi.org/10.1038/nrd2133 PMID: 16955068

[349] Kostrouchová, M.; Kostrouch, Z.; Kostrouchová, M. Valproic acid, a molecular lead to multiple regulatory pathways. *Folia Biol.,* **2007**, *53*(2), 37-49.
PMID: 17448293

[350] Ganai, S.A.; Malli Kalladi, S.; Mahadevan, V. HDAC inhibition through valproic acid modulates the methylation profiles in human embryonic kidney cells. *J. Biomol. Struct. Dyn.,* **2015**, *33*(6), 1185-1197.
http://dx.doi.org/10.1080/07391102.2014.938247 PMID: 25012937

[351] Blaheta, R.A.; Nau, H.; Michaelis, M.; Cinatl, J., Jr Valproate and valproate-analogues: Potent tools to fight against cancer. *Curr. Med. Chem.,* **2002**, *9*(15), 1417-1433.
http://dx.doi.org/10.2174/0929867023369763 PMID: 12173980

[352] Yoon, S.; Choi, J.; Lee, W.; Do, J. Genetic and epigenetic etiology underlying autism spectrum disorder. *J. Clin. Med.,* **2020**, *9*(4), 966.
http://dx.doi.org/10.3390/jcm9040966 PMID: 32244359

[353] Volmar, C.H.; Wahlestedt, C. Histone deacetylases (HDACs) and brain function. *Neuroepigenetics,* **2015**, *1*, 20-27.
http://dx.doi.org/10.1016/j.nepig.2014.10.002

[354] Krämer, O.H.; Zhu, P.; Ostendorff, H.P.; Golebiewski, M.; Tiefenbach, J.; Peters, M.A.; Brill, B.; Groner, B.; Bach, I.; Heinzel, T.; Göttlicher, M. The histone deacetylase inhibitor valproic acid selectively induces proteasomal degradation of HDAC2. *EMBO J.,* **2003**, *22*(13), 3411-3420.
http://dx.doi.org/10.1093/emboj/cdg315 PMID: 12840003

[355] Kouzarides, T. Chromatin modifications and their function. *Cell,* **2007**, *128*(4), 693-705.
http://dx.doi.org/10.1016/j.cell.2007.02.005 PMID: 17320507

[356] Hezroni, H.; Sailaja, B.S.; Meshorer, E. Pluripotency-related, valproic acid (VPA)-induced genome-wide histone H3 lysine 9 (H3K9) acetylation patterns in embryonic stem cells. *J. Biol. Chem.,* **2011**, *286*(41), 35977-35988.
http://dx.doi.org/10.1074/jbc.M111.266254 PMID: 21849501

[357] Lee, JH; Hart, SRL; Skalnik, DG Histone deacetylase activity is required for embryonic stem cell differentiation. *genesis.,* **2004**, *38*(1), 32-38.

[358] Qiao, Y.; Wang, R.; Yang, X.; Tang, K.; Jing, N. Dual roles of histone H3 lysine 9 acetylation in human embryonic stem cell pluripotency and neural differentiation. *J. Biol. Chem.,* **2015**, *290*(4), 2508-2520.
http://dx.doi.org/10.1074/jbc.M114.603761 PMID: 25519907

[359] Gandhi, S.; Mitterhoff, R.; Rapoport, R.; Farago, M.; Greenberg, A.; Hodge, L.; Eden, S.; Benner, C.; Goren, A.; Simon, I. Mitotic H3K9ac is controlled by phase-specific activity of HDAC2, HDAC3, and SIRT1. *Life Sci. Alliance,* **2022**, *5*(10), e202201433.
http://dx.doi.org/10.26508/lsa.202201433 PMID: 35981887

[360] Lagger, G.; O'Carroll, D.; Rembold, M.; Khier, H.; Tischler, J.; Weitzer, G.; Schuettengruber, B.; Hauser, C.; Brunmeir, R.; Jenuwein, T.; Seiser, C. Essential function of histone deacetylase 1 in proliferation control and CDK inhibitor repression. *EMBO J.,* **2002**, *21*(11), 2672-2681.
http://dx.doi.org/10.1093/emboj/21.11.2672 PMID: 12032080

[361] Kim, K.C.; Choi, C.S.; Gonzales, E.L.T.; Mabunga, D.F.N.; Lee, S.H.; Jeon, S.J.; Hwangbo, R.; Hong, M.; Ryu, J.H.; Han, S.H.; Bahn, G.H.; Shin, C.Y. Valproic acid induces telomerase reverse transcriptase expression during cortical development. *Exp. Neurobiol.,* **2017**, *26*(5), 252-265.
http://dx.doi.org/10.5607/en.2017.26.5.252 PMID: 29093634

[362] Tung, E.W.Y.; Winn, L.M. Epigenetic modifications in valproic acid-induced teratogenesis. *Toxicol. Appl. Pharmacol.,* **2010**, *248*(3), 201-209.
http://dx.doi.org/10.1016/j.taap.2010.08.001 PMID: 20705080

