Send Orders for Reprints to reprints@benthamscience.net

168 *Current Neuropharmacology,* **2020**, *18,* **168-187**

REVIEW ARTICLE

An Overview of the Heterogeneity of Major Depressive Disorder: Current Knowledge and Future Prospective

Kaipuzha Venu Athira[1,2,4], Sikta Bandopadhyay[2], Pavan Kumar Samudrala[1], V.G.M. Naidu[1], Mangala Lahkar[3] and Sumana Chakravarty[2,*]

[1]*Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Guwahati, 781125, Assam, India;* [2]*Applied Biology Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Uppal Road, Hyderabad 500007, India;* [3]*Department of Pharmacology, Gauhati Medical College, Guwahati, 781032, Assam, India;* [4]*Department of Pharmacology, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi, 682 041, Kerala, India*

ARTICLE HISTORY

Received: January 21, 2019
Revised: August 05, 2019
Accepted: September 27, 2019

DOI:
10.2174/1570159X17666191001142934

Abstract: Major depressive disorder (MDD) is estimated to impose maximum debilitating effects on the society by 2030, with its critical effects on health, functioning, quality of life and concomitant high levels of morbidity and mortality. Yet, the disease is inadequately understood, diagnosed and treated. Moreover, with the recent drastic rise in the pace of life, stress has materialized as one of the most potent environmental factors for depression. In this scenario, it is important to understand the modern pathogenetic hypotheses and mechanisms, and possibly try to shift from the traditional approaches in depression therapy. These include the elaboration of pathophysiological changes in heterogeneous systems such as genetic, epigenetic, serotonergic, noradrenergic, gamma-aminobutyric acid, glutamatergic and endocannabinoid systems, neurotrophic factors, HPA axis, immune system as well as cellular stress mechanisms. These components interact with each other in a complex matrix and further elucidation of their mechanism and cascade pathways are needed. This might aid in the identification of MDD subtypes as well as the development of sophisticated biomarkers. Further, characterization might also aid in developing multitargeted therapies that hold much promise as compared to the conventional monoamine based treatment. New candidate pharmacons, refined psychotherapeutic modalities, advanced neuro-surgical and imaging techniques as well as the implementation of pharmacokinetic, pharmacogenetic prescribing guidelines constitute the emerging expanses of MDD treatment.

Keywords: Stress, MDD, neurotransmitter, neurotrophic factor, hypothalamic-pituitary-adrenal axis, immune system, genetics, epigenetics.

1. INTRODUCTION

Depression is a disease that imposes a severe burden on the global population with a lifetime risk close to 15% [1]. Around 350 million people are estimated to be affected [2], with women twice diagnosed as compared to men [3, 4]. With its critical effects on the quality of day to day functioning [5], major depressive disorder (MDD) is set to create a greater societal and economic burden worldwide by 2030 [6]. Whereas the existing armamentarium of antidepressants contains numerous and widely used agents, the morbidity and mortality continue to increase, especially from suicide [7]. Even the effectiveness of serotonin and noradrenaline reuptake inhibitors (SSRI and SNRI, respectively) - the frontline class of antidepressant treatment, are delimited by the lower success rate; 30% of depressed patients are pharmacoresistant [8, 9]. Moreover, in depression, the path to successful treatment has to overcome hurdles like delayed onset of effectiveness and undesirable side effects of therapeutic agents (such as gastrointestinal symptoms, agitation, sleep and weight changes, and sexual dysfunction) [10, 11], along with the episodic course, with complete remission, and a recurrent course, with short periods of remission between episodes as well as progression to chronic form of depression that is resistant to treatment [6]. The risk of recurrence is partly associated with neurobiological vulnerabilities [12] and is higher with younger age and if there is a family history of depression [13]. Even untreated gestational depression, as well as depressive symptoms during pregnancy, can have detrimental effects on the developing fetus [14]. Thus, there is a need to develop sophisticated clinical markers along with better tolerated and effective pharmacotherapeutics for the timely diagnosis, prognosis and treatment of de-

*Address correspondence to this author at the Applied Biology Division, CSIR- Indian Institute of Chemical Technology (IICT), Tarnaka, Hyderabad-500 007 (A.P.); Tel: +91 040 27191856; Fax: 040 27193189;
E-mails: sumanachak@iict.res.in; sumana98@gmail.com

1570-159X/20 $65.00+.00

pression. This can be achieved only through a study of the mechanisms and pathogenesis of MDD.

2. THE PATHOGENESIS OF DEPRESSION

The term "depression" was first associated with the condition of low spirits by Samuel Johnson in the 1750s [15]. Through the years, numerous theories varying in scope were put forward and have eventually emerged with an environmental, social and evolutionary perspective according to which depression could be considered an evolutionary adaptation to deleterious social environment [16, 17]. Evidently, with the recent drastic rise in the pace of life, stress has become one of the most potent environmental factors for depression. In a healthy individual, a stress response is a homeostatic mechanism that aids optimum physiological and psychological functioning. When there are repeated stressor events, the individual gets affected through the unresolvable personal despair caused by the accumulation of psychological and physical demands, known as allostatic load [18]. The resulting induction of pathogenetic mechanisms is considered to disrupt the body's internal homeostasis [6]. It is well understood that the neuropsychological aspect of allostasis is maintained by the mediators comprising of the autonomic nervous system, neuroendocrine system, immune system and the associated elements such as catecholamines, hormones and inflammatory mediators [6, 19]. Further, the diathesis-stress model proposed that a genetically vulnerable individual might be more inclined towards the development of depression on exposure to stressful events in the course of life [20]. Incidents affecting nervous system development such as prenatal, postnatal or peri- adolescent events might also play a role [21-23].

Recently, Gold proposed depression as a dysregulation of the adaptive response, an innate mechanism that tries to restore the homeostatic level altered by chronic stress [24]. Gold added that MDD could spread in a metastatic mode from the brain to peripheral areas *via* activation of a stress system cascade. Eventually, it could progress to multiple systemic pathologies such as inflammation, prothrombotic state and insulin resistance, resulting in the development of co-morbid illnesses like coronary artery disease, osteoporosis and diabetes. On this basis, Gold suggested the application of multiple interventions at various loci to effectively treat depression, especially when there is a failure of existing medications [24].

Animal models of depression based on various forms of stress elicitation such as chronic mild stress [25, 26], learned helplessness [27], repeated social defeat stress [28-30], separation from group housing [31], social dominance/ subordination [32] and neonatal separation (early life stress model) [33, 34] corroborate with the above findings and are widely used for the evaluation of antidepressant candidates.

2.1. Environmental Effects on Genes and Epigenetic Interactions

While the heritability factor accounts for a $1/3^{rd}$ of the risk for developing MDD, environmental influence is purported to the remaining $2/3^{rd}$ [35, 36]. The gene-environment interactions could mediate catastrophic insults in the brain by altering structures including limbic and cortical brain areas, leading to functional abnormalities associated with alertness, arousal, behavior, thoughts, learning and memory. Epigenetic mechanisms, defined as chromatin changes capable of modifying gene expression without any modification in a DNA sequence, might be mediating these interactions. Recently, environmental events and behavioral experience have been reported to cause changes in various epigenetic markers, such as histone acetylation (*via* histone acetyltransferases and histone deacetylases (HDAC)) and methylation (*via* histone methyltransferases) as well as DNA methylation (*via* DNA methyltransferases) on specific gene loci controlling neuronal plasticity, thereby modulating the vulnerability or resilience to the development of MDD [36-39]. Exposure to various environmental factors can also modulate the expression and function of several miRNAs in the nervous system affecting adaptive mechanisms [40]. Epigenetic modifications in brain regions such as paraventricular nucleus (PVN) of the hypothalamus, prefrontal cortex, hippocampus, amygdala, nucleus accumbens, dorsal raphe, locus coeruleus and ventral tegmental area *via* experimental manipulations have been demonstrated to potently control stress responses, mood as well as antidepressant treatment response [37]. For instance, a significant increase in HDAC activity was reported in the nucleus accumbens of maternally deprived rats, which was found to be reversed by ketamine and imipramine treatment [41]. Moreover, epigenetic mechanisms might also be related to the individual differences in stress susceptibility, the intergenerational/transgenerational transmission of stress susceptibility, difference in psychiatric disease susceptibility between monozygotic twins as well as the difference in gender susceptibility to depression [42, 43], and the inconsistency in the genetic association studies of MDD [44]. Further, the genetic background can influence the consequence of chronic stress, which could be partially mediated by DNA sequence -directed alterations in epigenetic markers. In this regard, chronic mild stress was reported to induce depressive-like behavior in BALB/C mice, while C57BL/6 mice were not affected. The basis of such an observation was proposed to be the differences in methylation patterns at the glial cell-derived neurotrophic factor (GDNF) promoter [45]. Moreover, chronic administration of escitalopram in the Flinders Sensitive Line (FSL) genetic model of depression was reported to mediate antidepressant effects *via* epigenetic alterations in the P11 promoter region [46]. Another major revelation is the antidepressant potential of HDAC inhibitors [47], including sodium butyrate [48], trichostatin A [49], MS-275 [50] and vorinostat [51, 52]. Interestingly, the administration of HDAC inhibitors is reported to augment the effect of antidepressants, thus the combination is proposed as valuable for the treatment-resistant depression.