[363] Wang, Z.; Xu, L.; Zhu, X.; Cui, W.; Sun, Y.; Nishijo, H.; Peng, Y.; Li, R. Demethylation of specific Wnt/β-catenin pathway genes and its upregulation in rat brain induced by prenatal valproate exposure. *Anat. Rec.,* **2010**, *293*(11), 1947-1953.
http://dx.doi.org/10.1002/ar.21232 PMID: 20734317

[364] He, Y.; Mei, H.; Yu, H.; Sun, S.; Ni, W.; Li, H. Role of histone deacetylase activity in the developing lateral line neuromast of zebrafish larvae. *Exp. Mol. Med.,* **2014**, *46*(5), e94-e94.
http://dx.doi.org/10.1038/emm.2014.18 PMID: 24810423

[365] Leung, C.S.; Rosenzweig, S.J.; Yoon, B.; Marinelli, N.A.; Hollingsworth, E.W.; Maguire, A.M.; Cowen, M.H.; Schmidt, M.; Imitola, J.; Gamsiz Uzun, E.D.; Lizarraga, S.B. Dysregulation of the chromatin environment leads to differential alternative splicing as a mechanism of disease in a human model of autism spectrum disorder. *Hum. Mol. Genet.,* **2023**, *32*(10), 1634-1646.
http://dx.doi.org/10.1093/hmg/ddad002 PMID: 36621967

[366] Boudadi, E.; Stower, H.; Halsall, J.A.; Rutledge, C.E.; Leeb, M.; Wutz, A.; O'Neill, L.P.; Nightingale, K.P.; Turner, B.M. The histone deacetylase inhibitor sodium valproate causes limited transcriptional change in mouse embryonic stem cells but selectively overrides Polycomb-mediated Hoxb silencing. *Epigenetics Chromatin,* **2013**, *6*(1), 11.
http://dx.doi.org/10.1186/1756-8935-6-11 PMID: 23634885

[367] Guerra, M.; Medici, V.; Weatheritt, R.; Corvino, V.; Palacios, D.; Geloso, M.C.; Farini, D.; Sette, C. Fetal exposure to valproic acid dysregulates the expression of autism-linked genes in the developing cerebellum. *Transl. Psychiatry,* **2023**, *13*(1), 114.
http://dx.doi.org/10.1038/s41398-023-02391-9 PMID: 37019889

[368] Hara, Y.; Ago, Y.; Takano, E.; Hasebe, S.; Nakazawa, T.; Hashimoto, H.; Matsuda, T.; Takuma, K. Prenatal exposure to valproic acid increases miR-132 levels in the mouse embryonic brain. *Mol. Autism,* **2017**, *8*(1), 33.
http://dx.doi.org/10.1186/s13229-017-0149-5 PMID: 28670439

[369] Jung, G.A.; Yoon, J.Y.; Moon, B.S.; Yang, D.H.; Kim, H.Y.; Lee, S.H.; Bryja, V.; Arenas, E.; Choi, K.Y. Valproic acid induces differentiation and inhibition of proliferation in neural progenitor cells *via* the beta-catenin-Ras-ERK-p21Cip/WAF1 pathway. *BMC Cell Biol.,* **2008**, *9*(1), 66.
http://dx.doi.org/10.1186/1471-2121-9-66 PMID: 19068119

[370] Basu, S.N.; Kollu, R.; Banerjee-Basu, S. AutDB: a gene reference resource for autism research. *Nucleic Acids Res.,* **2009**, *37*(Database issue), D832-D836.
http://dx.doi.org/10.1093/nar/gkn835 PMID: 19015121

[371] Baumann, C.; Zhang, X.; Zhu, L.; Fan, Y.; De La Fuente, R. Changes in chromatin accessibility landscape and histone H3 core acetylation during valproic acid-induced differentiation of embryonic stem cells. *Epigenetics Chromatin,* **2021**, *14*(1), 58.
http://dx.doi.org/10.1186/s13072-021-00432-5 PMID: 34955095

[372] Yuan, J.; Pu, M.; Zhang, Z.; Lou, Z. Histone H3-K56 acetylation is important for genomic stability in mammals. *Cell Cycle,* **2009**, *8*(11), 1747-1753.
http://dx.doi.org/10.4161/cc.8.11.8620 PMID: 19411844

[373] Tessarz, P.; Kouzarides, T. Histone core modifications regulating nucleosome structure and dynamics. *Nat. Rev. Mol. Cell Biol.,* **2014**, *15*(11), 703-708.
http://dx.doi.org/10.1038/nrm3890 PMID: 25315270

[374] Xie, W.; Song, C.; Young, N.L.; Sperling, A.S.; Xu, F.; Sridharan, R.; Conway, A.E.; Garcia, B.A.; Plath, K.; Clark, A.T.; Grunstein, M. Histone h3 lysine 56 acetylation is linked to the core transcriptional network in human embryonic stem cells. *Mol. Cell,* **2009**, *33*(4), 417-427.
http://dx.doi.org/10.1016/j.molcel.2009.02.004 PMID: 19250903