In the case of genome-wide association (GWA) studies, while, most of the studies were not successful in finding an association between susceptibility genes and MDD, a recent analysis has reported a strong association between MDD and 42 gene sets [53, 54]. These include proteins coding for known targets of antidepressant medications [55], clock gene to be one of them [56]. Moreover, genetic polymorphisms are reported in genes such as BMAL1 (ARNTL1), CLOCK, NPAS2, PER3, CRY1, RORA and TIMELESS [57-59], out of which only RORA has been supported in more powerful GWAS [60-62]. Chronic unpredictable stress-related

changes in the suprachiasmatic nucleus might be influenced by clock-stress interactions as reported from a transient decrease in Per2 amplitude [63, 64]. Others include apolipoprotein E (APOE ε2 and APOE ε4), guanine nucleotide-binding protein (GND3), methylenetetrahydrofolate reductase (MTHFR 677T), dopamine transporter (SLC6A3), the serotonin transporter (SLC6A4) and the dopamine receptor gene (DRD4), have been reported to have significant relationships with MDD [65, 66]. These findings indicate that genetic, as well as epigenetic characterization, is imperative in the understanding of depression neurobiology.

2.2. Biochemical and Physiological Alterations

Ever since early observations, the influence of depression has focused predominantly on the biochemical and physiological alterations. These include changes in the levels and functions of neurotransmitters, neuromodulators, neurotrophic factors, HPA axis components and immune molecules.

2.2.1. Neurotransmitters/neuromodulators

Repeated exposure to stressful stimuli is reported to elicit depression through modulation of neural excitability and neurotransmitter systems. Accordingly, psychopharmacology of depression has conventionally focused on neurotransmitters including 5-hydroxytryptamine (5-HT), noradrenaline, dopamine and acetylcholine [67-69]; their synthesis, intracellular trafficking, degradation, re-uptake and effect on both presynaptic and postsynaptic receptors [70]. Originally, it was a serendipitous discovery that found increasing monoamine concentration in the synapses which could attenuate depressive symptoms, thereby linking the deficiency of monoamines to the depression pathogenesis. In this line, pharmacological agents were developed, and thus the first generation antidepressants, monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA) came into use in the 1950s. Due to their limitations including low tolerance and toxicity, subsequently, SSRI, SNRI and atypical antidepressants were developed for better clinical application [71, 72].

2.2.1.1. Monoaminergic System

In fact, the monoaminergic hypothesis of depression is the most widely accepted one; predominantly, '5-HT hypothesis of depression' according to which a deficiency of the synaptic 5-HT concentration could result from increased degradation by MAO, or an increase in its reuptake [73, 74]. Indeed, alterations in postsynaptic 5-HT signaling in corticolimbic structures might be strongly associated with the vegetative, emotional, endocrine and cognitive aspects of MDD [75, 76]. Recently, P11 was shown to mediate antidepressant effects through the amplification of serotonergic signaling *via* regulation of 5-HT receptor trafficking and regulation of gene transcription *via* p11/annexin A2/ SMARCA3 [77]. However, 5-HT agonists do not work on all MDD patients [78]. Moreover, there is a delay in getting therapeutic benefits after initiation of treatment even though there is a rapid increase in extracellular 5-HT levels as well as the necessity of chronic treatment [79]. The deficiency of monoamines cannot be considered as the sole pathophysiology of MDD, as the same alone cannot precipitate a full MDD clinical phenotype, albeit the occurrence in cases with a previous history [18]. MDD may also be developed following a reduction in noradrenaline and dopamine production as well as increased cholinergic transduction [6]. Hence, it is imperative that studies should be explorative beyond the traditional hypotheses of monoamines in depression.

2.2.1.2. Dopaminergic System

The dopaminergic hypothesis of depression relates the disorder to a deficiency of extracellular dopamine levels, especially a dysfunction of dopaminergic neurotransmission within the mesolimbic system contributing to symptoms such as anhedonia, psychomotor retardation and loss of motivation [80, 81]. Further, the expression and function of the D_3 receptor, a dopamine receptor subtype located in pre-and postsynaptic membranes in brain areas regulating motivation and reward-related behavior, has also been reported to be downregulated in stress and depression [81, 82]. Moreover, the antidepressant effects of amineptine, bupropion and nomifensine were associated with selective inhibition of the dopaminergic uptake, suggesting the potential role of enhanced dopaminergic neurotransmission in the adaptive changes related to antidepressant activity [83-85]. Further, the antidepressant activity of aripiprazole and cariprazine might be mediated by their partial agonist activity at D_3 receptors [86-88]. Furthermore, chronic antidepressant treatments have been reported to potentiate dopaminergic transmission in the mesolimbic system, characterized by an increased motor response to dopamine D_2-like agonists [89]. Interestingly, dopaminergic neurotransmission is reported to be enhanced by other neural circuits [90]. For instance, the behavioral effects of antidepressant treatment could be mediated by serotonin-induced dopamine release as well as a brain-derived neurotrophic factor (BDNF) regulated expression of D_3 receptors in brain areas [91, 92]. Thus, enhancing dopaminergic function, especially targeting D_3 receptor might be a promising strategy to increase the therapeutic response in MDD [93].

2.2.1.3. Glutamate-GABA ergic System

Neurotransmission in the brain is regulated mostly by excitatory glutamate, then a relatively smaller inhibitory GABA component and a much smaller number of monoamine neurons [94]. As a corollary, both GABAergic deficit [95] and glutamate [94, 96] hypotheses were put forward to define the etiological sequel of MDD. GABAergic deficits in the brain contributing to MDD include the reduced concentration of GABA, altered function of GABAergic interneurons, changes in the levels and function of GABA receptors, along with alterations in changes in chloride homeostasis [97]. Whereas glutamate related changes involve malfunction in its release, clearance, metabolism, synaptic plasticity, postsynaptic receptor stimulation, intracellular signaling as well as associated changes in glial cell number and function [94]. Recent evidences suggest that monoamine-based antidepressant medications, as well as non-pharmacological interventions, might ultimately modify GABAergic and/or glutamatergic deficits also [24, 95]. While the conventional antidepressants take weeks or months, interestingly ketamine, a glutamate/N-methyl-D-aspartate (NMDA) receptor

antagonist was shown to reverse symptoms of depression within 2 h of administration in treatment-refractory patients [98]. This might be the most promising development in the arena of the discovery of fast-acting antidepressants lately. The rapid effects of ketamine may be related to the mammalian target of rapamycin (mTOR) signaling and brain-derived neurotrophic factor (BDNF) [99, 100]. GLYX-13, a glycine site NMDA receptor partial agonist has also shown fast onset antidepressant action in clinical trials [101]. Moreover, a recent mouse study clearly indicated that at the metabolic level as well as at the molecular level, the pathways of glutamate and GABA, were affected in depression, even with a correlation between related gene expression [30]. These findings propose that GABA/glutamatergic system are key mediators of psychiatric pathology, hence should be given more focus in the treatment of depression.

2.2.1.4. Endocannabinoid (eCB) Signaling System

The endocannabinoid signaling (ECS) system mediates long and short term synaptic plasticity and is involved in reward, fear, memory extinction and stress [102]. As all of these fundamental processes are dysregulated in MDD, ECS deserves distinctive attention. A reduction in the ECS along with biochemical and genetic changes in ECS members (the cannabinoid receptors types 1 and 2 (CB1 and CB2), endocannabinoids anandamide (N- arachidonoyl-ethanolamine, AEA) and 2- arachidonoylglycerol (2-AG) and enzymes for their degradation, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) could underlie the depressive disorder. In particular, reduced CB1R-mediated ECS reduces drive toward reward, increases anxiety and decreases extinction of aversive memories; therefore pharmacological blockade of CB1R signaling is reported to predispose humans to depression, particularly those with previous depressive episodes [72]. The neuronal subpopulations also express the CB1 receptors, such as the dorsal raphe nucleus [103], the locus coeruleus [104], GABAergic interneurons (high CB1 receptor levels) and glutamatergic neurons (relatively low CB1 receptor levels) [105] and may be associated with the psychotropic and non- psychotropic effects of CB1 receptor activation. Moreover, increased ECS is hypothesized to mimic the effects of conventional antidepressants to enhance serotonergic and noradrenergic signaling, maintain hedonia during chronic stress, suppress HPA axis hyperactivity and increase hippocampal BDNF expression and neurogenesis. Further, acute or chronic treatment with pharmacological agents that modulate cannabinoid receptors, endogenous cannabinoids, synthetic nonspecific CB1/CB2 receptor agonists, selective CB1 receptor agonists and agents that inhibit endocannabinoids deactivation or cellular reuptake are reported to elicit antidepressant-like effects [72, 102]. Notably, CB1 receptor ligands may cause unwanted psychotropic effects while CB2 receptor activation may be safer, yet the evidences are controversial to commend application. FAAH inhibitors may have fewer adverse effects than direct CB1R agonists. Further, transient receptor potential vanilloid 1 (TRPV1) channel was proposed as an additional ECS "player" in mood regulation as they are found co-localized with CB1 receptors in multiple brain areas. Recently, N-Arachidonoylserotonin, a dual blocker of FAAH/ TRPV1 was shown to reverse the stress-induced behavioral despair in rats through the normalization of the HPA axis dysregulation and in part with an elevation of anandamide levels [106]. Thus, studies have demonstrated that psychological and physiological stresses can induce changes in circulating endocannabinoids that are sensitive to the specifics of the stressor. The circulating endocannabinoids may be related to energy balance regulation, immune as well as endocrine responses to stress. For example, suppressed 2-AG could contribute to an increased inflammatory state seen in depression [102]. Further, endocannabinoids may be a mediator of the coincidence between cardiovascular morbidity and MDD [107]. Importantly, genetic polymorphisms in the ECS can confer resistance or vulnerability to depression. These data suggest that circulating endocannabinoids levels may be used in a personalized medicine approach to diagnose "low eCB" depression subtype that might be more amenable to ECS-mediated therapies [102].