[375] Osumi, N.; Shinohara, H.; Numayama-Tsuruta, K.; Maekawa, M. Concise review: Pax6 transcription factor contributes to both embryonic and adult neurogenesis as a multifunctional regulator. *Stem Cells,* **2008**, *26*(7), 1663-1672.
http://dx.doi.org/10.1634/stemcells.2007-0884 PMID: 18467663

[376] Duan, D.; Fu, Y.; Paxinos, G.; Watson, C. Spatiotemporal expression patterns of Pax6 in the brain of embryonic, newborn, and adult mice. *Brain Struct. Funct.,* **2013**, *218*(2), 353-372. http://dx.doi.org/10.1007/s00429-012-0397-2 PMID: 22354470

[377] Kroll, T.T.; O'Leary, D.D.M. Ventralized dorsal telencephalic progenitors in Pax6 mutant mice generate GABA interneurons of a lateral ganglionic eminence fate. *Proc. Natl. Acad. Sci.,* **2005**, *102*(20), 7374-7379. http://dx.doi.org/10.1073/pnas.0500819102 PMID: 15878992

[378] Sansom, S.N.; Griffiths, D.S.; Faedo, A.; Kleinjan, D.J.; Ruan, Y.; Smith, J. The level of the transcription factor Pax6 is essential for controlling the balance between neural stem cell self-renewal and neurogenesis. *PLoS Genet.,* **2009**, *5*(6), e1000511. http://dx.doi.org/10.1371/journal.pgen.1000511

[379] Yuan, X.; Dai, M.; Xu, D. TERT promoter mutations and GABP transcription factors in carcinogenesis: More foes than friends. *Cancer Lett.,* **2020**, *493*, 1-9. http://dx.doi.org/10.1016/j.canlet.2020.07.003 PMID: 32768523

[380] Tan, Y.; Xue, Y.; Song, C.; Grunstein, M. Acetylated histone H3K56 interacts with Oct4 to promote mouse embryonic stem cell pluripotency. *Proc. Natl. Acad. Sci.,* **2013**, *110*(28), 11493-11498. http://dx.doi.org/10.1073/pnas.1309914110 PMID: 23798425

[381] Ye, F.; Chen, Y.; Hoang, T.; Montgomery, R.L.; Zhao, X.; Bu, H.; Hu, T.; Taketo, M.M.; van Es, J.H.; Clevers, H.; Hsieh, J.; Bassel-Duby, R.; Olson, E.N.; Lu, Q.R. HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the β-catenin-TCF interaction. *Nat. Neurosci.,* **2009**, *12*(7), 829-838. http://dx.doi.org/10.1038/nn.2333 PMID: 19503085

[382] Jamadagni, P.; Breuer, M.; Schmeisser, K.; Cardinal, T.; Kassa, B.; Parker, J.A.; Pilon, N.; Samarut, E.; Patten, S.A. Chromatin remodeller CHD7 is required for GABAergic neuron development by promoting PAQR3 expression. *EMBO Rep.,* **2021**, *22*(6), e50958. http://dx.doi.org/10.15252/embr.202050958 PMID: 33900016

[383] Mello, M.L.S. Sodium Valproate-Induced Chromatin Remodeling. *Front. Cell Dev. Biol.,* **2021**, *9*, 645518. http://dx.doi.org/10.3389/fcell.2021.645518 PMID: 33959607

[384] Simonini, M.V.; Camargo, L.M.; Dong, E.; Maloku, E.; Veldic, M.; Costa, E.; Guidotti, A. The benzamide MS-275 is a potent, long-lasting brain region-selective inhibitor of histone deacetylases. *Proc. Natl. Acad. Sci.,* **2006**, *103*(5), 1587-1592. http://dx.doi.org/10.1073/pnas.0510341103 PMID: 16432198

[385] Dong, E.; Guidotti, A.; Grayson, D.R.; Costa, E. Histone hyperacetylation induces demethylation of reelin and 67-kDa glutamic acid decarboxylase promoters. *Proc. Natl. Acad. Sci.,* **2007**, *104*(11), 4676-4681. http://dx.doi.org/10.1073/pnas.0700529104 PMID: 17360583

[386] Tremolizzo, L.; Carboni, G.; Ruzicka, W.B.; Mitchell, C.P.; Sugaya, I.; Tueting, P.; Sharma, R.; Grayson, D.R.; Costa, E.; Guidotti, A. An epigenetic mouse model for molecular and behavioral neuropathologies related to schizophrenia vulnerability. *Proc. Natl. Acad. Sci.,* **2002**, *99*(26), 17095-17100. http://dx.doi.org/10.1073/pnas.262658999 PMID: 12481028

[387] Rocha, M.A.; Veronezi, G.M.B.; Felisbino, M.B.; Gatti, M.S.V.; Tamashiro, W.M.S.C.; Mello, M.L.S. Sodium valproate and 5-aza-2′-deoxycytidine differentially modulate DNA demethylation in G1 phase-arrested and proliferative HeLa cells. *Sci. Rep.,* **2019**, *9*(1), 18236. http://dx.doi.org/10.1038/s41598-019-54848-x PMID: 31796828

[388] Marchion, D.C.; Bicaku, E.; Daud, A.I.; Sullivan, D.M.; Munster, P.N. Valproic acid alters chromatin structure by regulation of chromatin modulation proteins. *Cancer Res.,* **2005**, *65*(9), 3815-3822. http://dx.doi.org/10.1158/0008-5472.CAN-04-2478 PMID: 15867379

[389] Palsamy, P.; Bidasee, K.R.; Shinohara, T. Valproic acid suppresses Nrf2/Keap1 dependent antioxidant protection through induction of endoplasmic reticulum stress and Keap1 promoter DNA demethylation in human lens epithelial cells. *Exp. Eye Res.,* **2014**, *121*, 26-34. http://dx.doi.org/10.1016/j.exer.2014.01.021 PMID: 24525405

[390] Detich, N.; Bovenzi, V.; Szyf, M. Valproate induces replication-independent active DNA demethylation. *J. Biol. Chem.,* **2003**, *278*(30), 27586-27592. http://dx.doi.org/10.1074/jbc.M303740200 PMID: 12748177

[391] Milutinovic, S.; D'Alessio, A.C.; Detich, N.; Szyf, M. Valproate induces widespread epigenetic reprogramming which involves demethylation of specific genes. *Carcinogenesis,* **2007**, *28*(3), 560-571. http://dx.doi.org/10.1093/carcin/bgl167 PMID: 17012225

[392] Dong, E.; Chen, Y.; Gavin, D.P.; Grayson, D.R.; Guidotti, A. Valproate induces DNA demethylation in nuclear extracts from adult mouse brain. *Epigenetics,* **2010**, *5*(8), 730-735. http://dx.doi.org/10.4161/epi.5.8.13053 PMID: 20716949

[393] Tan, N.N.; Tang, H.L.; Lin, G.W.; Chen, Y.H.; Lu, P.; Li, H.J.; Gao, M.M.; Zhao, Q.H.; Yi, Y.H.; Liao, W.P.; Long, Y.S. Epigenetic downregulation of scn3a expression by valproate: A possible role in its anticonvulsant activity. *Mol. Neurobiol.,* **2017**, *54*(4), 2831-2842. http://dx.doi.org/10.1007/s12035-016-9871-9 PMID: 27013471

[394] Park, J.; Lee, K.; Kim, K.; Yi, S.J. The role of histone modifications: From neurodevelopment to neurodiseases. *Signal Transduct. Target. Ther.,* **2022**, *7*(1), 217. http://dx.doi.org/10.1038/s41392-022-01078-9 PMID: 35794091

[395] Göttlicher, M.; Minucci, S.; Zhu, P.; Krämer, O.H.; Schimpf, A.; Giavara, S.; Sleeman, J.P.; Lo Coco, F.; Nervi, C.; Pelicci, P.G.; Heinzel, T. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J.,* **2001**, *20*(24), 6969-6978. http://dx.doi.org/10.1093/emboj/20.24.6969 PMID: 11742974

[396] Emmett, M.J.; Lazar, M.A. Integrative regulation of physiology by histone deacetylase 3. *Nat. Rev. Mol. Cell Biol.,* **2019**, *20*(2), 102-115. http://dx.doi.org/10.1038/s41580-018-0076-0 PMID: 30390028

[397] Hayakawa, T.; Nakayama, J. Physiological roles of class I HDAC complex and histone demethylase. *J. Biomed. Biotechnol.,* **2011**, *2011*, 1-10. http://dx.doi.org/10.1155/2011/129383

[398] Mello, M.L.S.; Rocha, M.A.; de Campos, V.B. Sodium valproate modulates the methylation status of lysine residues 4, 9 and 27 in histone H3 of HeLa cells. *Curr. Mol. Pharmacol.,* **2023**, *16*(2), 197-210. http://dx.doi.org/10.2174/1874467215666220316110405 PMID: 35297358

[399] Marinova, Z.; Leng, Y.; Leeds, P.; Chuang, D.M. Histone deacetylase inhibition alters histone methylation associated with heat shock protein 70 promoter modifications in astrocytes and neurons. *Neuropharmacology,* **2011**, *60*(7-8), 1109-1115. http://dx.doi.org/10.1016/j.neuropharm.2010.09.022 PMID: 20888352

[400] Nightingale, K.P.; Gendreizig, S.; White, D.A.; Bradbury, C.; Hollfelder, F.; Turner, B.M. Cross-talk between histone modifications in response to histone deacetylase inhibitors: MLL4 links histone H3 acetylation and histone H3K4 methylation. *J. Biol. Chem.,* **2007**, *282*(7), 4408-4416. http://dx.doi.org/10.1074/jbc.M606773200 PMID: 17166833

[401] Rahhal, R.; Seto, E. Emerging roles of histone modifications and HDACs in RNA splicing. *Nucleic Acids Res.,* **2019**, *47*(10), 4911-4926. http://dx.doi.org/10.1093/nar/gkz292 PMID: 31162605

[402] Hnilicová, J.; Hozeifi, S.; Dušková, E.; Icha, J.; Tománková, T.; Staněk, D. Histone deacetylase activity modulates alternative splicing. *PLoS One.,* **2011**, *6*(2), e16727. http://dx.doi.org/10.1371/journal.pone.0016727