2.2.2. Neurotrophic Factors

Postmortem brains from depressed patients revealed volumetric decreases characterized by decreased dendritic branching and spine density in neurons of the hippocampus along with subgenual and dorsolateral prefrontal cortex [108]. Studies have linked these alterations to the decrement in neurotrophic factors that regulate plasticity within the adult brain [109-111]. Neuroplasticity is a dynamic mechanism of the nervous system comprising of structural and functional components that enables its adaptation to environmental challenges *via* neuronal remodeling, especially across synapses. The neurotrophic factors include nerve growth factor (NGF), BDNF, neurotrophin (NT- 3 and NT-4/5), GDNF, Insulin-like Growth Factor (IGF), Vascular Growth Factor (VGF), Fibroblast Growth Factor (FGF) and S100 calcium-binding protein B (S100B) [112-114]. On interaction with their specific receptors, they mediate activation of various signaling pathways including phospholipase Cγ (PLCγ), phosphoinositide 3 kinase (PI3K)/Akt, tyrosine kinase and extracellular signal-regulated kinase (ERK) pathways, thereby regulating cell viability and synaptic functioning in the peripheral and central nervous systems (CNS) [112, 115-117]. A deficiency in these adaptive mechanisms of neuroplasticity might result in increased susceptibility to environmental challenges and resultant psychopathological effects [118]. These anti-neuroplastic changes include a reduction in proliferation of neural stem cells, neurotrophin levels, the survival of neuroblasts and immature neurons, spine density as well as damage in neurocircuitry, especially cortical-striatal-limbic circuits. There is increasing evidence of neurotrophic factor associated alterations including single nucleotide polymorphisms (SNPs) in different tissue samples, such as post- mortem brain tissue, cerebrospinal fluid, plasma, serum and buccal samples from patients with MDD [113, 119-121].

2.2.2.1. BDNF

Among the entire neurotrophin family, BDNF has emerged as a key mediator (giving rise to BDNF hypothesis of depression), not only because of its significant role in brain plasticity, but also of its role in the regulation of expression and secretion [122], defense against cell death induction [123] and maintenance of neural circuits [124]. Due

to the complexity in the genomic structure of BDNF, there exist distinct transcriptional, translational and post-translational regulatory mechanisms. Evidently, for a single BDNF protein, there are distinct mRNA transcripts [125]. These transcripts vary in their distribution as well as translation efficacy and are differentially regulated by stress and antidepressant treatments, resulting in contrasting functional effects [126]. BDNF promotes the survival of neurons in the CNS by binding to tyrosine kinase receptor B (TrkB) receptors [127]. Adult neurogenesis within the subgranular zone of the dentate gyrus of the hippocampus is instrumental in spatial learning [128], pattern discrimination [129], contextual memory and mood regulation [130] along with the recognition of stressors that are threatening [129]. While acute, mild, controllable stress is reported to induce neurogenesis [131]; prolonged uncontrollable stress causes depletion of BDNF, decreasing pattern recognition, thereby, compromising the capacity to deal with stressors and cognitive functioning.

Remarkably, antidepressant drug treatments, including serotonergic and non-serotonergic medications [132-134] as well as non-pharmacological interventions such as electroconvulsive shock [135], transcranial magnetic stimulation [136], and exercise [137, 138], have been reported to increase neurogenesis. Hence, it could be assumed that non-serotonergic pathways might also be associated with antidepressant-stimulated neurogenesis [18]. However, a recent 6-week placebo-controlled trial in MDD patients treated with transcranial direct current stimulation and sertraline (separately and combined), revealed an absence of significant change in plasma levels of NT-3, NT-4, NGF and GDNF even with significant improvement in depressive symptoms [139]. Moreover, blocking neurogenesis per se did not develop symptoms of depression [140]. Even hypotheses relating to depression vulnerability and an SNP in BDNF, causing an aminoacid substitution of valine (Val) to methionine (Met) at codon 66 (Val66Met) are met with contrasting observations [120, 126]. The discrepancies in the role of neurotrophic factors in MDD pathophysiology and antidepressant efficacy may be due to the methodological differences associated with different study models particularly due to varying sample size, disease subtypes, ethnicity, genetics, dosing schedules, scales of assessment, sampling time and sample source.

2.2.3. HPA Axis

Based on the conviction that early life trauma and repeated psychosocial stress are potent risk factors for depression; studies have identified that HPA axis dysregulation and concomitant rise in glucocorticoid (GC) and corticotropin-releasing hormone (CRH) levels along with the failure of dexamethasone suppression of GC and decrease in GC sensitivity, as the hallmark features of MDD [63]. Studies over the last 40 years have identified stress-responsive HPA axis dysregulation to be the most consistent biological mechanism, with the toxicity arising from excessive GC release [141, 142].

2.2.3.1. HPA axis/CRH System

Hippocampus predominantly governs the release of CRH and arginine-vasopressin (AVP) from the PVN of the hypothalamus. Amygdala, bed nucleus of the stria terminalis (BNST) and other brain stem nuclei also provide input to the CRH neurons in the PVN [143]. Stress activates this neural circuit to release CRH into the hypothalamohypophyseal portal system, where it binds to CRH receptors on corticotrophs in the anterior pituitary, to further promote the synthesis of proopiomelanocortin (POMC) and release its post-translation products that include adrenocorticotropic hormone (ACTH) [144, 145]. ACTH is also released by the action of AVP on the vasopressin 1b (V1b) receptor and this pathway is predominant during chronic stress [146, 147]. Chronic stress also promotes CRH-mediated activation of locus ceruleus and sympathomedullary system to release norepinephrine and epinephrine, which in turn activates the CRH release [24]. CRH acts to coordinate the neuroendocrine, immune, autonomic, behavioral and cognitive responses of mammals to stress [145]. ACTH, in turn, stimulates the production of GCs (cortisol in humans and corticosterone in rodents) from the adrenal cortex into the bloodstream [148]. Once inside the cell, GCs interact with their receptors, the mineralocorticoid receptor (MR, type 1) and the glucocorticoid receptor (GR; type 2), to mediate numerous functions in almost every tissue of the body. It is interesting to note that around 5% of the genome are targets for GCs [148]. Moreover, GR is extensively expressed in neurons and glia. As GR possesses a low affinity towards GCs, under normal physiological concentrations, GR is barely occupied but becomes activated when there is rise in GC levels such as during diurnal maximum, ultradian pulses or a stress response [149-151]. The activated GR, in turn, stimulates an inhibitory feedback to HPA axis through the fornix, the bundle of axons linking hippocampus to hypothalamus [24, 152]. The feedback inhibition occurs on the level of CRF, AVP and ACTH, thereby leading to reduction of HPA axis activity [152, 153]. This regulatory feedback loop and resultant HPA axis function are found disrupted in ~50% of patients with affective disorders [154]. A decrease in hippocampal activity along with an increase in amygdala activity may cause the dysregulation of this negative feedback mechanism of GCs [6]. Further, BNST may be involved in the regulation of the HPA axis as its anterior section mediates activation causing CORT release while the posterior section mediates inhibition of HPA axis activation *via* GABAergic projections to the paraventricular nucleus. The associated changes in depressed patients include a rise in cortisol levels in plasma, saliva and urine as well as increased size and activity of adrenals and pituitary [155, 156]. There are reports that MDD patients with psychotic features, particularly, show elevated HPA axis activity as compared to nonpsychotic depressives or healthy controls [156]. The clinical manifestations, however, can be differential, and on this basis, MDD is categorized into two distinct subtypes, melancholic and atypical depression. 31-62% of MDD cases are reported to be atypical [157]. Melancholic and atypical subtypes are considered to be the clinical antithesis of each other [24].