[403] Su, C.H.; D, D.; Tarn, W.Y. Alternative splicing in neurogenesis and brain development. *Front. Mol. Biosci.,* **2018**, *5*, 12. http://dx.doi.org/10.3389/fmolb.2018.00012 PMID: 29484299

[404] Engal, E.; Baker, M.; Salton, M. The chromatin roots of abnormal splicing in autism. *Trends Genet.,* **2022**, *38*(9), 892-894. http://dx.doi.org/10.1016/j.tig.2022.06.001 PMID: 35750536

[405] Sun, W.; Poschmann, J.; Cruz-Herrera del Rosario, R.; Parikshak, N.N.; Hajan, H.S.; Kumar, V.; Ramasamy, R.; Belgard, T.G.; Elanggovan, B.; Wong, C.C.Y.; Mill, J.; Geschwind, D.H.; Prabhakar, S. Histone acetylome-wide association study of autism spectrum disorder. *Cell,* **2016**, *167*(5), 1385-1397.e11. http://dx.doi.org/10.1016/j.cell.2016.10.031 PMID: 27863250

[406] Elgamal, M.; Moustafa, Y.; Ali, A.; El-Sayed, N.; Khodeer, D. Mechanisms of valproic acid-induced autism: Canonical wnt-β-

catenin pathway. *Records of Pharmaceutical and Biomedical Sciences,* **2023**, *7*(3), 51-62.
http://dx.doi.org/10.21608/rpbs.2023.189540.1205

[407] Mulligan, K.A.; Cheyette, B.N.R. Wnt signaling in vertebrate neural development and function. *J. Neuroimmune Pharmacol.,* **2012**, *7*(4), 774-787.
http://dx.doi.org/10.1007/s11481-012-9404-x PMID: 23015196

[408] Rosso, S.B.; Inestrosa, N.C. WNT signaling in neuronal maturation and synaptogenesis. *Front. Cell. Neurosci.,* **2013**, *7*, 103.
http://dx.doi.org/10.3389/fncel.2013.00103 PMID: 23847469

[409] Kwan, V.; Unda, B.K.; Singh, K.K. Wnt signaling networks in autism spectrum disorder and intellectual disability. *J. Neurodev. Disord.,* **2016**, *8*(1), 45.
http://dx.doi.org/10.1186/s11689-016-9176-3 PMID: 27980692

[410] Phiel, C.J.; Zhang, F.; Huang, E.Y.; Guenther, M.G.; Lazar, M.A.; Klein, P.S. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J. Biol. Chem.,* **2001**, *276*(39), 36734-36741.
http://dx.doi.org/10.1074/jbc.M101287200 PMID: 11473107

[411] Takai, N.; Desmond, J.C.; Kumagai, T.; Gui, D.; Said, J.W.; Whittaker, S.; Miyakawa, I.; Koeffler, H.P. Histone deacetylase inhibitors have a profound antigrowth activity in endometrial cancer cells. *Clin. Cancer Res.,* **2004**, *10*(3), 1141-1149.
http://dx.doi.org/10.1158/1078-0432.CCR-03-0100 PMID: 14871994

[412] Digel, W.; Lübbert, M. DNA methylation disturbances as novel therapeutic target in lung cancer: Preclinical and clinical results. *Crit. Rev. Oncol. Hematol.,* **2005**, *55*(1), 1-11.
http://dx.doi.org/10.1016/j.critrevonc.2005.02.002 PMID: 15886007

[413] Nie, X.; Liu, H.; Liu, L.; Wang, Y.D.; Chen, W.D. Emerging roles of Wnt ligands in human colorectal cancer. *Front. Oncol.,* **2020**, *10*, 1341.
http://dx.doi.org/10.3389/fonc.2020.01341 PMID: 32923386

[414] Kumar, S.; Reynolds, K.; Ji, Y.; Gu, R.; Rai, S.; Zhou, C.J. Impaired neurodevelopmental pathways in autism spectrum disorder: A review of signaling mechanisms and crosstalk. *J. Neurodev. Disord.,* **2019**, *11*(1), 10.
http://dx.doi.org/10.1186/s11689-019-9268-y PMID: 31202261

[415] Martin, P-M.; Yang, X.; Robin, N.; Lam, E.; Rabinowitz, J.S.; Erdman, C.A.; Quinn, J.; Weiss, L.A.; Hamilton, S.P.; Kwok, P-Y.; Moon, R.T.; Cheyette, B.N.R. A rare WNT1 missense variant overrepresented in ASD leads to increased Wnt signal pathway activation. *Transl. Psychiatry,* **2013**, *3*(9), e301-e301.
http://dx.doi.org/10.1038/tp.2013.75 PMID: 24002087

[416] Wassink, T.H.; Piven, J.; Vieland, V.J.; Huang, J.; Swiderski, R.E.; Pietila, J.; Braun, T.; Beck, G.; Folstein, S.E.; Haines, J.L.; Sheffield, V.C. Evidence supporting WNT2 as an autism susceptibility gene. *Am. J. Med. Genet.,* **2001**, *105*(5), 406-413.
http://dx.doi.org/10.1002/ajmg.1401 PMID: 11449391