Repeated administration of corticosterone (CORT) to rodents has shown to model chronic stress associated HPA axis dysregulation and concomitant depressive-like behavior; so is increasingly being utilized to evaluate potential antidepressant candidates [52, 158, 159]. These studies have revealed a significant association between hypercortisolemia

and the reduction of BDNF levels in depression [160]. Excess GCs may be associated with hippocampal atrophy and volume reductions *via* GC receptor mediated decrease in subgranular zone proliferation [161]. Conversely, patients with Cushing's syndrome exhibit a rise in circulating cortisol level as well as hippocampal atrophy and associated depressive symptoms [161]. Neurogenesis, in turn, can reduce the cortisol response to stress and its inhibition causes a delay in returning GC levels to its baseline [161]. In chronic uncontrollable stress, the reciprocal interactions of the HPA axis and neurogenesis can progress to a vicious cycle that can lead to depressive illness. Based on the light of the above evidences, the HPA axis is increasingly targeted for discovering new antidepressants such as antagonists of CRF1, GR and VIb receptors. However, successful clinical translation is yet to be achieved [153]. The major uncertainty is either to stimulate an impaired GR or to attenuate a hyperactive GR, to control MDD [162].

2.2.4. Immune-inducing Molecules

In the early 1990s, Maes *et al*. observed that there is an increase in proinflammatory cytokines in patients with MDD which correlated with the severity of illness and measures of HPA axis hyperactivity [163-166]. This led to the proposition of macrophage hypothesis of depression [167] (or cytokine hypothesis of depression [168]), according to which external and internal stressors prompt development of depressive behavior by immune hyperactivation characterized by the increase in levels of proinflammatory cytokines (interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α)) and C-reactive protein (CRP). There can also be changes in function and number of natural killer (NK) cells, activation of cell-mediated immunity with the rise in CD4+/CD8+T cell ratio [169, 170], increase in number of activated T cells with markers CD2+ CD25+, CD3+ CD25+ and HLA-DR+ [171], rise in IL-2R level [172], increase in B cell subsets [173, 174] and changed Th1/Th2 cytokine and Treg balance [175, 176].

The immune molecules may be acting through multiple neural, cellular and humoral mechanisms in the brain to mediate either neuroprotective or neurodegenerative effects [177, 178]. Cytokines, which are humoral mediators of immunity, are produced primarily by microglia, but can also be produced by astrocytes and to some extent by neurons and oligodendrocytes, and can act as important modulators of mood [179]. External and internal stressors may also compromise the intestinal barrier leading to increased translocation of lipopolysaccharide (LPS) from gram-negative bacteria, which further mediates systemic as well as central inflammation, characterized by persistent activation of microglia and cytokines in the brain, resulting in sickness behavior ("leaky gut" hypothesis) [180]. Cytokine receptors within the CNS could be activated by peripherally as well as centrally synthesized cytokines [181]. Peripheral cytokines mediate the effects either by direct action on the brain after passive entry through the leaky regions in the blood-brain barrier (BBB) or active transport across BBB or binding to cell-surface proteins on endothelial cells, or *via* the transmission of cytokine signals through afferent vagus nerve fibers [182, 183]. Furthermore, interferon-α (IFN-α) injections were reported to cause depressive symptoms in 20–50% of cancer and hepatitis C patients [184], as well as a rise in the levels of sIL-2r, IL-6 and TNF-α in serum [185]. Accordingly, LPS, IL-1β, IFN-α or BCG injections in animals were used to develop inflammation-associated models of depression which further confirmed the relationship between inflammation, monoamine and neuroendocrine function [183]. In corroboration, pre-clinical and clinical studies revealed the effectiveness of conventional antidepressant treatments against cytokine-induced depression [182, 186].

Moreover, inflammatory molecules such as pro-inflammatory cytokines have the potential to be developed as a biomarker for MDD, especially for vascular depression where there is an increased risk for future cardiovascular diseases and depression [186]. For example, determination of the levels of CRP, IL-1β and TNF-α [186, 187] along with circulating leukocyte subsets [188] can serve as predictors of antidepressant treatment response in MDD. Thus, the association between inflammation and depression is possibly bidirectional, whose strength and direction may be determined by the specific cluster of symptoms, comorbidities, type of immune markers as well as population demographics. A divergent set of observation has also been reported which was based on immune suppression that includes reduction in levels and functions of NK cells and T cells [189]. Interestingly, in a recent study, clinical features of inflammation-associated depression were found to be age-related with young patients having a first depressive episode exhibiting a down-regulated monocyte gene expression profile; patients aged 28 years with a recurrent disease revealed upregulation [190]. Moreover, there are reports that immune suppression, as well as activation, can co-occur within the same MDD patient [191, 192].

2.2.4.1. Neurochemical, Neuroendocrine and Neuroimmune Interactions

The biochemical and physiological systems are not solitary mediators of MDD; rather interact with each other in a multidirectional network to mediate the progression of the disorder [193]. An elaboration of these mechanisms is needed to establish the linkup between different hypotheses of MDD and delineate the interactive matrix of pathophysiological components. The identification of the depressogenic role of indoleamine-pyrrole 2,3-dioxygenase (IDO) marked the fit of the cytokine and 5- HT hypothesis in MDD. Stress is reported to induce LPS, proinflammatory cytokines and oxidative stress, which in turn activates macrophages and other immunoregulatory cells to secrete IDO [186]. IDO catalyzes the rate-limiting step in the degradation of tryptophan to kynurenine, thus diverting tryptophan from the 5-HT synthetic route [183]. Kynurenine possess many immunomodulatory effects [194, 195] and is further metabolized into 3-hydroxykynurenine (generates free radicals causing oxidative stress), quinolinic acid (highly neurotoxic; directly damage neurons and function as a NMDA receptor agonist, provoke increase in oxidative and nitrosative stress, disrupt neuron glial communication and BBB integrity, inhibit ATP production by mitochondria), and kynurenic acid (neuroprotective; functions as antagonists of NMDA, α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid and kainite receptors, also regulate glutamate and dopamine levels) [196]. These tryptophan catabolites (TRYCATs) are also

formed following induction of tryptophan 2,3-dioxygenase (TDO) by GCs, which are found elevated in MDD. Thus the new '5- HT' hypothesis' of depression has been proposed according to which the activation of TRYCAT pathway was linked with the development of MDD through tryptophan depletion [197]. The reduction in plasma tryptophan level was also reported to be related to the decrease in serum albumin, to which it loosely binds. Kynurenine/tryptophan ratio and TRYCAT level were significantly associated with the affective symptoms observed in early puerperium. Further, in MDD, subchronic conditions with an activated counter anti-inflammatory response system (CARS) may exist, marked by a normal kynurenine/tryptophan ratio and reduced levels of plasma tryptophan [198-200].

Recent pathological evidences in MDD include activation of microglia and inflammasome mediated pathways [201, 202]. Microglia being the predominant immune cell in the brain, mediates immunosurveillance for pathogens, apoptotic cells and cellular debris [203]. The enduring presence of risk factors including oxidative stress, toxins, injury, vascular insults or genetic polymorphisms is reported to activate danger-associated molecular pattern (DAMP) detectors within the innate immune system, such as toll-like receptors (TLRs) and receptors for highly glycosylated end products (RAGEs), leading to chronic overproduction of proinflammatory cytokines, TNF- α, IL- 1β, and IL-6 [204]. Further, immune-mediated activation of pathogen-associated molecular pattern molecules (PAMPs) are also reported to contribute to the pathogenesis of MDD [183]. DAMPs signal through TLRs for the formation of the inflammasome, a multi-molecular signaling complex [205, 206]. Of particular relevance in MDD is the NLRP (Nucleotide-binding domain, Leucine-Rich Repeat, Pyrin domain-containing proteins)3 inflammasome, the only known inflammasome that requires a priming stimulus by GCs. This may serve as the link between stress, GC and neuroinflammation. NLRP3 inflammasome also requires a secondary stimulus by ATP [207]. NLRP3 acts by forming a scaffold with the adapter protein apoptosis-associated speck-like protein (ASC) which possesses a caspase recruitment domain, thereby mediating the formation of caspase-1, which in turn mediates formation and release of IL-1β [208]. IL-1β is an important mediator of sickness response and thereby coordinates peripheral and central host defense responses to danger [209]. Physiological alterations in ion fluxes, mitochondrial function, reactive oxygen species (ROS) levels and endosome integrity can activate NLRP inflammasomes [210]; suggestive of the involvement of these mechanisms in MDD [211]. Furthermore, DAMPs released from BBB endothelium and epithelial lining of the body may activate SNS as well as the HPA axis to mediate peripheral inflammatory response [212]. This pathway which is modulated by adrenergic and GC receptors on immune cells and associated inflammatory reflex is dysregulated in chronic stress due to altered GC receptor sensitivity [213-216]. It is important to note that, during a fight or flight response, an initial increase in GC level occurs which mediates anti-inflammatory response, followed by a persistent decrease of GC below the threshold level, promoting microglial sensitization, a mechanism to combat the subsequent immunologic threat. Further, psychological stress is reported to induce reactive granulopoiesis (increase in neutrophil number) and subsequent rise in the levels of circulating monocyte, especially, Ly6Chi cells. These monocytes are chemotactically attracted by the cytokines to distinct brain areas, activate the cytokine receptors and modulate synaptic plasticity [216, 217]. Based on these observations, it is highly feasible that the immune system and HPA axis function in an interactive matrix to integrate the physiological effects. Moreover, in MDD, inflammation may be linked to alterations in neuroplasticity *via* reduction of BDNF through direct action of cytokines [218-220] or cytokine-mediated effects on neurotransmitters such as glutamate [221] and GABA [222].

2.3. Cellular Stress Mechanisms

2.3.1. Oxidative and Nitrosative Stress

Oxidative and nitrosative stress (O&NS) is a result of the imbalance between the levels of ROS/ reactive nitrogen species (RNS) and antioxidants, leading to the damage of cellular constituents. According to past studies, it is assumed that metabolic stress together with O&NS, poses a greater risk of morbidity and mortality in MDD patients [223, 224]. In MDD, the levels of endogenous antioxidants such as reduced glutathione (GSH), catalase, superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx), coenzyme Q10, zinc and vitamin E are reported to be decreased in plasma and brain. Interestingly, MDD patients in a (sub)acute phase of illness showed a rise in peroxide levels, while the levels tend to become normal in chronic cases [225]. Moreover, susceptibility to oxidative stress in MDD may be affected by gender as higher plasma peroxide levels were more found in depressed males as compared to females [226]. Furthermore, O&NS may be causing (auto)immune responses by converting inactive autoepitopes to immunogenic neoantigens. Evidently, the rise in levels of plasma IgG antibodies against oxidized low-density lipoprotein as well as IgM-mediated responses against membrane fatty acids and NO modified amino-acids, are observed in MDD. The role of O&NS in MDD pathogenesis is further strengthened by its association with polymorphisms in O&NS genes, like catalase, SOD, cyclooxygenase (COX)-2 and myeloperoxidase (MPO). In corroboration with these findings, antidepressants have demonstrated the ability to improve antioxidant levels and reverse O&NS induced damage whereas numerous antioxidants have exhibited antidepressive effects [223]. It is noteworthy that ROS also has the role of secondary messenger and is fundamental for neurobiological processes such as cell growth, proliferation, differentiation, migration and adhesion, regulation of gene expression, immune responses, control of the intracellular redox-related signaling pathways and cell death [227]. Increased oxidative stress can result in mitochondrial dysfunction and MDD has been associated with dysfunctional mitochondria [228] and damaged mitochondrial ultrastructure [229]. As ROS is a by-product of monoamine oxidase activity, it has got an important role in the inactivation of monoaminergic neurotransmitters; hence might be significant in the pathogenesis of MDD [230].

While O&NS leads to the loss of adaptive potential of cells to the alterations in redox homeostasis, causing eventual cell death, inflammatory damage is reported to cause

additive effects in the neuroprogression of MDD [227]. The two transcription factors, nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and nuclear factor-κB (NF-κB) are key components of the O&NS and inflammation cascade; both are implicated in MDD [227, 231, 232]. Various signaling pathways, including mitogen-activated protein kinases (MAPK) [233] and PI3K/ AKT/GSK3/mTOR pathways [234] are also important in the neuroprogression of MDD. Further, in MDD, ROS generated by IFN-γ from macrophages is reported to decrease the levels of 5,6,7,8-tetrahydrobiopterin, a cofactor involved in the biosynthesis of monoamine neurotransmitters [233].

2.3.2. Endoplasmic Reticulum Stress

Psychological stress associated HPA axis activation, rise in cytokine level, dopamine auto-oxidation and glutamatergic receptor activation are reported to elicit cellular stress response [235]. A highly intense stressful situation may enhance glutamate neurotransmission that can result in neuronal hyperexcitability which in turn demands extra protein synthesis. This can result in a critical situation, called endoplasmic reticulum (ER) stress, if the ER fails to effectively fold normal proteins as per the increased demand in function [236, 237]. To overcome ER stress and to promote cell survival, ER normally possesses a sophisticated stress response mechanism, called the unfolded protein response (UPR) [238]. Over time, misfolded proteins are removed to the cytoplasm from ER for ER-associated degradation (ERAD). Thus, the ERAD and its molecular chaperones promote cellular survival under ER stress by preventing the accumulation of toxic protein aggregates [239]. However, an elevated systemic and brain ER stress response is reported to underlie depression in humans and animals [240, 241]. Moreover, ER stress-associated ailments such as cardiovascular disease have shown a higher incidence of depression [240], which is further elaborated by Gold *et al*., linking ER stress and parainflammation in the development of affective illness through the dysregulation of a stress response. Therapeutic strategies such as valproate and lithium are reported to modulate ER stress-related targets in favour of cell rescue [237]. Novel targets for MDD therapy may include central insulin, klotho and peroxisome proliferator-activated receptor-γ (PPAR-γ) systems, as they are reported to contain ER stress [237]. Further, agonists of the sigma-1 receptor, a novel ligand-operated ER chaperone that regulates bioenergetics, free radical production, UPR and cytokine signaling, have been reported to improve depressive symptoms [235]. These findings imply that targeting ER stress associated components may provide novel targets for MDD drug development.

2.3.3. Mitochondrial Alterations

Mitochondrial dysfunction is also important in the pathogenesis of MDD and forms the basis of the "mitochondrial psychiatry model of depression". The significant correlation came from the observations of psychiatric symptoms in mitochondrial illness and mitochondrial alterations in psychiatric diseases [241]. Modifications in translational products linked to the function of mitochondria reduced gene expression of mitochondrial DNA (mtDNA)-encoded transcripts and changes in components of electron transport chain might be the important links between mitochondrial dysfunction and MDD [242-244]. Notably, susceptibility to develop MDD can be maternally inherited through mtDNA as mtDNA sequence variants are capable of inducing mitochondrial dysfunction, which in turn predispose individual towards MDD development [245]. A mitochondrial function could be pharmacologically modified, as shown by the ability of imipramine and harmine to modulate creatine kinase and mitochondrial respiratory chain activities in rat brain areas in a dose and treatment-related manner [246].

3. POTENTIAL THERAPEUTIC CONSIDERATIONS

The search for novel therapeutic strategies is a "hot topic" in neuroscience and the first step forward is to validate and integrate the emerging pathogenetic mechanisms and newer targets into the current therapeutic understanding of MDD. Brain neuropeptides including CRF, urocortin, AVP, substance P, neuropeptide Y, neuropeptide S, galanin, oxytocin and pituitary adenylate-cyclase activating polypeptide; not only participate in stress physiology, but also have immense clinical relevance as novel targets in stress-induced MDD [247]. Further, the circadian rhythm is reported to be bidirectionally linked with depression. In particular, the development of symptoms or recurrence of seasonal depression is associated with changes in circadian rhythms [248]. Melatonin or bright light is reported to modulate circadian rhythm and can be used as an adjunct to classical antidepressants. Another novel approach is the development of antidepressants with intrinsic chronobiotic properties. One such promising candidate is agomelatine, which possesses joint MT1 and MT2 antagonism and 5- HT2C receptor inhibition [249]. An additional remarkable finding is the common transcriptional responses implicating distinct elements of the circadian clock by two rapid-acting antidepressant strategies, low-dose ketamine and sleep deprivation therapies; thereby projecting new targets for rapid and improved treatment based on chronopharmacological strategies [250]. Another possible approach that needs further scientific elaboration and validation is the use of omega-3 polyunsaturated fatty acids (PUFA) for both the prevention and treatment of depression [251]. The beneficial role of PUFA includes maintaining the brain structures and preserving their function by interacting with phospholipid metabolism and, hence, the modulation of signal transduction; as well as preventing or decreasing the inflammatory status occurring during depression [252]. In addition, these biological systems may be targeted to develop reliable biomarkers which in conjunction with new *in vivo* imaging techniques can be used to diagnose depression subtypes. More importantly, preclinical studies need to shed their exclusive focus on male subjects, incorporate females and examine sex as a variable to develop an effective treatment for all, since the higher prevalence of depression and comorbidities are found in women than men [43]. Stress-regulated transcriptional changes in the hypothalamus [26] and other related gene expressions in the prefrontal cortex [253] in the mouse are already indicative of the fact that these changes are sex-specific and ovarian hormone-dependent, warrants the sex variable in MDD therapy.