[417] Marui, T.; Funatogawa, I.; Koishi, S.; Yamamoto, K.; Matsumoto, H.; Hashimoto, O.; Jinde, S.; Nishida, H.; Sugiyama, T.; Kasai, K.; Watanabe, K.; Kano, Y.; Kato, N. Association between autism and variants in the wingless-type MMTV integration site family member 2 (WNT2) gene. *Int. J. Neuropsychopharmacol.,* **2010**, *13*(4), 443-449.
http://dx.doi.org/10.1017/S1461145709990903 PMID: 19895723

[418] Levy, D.; Ronemus, M.; Yamrom, B.; Lee, Y.; Leotta, A.; Kendall, J.; Marks, S.; Lakshmi, B.; Pai, D.; Ye, K.; Buja, A.; Krieger, A.; Yoon, S.; Troge, J.; Rodgers, L.; Iossifov, I.; Wigler, M. Rare *de novo* and transmitted copy-number variation in autistic spectrum disorders. *Neuron,* **2011**, *70*(5), 886-897.
http://dx.doi.org/10.1016/j.neuron.2011.05.015 PMID: 21658582

[419] Lin, P.I.; Chien, Y.L.; Wu, Y.Y.; Chen, C.H.; Gau, S.S.F.; Huang, Y.S.; Liu, S.K.; Tsai, W.C.; Chiu, Y.N. The WNT2 gene polymorphism associated with speech delay inherent to autism. *Res. Dev. Disabil.,* **2012**, *33*(5), 1533-1540.
http://dx.doi.org/10.1016/j.ridd.2012.03.004 PMID: 22522212

[420] Krumm, N.; O'Roak, B.J.; Shendure, J.; Eichler, E.E. A *de novo* convergence of autism genetics and molecular neuroscience. *Trends Neurosci.,* **2014**, *37*(2), 95-105.
http://dx.doi.org/10.1016/j.tins.2013.11.005 PMID: 24387789

[421] Platt, R.J.; Zhou, Y.; Slaymaker, I.M.; Shetty, A.S.; Weisbach, N.R.; Kim, J.A.; Sharma, J.; Desai, M.; Sood, S.; Kempton, H.R.; Crabtree, G.R.; Feng, G.; Zhang, F. Chd8 mutation leads to autistic-like behaviors and impaired striatal circuits. *Cell Rep.,* **2017**, *19*(2), 335-350.
http://dx.doi.org/10.1016/j.celrep.2017.03.052 PMID: 28402856

[422] Thompson, B.A.; Tremblay, V.; Lin, G.; Bochar, D.A. CHD8 is an ATP-dependent chromatin remodeling factor that regulates β-catenin target genes. *Mol. Cell. Biol.,* **2008**, *28*(12), 3894-3904.
http://dx.doi.org/10.1128/MCB.00322-08 PMID: 18378692

[423] McBride, K.L.; Varga, E.A.; Pastore, M.T.; Prior, T.W.; Manickam, K.; Atkin, J.F.; Herman, G.E. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Res.,* **2010**, *3*(3), 137-141.
http://dx.doi.org/10.1002/aur.132 PMID: 20533527

[424] Zhou, T.; He, X.; Cheng, R.; Zhang, B.; Zhang, R.R.; Chen, Y.; Takahashi, Y.; Murray, A.R.; Lee, K.; Gao, G.; Ma, J. Implication of dysregulation of the canonical wingless-type MMTV integration site (WNT) pathway in diabetic nephropathy. *Diabetologia,* **2012**, *55*(1), 255-266.
http://dx.doi.org/10.1007/s00125-011-2314-2 PMID: 22016045

[425] DeSpenza, T., Jr; Carlson, M.; Panchagnula, S.; Robert, S.; Duy, P.Q.; Mermin-Bunnell, N.; Reeves, B.C.; Kundishora, A.; Elsamadicy, A.A.; Smith, H.; Ocken, J.; Alper, S.L.; Jin, S.C.; Hoffman, E.J.; Kahle, K.T. PTEN mutations in autism spectrum disorder and congenital hydrocephalus: developmental pleiotropy and therapeutic targets. *Trends Neurosci.,* **2021**, *44*(12), 961-976.
http://dx.doi.org/10.1016/j.tins.2021.08.007 PMID: 34625286

[426] Mahmood, U.; Ahn, S.; Yang, E.J.; Choi, M.; Kim, H.; Regan, P.; Cho, K.; Kim, H.S. Dendritic spine anomalies and PTEN alterations in a mouse model of VPA-induced autism spectrum disorder. *Pharmacol. Res.,* **2018**, *128*, 110-121.
http://dx.doi.org/10.1016/j.phrs.2017.08.006 PMID: 28823725

[427] Nicolini, C.; Ahn, Y.; Michalski, B.; Rho, J.M.; Fahnestock, M. Decreased mTOR signaling pathway in human idiopathic autism and in rats exposed to valproic acid. *Acta Neuropathol. Commun.,* **2015**, *3*(1), 3.
http://dx.doi.org/10.1186/s40478-015-0184-4 PMID: 25627160