Novel therapeutics for treatment-resistant MDD are emerging such as modulators on glutamatergic, cholinergic,

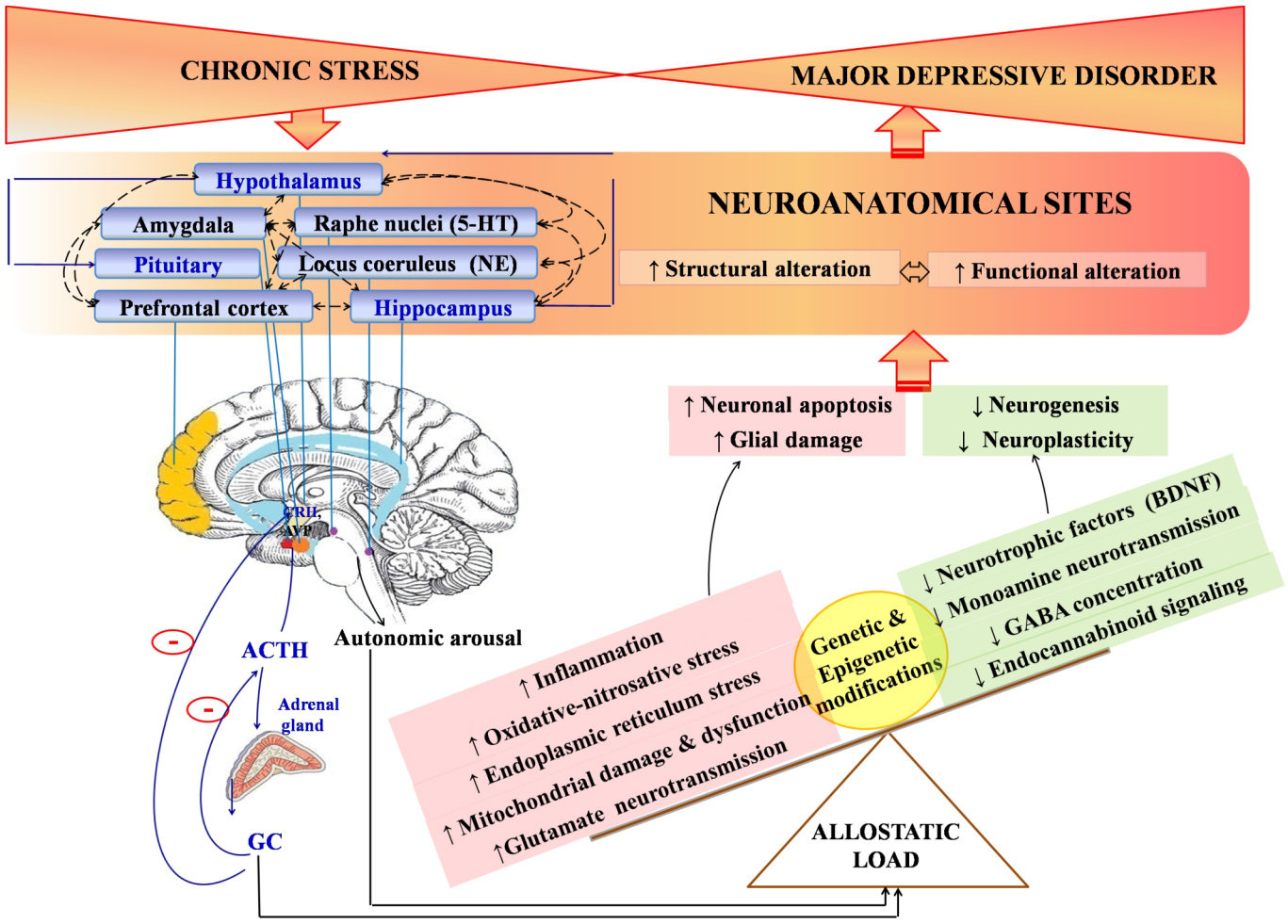

Fig. (1). The pathophysiological components of stress and MDD.

monoaminergic and opioid systems as well as nutraceuticals such as L-methylfolate and S-adenosyl-methionine [254]. Apart from previously mentioned ketamine and GLYX-13, pharmacological and non-pharmacological treatment methods such as electroconvulsive therapy, sleep deprivation, scopolamine and pindolol have been pursued a fast-onset antidepressant action as well as to be used in conjunction with classical antidepressants to decrease the delay in antidepressant onset [255]. Psychotherapeutic modalities such as cognitive-behavioral therapy (CBT) [2], cognitive behavioral analysis system of psychotherapy [256] and short term psychodynamic psychotherapy [256] are also being evolved into promising applications including treatment-resistant depression. Advances in neurosurgical techniques such as deep brain stimulation to the nucleus accumbens are also emerging to treat patients suffering from treatment-resistant depression [257]. Further, the development of treatment-specific biomarkers can guide antidepressant treatment selection *via* its potential to predict an individual's improvement to a specific treatment and non-responsiveness to an alternative treatment [258]. Furthermore, considering the association of genetic variation with the differential risk to benefit ratio of antidepressants, implementation of pharmacokinetic pharmacogenetic guidelines for prescribing antidepressants can bring precision medicine to psychiatry [259].

CONCLUSION WITH FUTURE PROSPECTIVE

The overall discussion reveals that MDD, a multifactorial disorder, is strongly associated with stress-related pathophysiological components (Fig. **1**). Each component has its own role in MDD phenotypes (Fig. **2**). The heterogeneity in molecular adaptations, signaling pathways, cells, brain areas as well as the neurocircuitry implicated, is integral in the pathophysiological changes associated with stress and MDD. In light of this, it could be stated that the damaging effects of stress on biology and behavior might be caused cumulatively by molecular, structural and functional alterations. Therefore, it is imperative that the diagnosis as well as treatment of MDD, be characterized based on the multitude of systems involved *viz*. serotonergic, noradrenergic, gamma-aminobutyric acid, glutamatergic and endocannabinoid systems, neurotrophic factors, HPA axis, immune system as well as cellular stress mechanisms including sex difference. These can aid in developing multitargeted therapies with more promise as compared to the standard treatment. In addition, brain stimulation therapies like deep brain stimulation and vagal nerve stimulation along with new classes of antidepressant-like vortioxetine, a multimodal antidepressant that acts as 5-HT transporter inhibitor, a 5-HT_3, 5-HT_{1D} and 5-HT_7 receptor antagonist, 5-HT_{1B} receptor partial agonist

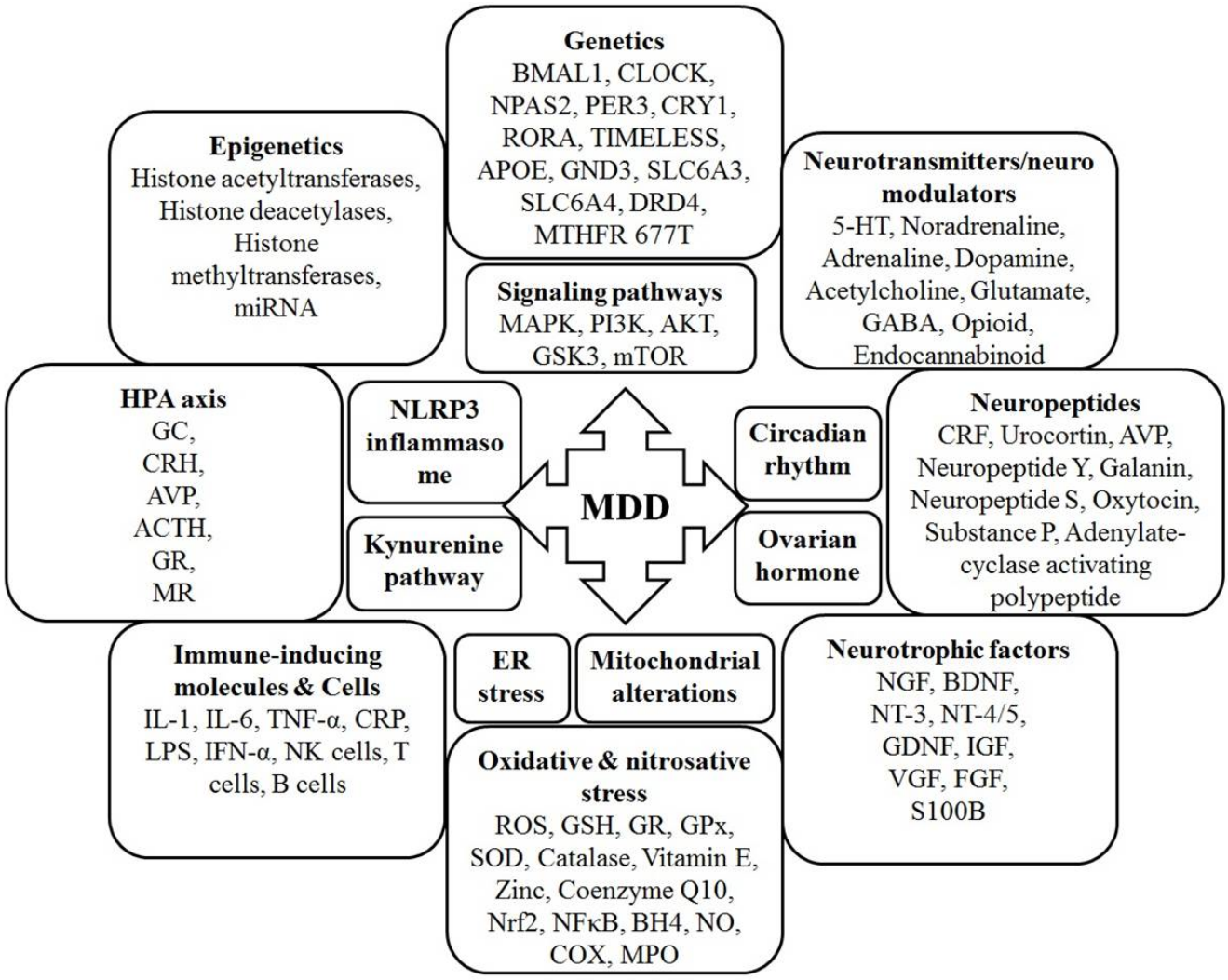

Fig. (2). The interactive matrix in stress and MDD.

and 5-HT_{1A} receptor agonist, may hold better assurance than the conventional antidepressants [260-262]. As a breakthrough in decades, esketamine, the S-enantiomer of racemic ketamine was recently approved by the FDA to use in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults [263]. Further, the paradigm shift from standard 'one-size-fits-all' treatment plan to individualized and personalized treatment may become the state of the art direction considering the assessment of individual biological properties and treatment response of the patients to MDD. Additionally, these characterizations may aid in the identification of MDD subtypes and the development of sophisticated clinical, endocrine, immune, inflammatory, imaging and genetic biomarkers. This might enable diagnostic and therapeutic modalities beyond the currently utilized symptom-based approach. Over the next few years, significant advances are expected to occur in the understanding and treatment of MDD, which hold much promise as compared to conventional monoamine based treatment.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The financial support was jointly provided by CSIR-Indian Institute of Chemical Technology, Hyderabad and National Institute of Pharmaceutical Education and Research (NIPER)-Guwahati, under the aegis of Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India. Grant number is [CSIR/NWP(2012-17)/BSC0115-miND].

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

The authors would also like to thank Dr. Arvind Kumar, Principal Scientist, CSIR-CCMB, Hyderabad for critical reading and Dr. Rachel Jesudasan for language editing of the manuscript and Dr. USN Murty, Director, (NIPER)-Guwahati for overall support. This manuscript is given as IICT/Pubs./2019/011 by the KIMS department of CSIR-IICT.

REFERENCES

[1] Kessler, R.C.; Berglund, P.; Demler, O.; Jin, R.; Merikangas, K.R.; Walters, E.E. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry,* **2005**, *62*(6), 593-602. [http://dx.doi.org/10.1001/archpsyc.62.6.593] [PMID: 15939837]

[2] Wiles, N.; Thomas, L.; Abel, A.; Ridgway, N.; Turner, N.; Campbell, J.; Garland, A.; Hollinghurst, S.; Jerrom, B.; Kessler, D.; Kuyken, W.; Morrison, J.; Turner, K.; Williams, C.; Peters, T.; Lewis, G. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. *Lancet,* **2013**, *381*(9864), 375-384. [http://dx.doi.org/10.1016/S0140-6736(12)61552-9] [PMID: 23219570]

[3] Weissman, M.M.; Bland, R.; Joyce, P.R.; Newman, S.; Wells, J.E.; Wittchen, H-U. Sex differences in rates of depression: cross-national perspectives. *J. Affect. Disord.,* **1993**, *29*(2-3), 77-84. [http://dx.doi.org/10.1016/0165-0327(93)90025-F] [PMID: 8300980]

[4] Wilhelm, K.; Mitchell, P.; Slade, T.; Brownhill, S.; Andrews, G. Prevalence and correlates of DSM-IV major depression in an Australian national survey. *J. Affect. Disord.,* **2003**, *75*(2), 155-162. [http://dx.doi.org/10.1016/S0165-0327(02)00040-X] [PMID: 12798255]

[5] Bijl, R.V.; Ravelli, A. Psychiatric morbidity, service use, and need for care in the general population: results of The Netherlands Mental Health Survey and Incidence Study. *Am. J. Public Health,* **2000**, *90*(4), 602-607. [http://dx.doi.org/10.2105/AJPH.90.4.602] [PMID: 10754976]

[6] Ogłodek, E.; Szota, A.; Just, M.; Moś, D.; Araszkiewicz, A. The role of the neuroendocrine and immune systems in the pathogenesis of depression. *Pharmacol. Rep.,* **2014**, *66*(5), 776-781. [http://dx.doi.org/10.1016/j.pharep.2014.04.009] [PMID: 25149980]

[7] Whiteford, H.A.; Degenhardt, L.; Rehm, J.; Baxter, A.J.; Ferrari, A.J.; Erskine, H.E.; Charlson, F.J.; Norman, R.E.; Flaxman, A.D.; Johns, N.; Burstein, R.; Murray, C.J.; Vos, T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet,* **2013**, *382*(9904), 1575-1586. [http://dx.doi.org/10.1016/S0140-6736(13)61611-6] [PMID: 23993280]

[8] Arroll, B.; Elley, C.R.; Fishman, T.; Goodyear-Smith, F.A.; Kenealy, T.; Blashki, G.; Kerse, N.; Macgillivray, S. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst. Rev.,* **2009**, *3*(3), CD007954. [http://dx.doi.org/10.1002/14651858.CD007954] [PMID: 19588448]

[9] Connolly, K.R.; Thase, M.E. Emerging drugs for major depressive disorder. *Expert Opin. Emerg. Drugs,* **2012**, *17*(1), 105-126. [http://dx.doi.org/10.1517/14728214.2012.660146] [PMID: 22339643]

[10] Rush, A.J.; Trivedi, M.H.; Wisniewski, S.R.; Nierenberg, A.A.; Stewart, J.W.; Warden, D.; Niederehe, G.; Thase, M.E.; Lavori, P.W.; Lebowitz, B.D.; McGrath, P.J.; Rosenbaum, J.F.; Sackeim, H.A.; Kupfer, D.J.; Luther, J.; Fava, M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychiatry,* **2006**, *163*(11), 1905-1917. [http://dx.doi.org/10.1176/ajp.2006.163.11.1905] [PMID: 17074942]

[11] Cassano, P.; Fava, M. Tolerability issues during long-term treatment with antidepressants. *Ann. Clin. Psychiatry,* **2004**, *16*(1), 15-25. [http://dx.doi.org/10.1080/10401230490281618] [PMID: 15147109]

[12] Maletic, V.; Robinson, M.; Oakes, T.; Iyengar, S.; Ball, S.G.; Russell, J. Neurobiology of depression: an integrated view of key findings. *Int. J. Clin. Pract.,* **2007**, *61*(12), 2030-2040. [http://dx.doi.org/10.1111/j.1742-1241.2007.01602.x] [PMID: 17944926]

[13] Hollon, S.D.; Shelton, R.C.; Wisniewski, S.; Warden, D.; Biggs, M.M.; Friedman, E.S.; Husain, M.; Kupfer, D.J.; Nierenberg, A.A.; Petersen, T.J.; Shores-Wilson, K.; Rush, A.J. Presenting characteristics of depressed outpatients as a function of recurrence: preliminary findings from the STAR*D clinical trial. *J. Psychiatr. Res.,* **2006**, *40*(1), 59-69. [http://dx.doi.org/10.1016/j.jpsychires.2005.07.008] [PMID: 16243357]

[14] Gentile, S. Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience,* **2017**, *342*, 154-166. [http://dx.doi.org/10.1016/j.neuroscience.2015.09.001] [PMID: 26343292]

[15] Rousseau, G. Depression's forgotten genealogy: notes towards a history of depression. *Hist. Psychiatry,* **2000**, *11*(41 Pt 1), 71-106. [http://dx.doi.org/10.1177/0957154X0001104104] [PMID: 11624608]

[16] Billings, A.G.; Cronkite, R.C.; Moos, R.H. Social-environmental factors in unipolar depression: comparisons of depressed patients and nondepressed controls. *J. Abnorm. Psychol.,* **1983**, *92*(2), 119-133. [http://dx.doi.org/10.1037/0021-843X.92.2.119] [PMID: 6863728]

[17] Allen, N.B.; Badcock, P.B. Darwinian models of depression: a review of evolutionary accounts of mood and mood disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2006**, *30*(5), 815-826. [http://dx.doi.org/10.1016/j.pnpbp.2006.01.007] [PMID: 16647176]

[18] Mahar, I.; Bambico, F.R.; Mechawar, N.; Nobrega, J.N. Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. *Neurosci. Biobehav. Rev.,* **2014**, *38*, 173-192. [http://dx.doi.org/10.1016/j.neubiorev.2013.11.009] [PMID: 24300695]

[19] McEwen, B.S. Mood disorders and allostatic load. *Biol. Psychiatry,* **2003**, *54*(3), 200-207. [http://dx.doi.org/10.1016/S0006-3223(03)00177-X] [PMID: 12893096]

[20] Monroe, S.M.; Simons, A.D. Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychol. Bull.,* **1991**, *110*(3), 406-425. [http://dx.doi.org/10.1037/0033-2909.110.3.406] [PMID: 1758917]

[21] Kendler, K.S.; Gardner, C.O.; Prescott, C.A. Toward a comprehensive developmental model for major depression in women. *Am. J. Psychiatry,* **2002**, *159*(7), 1133-1145. [http://dx.doi.org/10.1176/appi.ajp.159.7.1133] [PMID: 12091191]

[22] Kendler, K.S.; Gardner, C.O.; Prescott, C.A. Toward a comprehensive developmental model for major depression in men. *Am. J. Psychiatry,* **2006**, *163*(1), 115-124. [http://dx.doi.org/10.1176/appi.ajp.163.1.115] [PMID: 16390898]

[23] Kendler, K.S.; Kuhn, J.W.; Prescott, C.A. Childhood sexual abuse, stressful life events and risk for major depression in women. *Psychol. Med.,* **2004**, *34*(8), 1475-1482. [http://dx.doi.org/10.1017/S003329170400265X] [PMID: 15724878]

[24] Gold, P.W. The organization of the stress system and its dysregulation in depressive illness. *Mol. Psychiatry,* **2015**, *20*(1), 32-47. [http://dx.doi.org/10.1038/mp.2014.163] [PMID: 25486982]