[428] Yang, E.J.; Ahn, S.; Lee, K.; Mahmood, U.; Kim, H.S. Early behavioral abnormalities and perinatal alterations of PTEN/AKT pathway in valproic acid autism model mice. *PLoS One,* **2016**, *11*(4), e0153298.
http://dx.doi.org/10.1371/journal.pone.0153298 PMID: 27071011

[429] Barrett, C.E.; Hennessey, T.M.; Gordon, K.M.; Ryan, S.J.; McNair, M.L.; Ressler, K.J.; Rainnie, D.G. Developmental disruption of amygdala transcriptome and socioemotional behavior in rats exposed to valproic acid prenatally. *Mol. Autism,* **2017**, *8*(1), 42.
http://dx.doi.org/10.1186/s13229-017-0160-x PMID: 28775827

[430] Tung, E.W.Y.; Winn, L.M. Valproic acid increases formation of reactive oxygen species and induces apoptosis in postimplantation embryos: A role for oxidative stress in valproic acid-induced neural tube defects. *Mol. Pharmacol.,* **2011**, *80*(6), 979-987.
http://dx.doi.org/10.1124/mol.111.072314 PMID: 21868484

[431] Sztainberg, Y.; Zoghbi, H.Y. Lessons learned from studying syndromic autism spectrum disorders. *Nat. Neurosci.,* **2016**, *19*(11), 1408-1417.
http://dx.doi.org/10.1038/nn.4420 PMID: 27786181

[432] Varghese, M; Keshav, N; Jacot-Descombes, S; Warda, T; Wicinski, B; Dickstein, DL Autism spectrum disorder: Neuropathology and animal models. *Acta Neuropathol.,* **2017**, *134*(4), 537-566.
http://dx.doi.org/10.1007/s00401-017-1736-4

[433] Kim, K.C.; Gonzales, E.L.; Lázaro, M.T.; Choi, C.S.; Bahn, G.H.; Yoo, H.J.; Shin, C.Y. Clinical and neurobiological relevance of current animal models of autism spectrum disorders. *Biomol. Ther.,* **2016**, *24*(3), 207-243.
http://dx.doi.org/10.4062/biomolther.2016.061 PMID: 27133257

[434] Feil, R.; Fraga, M.F. Epigenetics and the environment: Emerging patterns and implications. *Nat. Rev. Genet.,* **2012**, *13*(2), 97-109.
http://dx.doi.org/10.1038/nrg3142 PMID: 22215131

[435] Good, K.V.; Vincent, J.B.; Ausió, J. MeCP2: The genetic driver of rett syndrome epigenetics. *Front. Genet.,* **2021**, *12*, 620859.
http://dx.doi.org/10.3389/fgene.2021.620859 PMID: 33552148

[436] Loke, Y.J.; Hannan, A.J.; Craig, J.M. The role of epigenetic change in autism spectrum disorders. *Front. Neurol.,* **2015**, *6*, 107.
http://dx.doi.org/10.3389/fneur.2015.00107 PMID: 26074864

[437] Balan, S.; Iwayama, Y.; Ohnishi, T.; Fukuda, M.; Shirai, A.; Yamada, A.; Weirich, S.; Schuhmacher, M.K.; Dileep, K.V.; Endo, T.; Hisano, Y.; Kotoshiba, K.; Toyota, T.; Otowa, T.; Kuwabara, H.; Tochigi, M.; Watanabe, A.; Ohba, H.; Maekawa, M.; Toyoshima, M.; Sasaki, T.; Nakamura, K.; Tsujii, M.; Matsuzaki, H.; Zhang, K.Y.J.; Jeltsch, A.; Shinkai, Y.; Yoshikawa, T. A loss-of-function variant in SUV39H2 identified in autism-spectrum disorder causes altered H3K9 trimethylation and dysregulation of protocadherin β-cluster genes in the developing brain. *Mol. Psychiatry,* **2021**, *26*(12), 7550-7559.
http://dx.doi.org/10.1038/s41380-021-01199-7 PMID: 34262135

[438] Balemans, M.C.M.; Huibers, M.M.H.; Eikelenboom, N.W.D.; Kuipers, A.J.; van Summeren, R.C.J.; Pijpers, M.M.C.A.; Tachibana, M.; Shinkai, Y.; van Bokhoven, H.; Van der Zee, C.E.E.M. Reduced exploration, increased anxiety, and altered social behavior: Autistic-like features of euchromatin histone methyltransferase 1 heterozygous knockout mice. *Behav. Brain Res.,* **2010**, *208*(1), 47-55.
http://dx.doi.org/10.1016/j.bbr.2009.11.008 PMID: 19896504

[439] Chen, E.S.; Gigek, C.O.; Rosenfeld, J.A.; Diallo, A.B.; Maussion, G.; Chen, G.G.; Vaillancourt, K.; Lopez, J.P.; Crapper, L.; Poujol, R.; Shaffer, L.G.; Bourque, G.; Ernst, C. Molecular convergence of neurodevelopmental disorders. *Am. J. Hum. Genet.,* **2014**, *95*(5), 490-508.
http://dx.doi.org/10.1016/j.ajhg.2014.09.013 PMID: 25307298

[440] Lin, C.W.; Septyaningtrias, D.E.; Chao, H.W.; Konda, M.; Atarashi, K.; Takeshita, K.; Tamada, K.; Nomura, J.; Sasagawa, Y.; Tanaka, K.; Nikaido, I.; Honda, K.; McHugh, T.J.; Takumi, T. A common epigenetic mechanism across different cellular origins underlies systemic immune dysregulation in an idiopathic autism mouse model. *Mol. Psychiatry,* **2022**, *27*(8), 3343-3354.
http://dx.doi.org/10.1038/s41380-022-01566-y PMID: 35491410

[441] Lin, C.W.; Ellegood, J.; Tamada, K.; Miura, I.; Konda, M.; Takeshita, K. An old model with new insights: Endogenous retroviruses drive the evolvement toward ASD susceptibility and hijack transcription machinery during development. *Mol. Psychiatry.,* **2023**. (Epub a head of print).
http://dx.doi.org/10.1038/s41380-023-01999-z

[442] Tseng, C.E.J.; McDougle, C.J.; Hooker, J.M.; Zürcher, N.R. Epigenetics of autism spectrum disorder: Histone deacetylases. *Biol. Psychiatry,* **2022**, *91*(11), 922-933.
http://dx.doi.org/10.1016/j.biopsych.2021.11.021 PMID: 35120709

[443] Cao, D.D.; Li, L.; Chan, W.Y. MicroRNAs: Key regulators in the central nervous system and their implication in neurological diseases. *Int. J. Mol. Sci.,* **2016**, *17*(6), 842.
http://dx.doi.org/10.3390/ijms17060842 PMID: 27240359

[444] Pejhan, S.; Del Bigio, M.R.; Rastegar, M. The MeCP2E1/E2-BDNF-*miR132* homeostasis regulatory network is region-dependent in the human brain and is impaired in rett syndrome patients. *Front. Cell Dev. Biol.,* **2020**, *8*, 763.
http://dx.doi.org/10.3389/fcell.2020.00763 PMID: 32974336

[445] Brown, E.A.; Lautz, J.D.; Davis, T.R.; Gniffke, E.P.; VanSchoiack, A.A.W.; Neier, S.C.; Tashbook, N.; Nicolini, C.; Fahnestock, M.; Schrum, A.G.; Smith, S.E.P. Clustering the autisms using glutamate synapse protein interaction networks from cortical and hippocampal tissue of seven mouse models. *Mol. Autism,* **2018**, *9*(1), 48.
http://dx.doi.org/10.1186/s13229-018-0229-1 PMID: 30237867

[446] Arakawa, H. From multisensory assessment to functional interpretation of social behavioral phenotype in transgenic mouse models for autism spectrum disorders. *Front. Psychiatry,* **2020**, *11*, 592408.
http://dx.doi.org/10.3389/fpsyt.2020.592408 PMID: 33329141

[447] Puścian, A.; Lęski, S.; Górkiewicz, T.; Meyza, K.; Lipp, H.P.; Knapska, E. A novel automated behavioral test battery assessing cognitive rigidity in two genetic mouse models of autism. *Front. Behav. Neurosci.,* **2014**, *8*, 140.
PMID: 24808839

[448] Jabarin, R.; Netser, S.; Wagner, S. Beyond the three-chamber test: Toward a multimodal and objective assessment of social behavior in rodents. *Mol. Autism,* **2022**, *13*(1), 41.
http://dx.doi.org/10.1186/s13229-022-00521-6 PMID: 36284353

[449] Argyropoulos, A.; Gilby, K.L.; Hill-Yardin, E.L. Studying autism in rodent models: reconciling endophenotypes with comorbidities. *Front. Hum. Neurosci.,* **2013**, *7*, 417.
http://dx.doi.org/10.3389/fnhum.2013.00417 PMID: 23898259

[450] Das, I.; Estevez, M.A.; Sarkar, A.A.; Banerjee-Basu, S. A multifaceted approach for analyzing complex phenotypic data in rodent models of autism. *Mol. Autism,* **2019**, *10*(1), 11.
http://dx.doi.org/10.1186/s13229-019-0263-7 PMID: 30911366

[451] Halsall, J.A.; Turan, N.; Wiersma, M.; Turner, B.M. Cells adapt to the epigenomic disruption caused by histone deacetylase inhibitors through a coordinated, chromatin-mediated transcriptional response. *Epigenetics Chromatin,* **2015**, *8*(1), 29.
http://dx.doi.org/10.1186/s13072-015-0021-9 PMID: 26380582

[452] Schaaf, C.P.; Zoghbi, H.Y. Solving the autism puzzle a few pieces at a time. *Neuron,* **2011**, *70*(5), 806-808.
http://dx.doi.org/10.1016/j.neuron.2011.05.025 PMID: 21658575