[25] Willner, P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. *Neuropsychobiology,* **2005**, *52*(2), 90-110. [http://dx.doi.org/10.1159/000087097] [PMID: 16037678]

[26] Karisetty, B.C.; Khandelwal, N.; Kumar, A.; Chakravarty, S. Sex difference in mouse hypothalamic transcriptome profile in stress-induced depression model. *Biochem. Biophys. Res. Commun.,* **2017**, *486*(4), 1122-1128. [http://dx.doi.org/10.1016/j.bbrc.2017.04.005] [PMID: 28385526]

[27] Yang, C.; Shirayama, Y.; Zhang, J-C.; Ren, Q.; Hashimoto, K. Peripheral interleukin-6 promotes resilience versus susceptibility to inescapable electric stress. *Acta Neuropsychiatr.,* **2015**, *27*(5), 312-316. [http://dx.doi.org/10.1017/neu.2015.36] [PMID: 26017899]

[28] Golden, S.A.; Covington, H.E., III; Berton, O.; Russo, S.J. A standardized protocol for repeated social defeat stress in mice. *Nat. Protoc.,* **2011**, *6*(8), 1183-1191. [http://dx.doi.org/10.1038/nprot.2011.361] [PMID: 21799487]

[29] Berton, O.; McClung, C.A.; Dileone, R.J.; Krishnan, V.; Renthal, W.; Russo, S.J.; Graham, D.; Tsankova, N.M.; Bolanos, C.A.; Rios,

M.; Monteggia, L.M.; Self, D.W.; Nestler, E.J. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science,* **2006**, *311*(5762), 864-868. [http://dx.doi.org/10.1126/science.1120972] [PMID: 16469931]

[30] Veeraiah, P.; Noronha, J.M.; Maitra, S.; Bagga, P.; Khandelwal, N.; Chakravarty, S.; Kumar, A.; Patel, A.B. Dysfunctional glutamatergic and γ-aminobutyric acidergic activities in prefrontal cortex of mice in social defeat model of depression. *Biol. Psychiatry,* **2014**, *76*(3), 231-238. [http://dx.doi.org/10.1016/j.biopsych.2013.09.024] [PMID: 24239130]

[31] Martin, A.L.; Brown, R.E. The lonely mouse: verification of a separation-induced model of depression in female mice. *Behav. Brain Res.,* **2010**, *207*(1), 196-207. [http://dx.doi.org/10.1016/j.bbr.2009.10.006] [PMID: 19819265]

[32] Kroes, R.A.; Panksepp, J.; Burgdorf, J.; Otto, N.J.; Moskal, J.R. Modeling depression: social dominance-submission gene expression patterns in rat neocortex. *Neuroscience,* **2006**, *137*(1), 37-49. [http://dx.doi.org/10.1016/j.neuroscience.2005.08.076] [PMID: 16289586]

[33] Varghese, A.K.; Verdú, E.F.; Bercik, P.; Khan, W.I.; Blennerhassett, P.A.; Szechtman, H.; Collins, S.M. Antidepressants attenuate increased susceptibility to colitis in a murine model of depression. *Gastroenterology,* **2006**, *130*(6), 1743-1753. [http://dx.doi.org/10.1053/j.gastro.2006.02.007] [PMID: 16697738]

[34] O'Mahony, S.M.; Marchesi, J.R.; Scully, P.; Codling, C.; Ceolho, A-M.; Quigley, E.M.; Cryan, J.F.; Dinan, T.G. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol. Psychiatry,* **2009**, *65*(3), 263-267. [http://dx.doi.org/10.1016/j.biopsych.2008.06.026] [PMID: 18723164]

[35] Saveanu, R.V.; Nemeroff, C.B. Etiology of depression: genetic and environmental factors. *Psychiatr. Clin. North Am.,* **2012**, *35*(1), 51-71. [http://dx.doi.org/10.1016/j.psc.2011.12.001] [PMID: 22370490]

[36] Duclot, F.; Kabbaj, M. Epigenetic mechanisms underlying the role of brain-derived neurotrophic factor in depression and response to antidepressants. *J. Exp. Biol.,* **2015**, *218*(Pt 1), 21-31. [http://dx.doi.org/10.1242/jeb.107086] [PMID: 25568448]

[37] Vialou, V.; Feng, J.; Robison, A.J.; Nestler, E.J. Epigenetic mechanisms of depression and antidepressant action. *Annu. Rev. Pharmacol. Toxicol.,* **2013**, *53*, 59-87. [http://dx.doi.org/10.1146/annurev-pharmtox-010611-134540] [PMID: 23020296]

[38] Tsankova, N.M.; Berton, O.; Renthal, W.; Kumar, A.; Neve, R.L.; Nestler, E.J. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat. Neurosci.,* **2006**, *9*(4), 519-525. [http://dx.doi.org/10.1038/nn1659] [PMID: 16501568]

[39] Pathak, S.S.; Maitra, S.; Chakravarty, S.; Kumar, A. Histone Lysine demethylases of JMJD2 or KDM4 family are important epigenetic regulators in reward circuitry in the etiopathology of depression. *Neuropsychopharmacology,* **2017**, *42*(4), 854-863. [http://dx.doi.org/10.1038/npp.2016.231] [PMID: 27711046]

[40] Codocedo, J.F.; Inestrosa, N.C. Environmental control of microRNAs in the nervous system: Implications in plasticity and behavior. *Neurosci. Biobehav. Rev.,* **2016**, *60*, 121-138. [http://dx.doi.org/10.1016/j.neubiorev.2015.10.010] [PMID: 26593111]

[41] Réus, G.Z.; Abelaira, H.M.; dos Santos, M.A.B.; Carlessi, A.S.; Tomaz, D.B.; Neotti, M.V.; Liranço, J.L.G.; Gubert, C.; Barth, M.; Kapczinski, F.; Quevedo, J. Ketamine and imipramine in the nucleus accumbens regulate histone deacetylation induced by maternal deprivation and are critical for associated behaviors. *Behav. Brain Res.,* **2013**, *256*, 451-456. [http://dx.doi.org/10.1016/j.bbr.2013.08.041] [PMID: 24004850]

[42] Yuan, T-F.; Li, A.; Sun, X.; Ouyang, H.; Campos, C.; Rocha, N.B.F.; Arias-Carrión, O.; Machado, S.; Hou, G.; So, K.F. Transgenerational inheritance of paternal neurobehavioral phenotypes: stress, addiction, ageing and metabolism. *Mol. Neurobiol.,* **2016**, *53*(9), 6367-6376. [http://dx.doi.org/10.1007/s12035-015-9526-2] [PMID: 26572641]

[43] Hodes, G.E.; Walker, D.M.; Labonté, B.; Nestler, E.J.; Russo, S.J. Understanding the epigenetic basis of sex differences in depression. *J. Neurosci. Res.,* **2017**, *95*(1-2), 692-702. [http://dx.doi.org/10.1002/jnr.23876] [PMID: 27870456]

[44] Feinberg, A.P. Phenotypic plasticity and the epigenetics of human disease. *Nature,* **2007**, *447*(7143), 433-440. [http://dx.doi.org/10.1038/nature05919] [PMID: 17522677]

[45] Chahrour, M.; Jung, S.Y.; Shaw, C.; Zhou, X.; Wong, S.T.; Qin, J.; Zoghbi, H.Y. MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science,* **2008**, *320*(5880), 1224-1229. [http://dx.doi.org/10.1126/science.1153252] [PMID: 18511691]

[46] Melas, P.A.; Rogdaki, M.; Lennartsson, A.; Björk, K.; Qi, H.; Witasp, A.; Werme, M.; Wegener, G.; Mathé, A.A.; Svenningsson, P.; Lavebratt, C. Antidepressant treatment is associated with epigenetic alterations in the promoter of P11 in a genetic model of depression. *Int. J. Neuropsychopharmacol.,* **2012**, *15*(5), 669-679. [http://dx.doi.org/10.1017/S1461145711000940] [PMID: 21682946]

[47] Chakravarty, S.; Bhat, U.A.; Reddy, R.G.; Gupta, P.; Kumar, A. *Histone Deacetylase inhibitors and psychiatric disorders in Epigenetics in Psychiatry*; Elsevier, **2014**, pp. 515-544.

[48] Schroeder, F.A.; Lin, C.L.; Crusio, W.E.; Akbarian, S. Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. *Biol. Psychiatry,* **2007**, *62*(1), 55-64. [http://dx.doi.org/10.1016/j.biopsych.2006.06.036] [PMID: 16945350]

[49] Hsing, C.-H.; Hung, S.-K.; Chen, Y.-C.; Wei, T.-S.; Sun, D.-P.; Wang, J.-J.; Yeh, C.-H. Histone deacetylase inhibitor trichostatin a ameliorated endotoxin-induced neuroinflammation and cognitive dysfunction. *Mediators of inflammation,* **2015**, *2015*. 1-11. [http://dx.doi.org/10.1155/2015/163140]

[50] Lin, H.; Geng, X.; Dang, W.; Wu, B.; Dai, Z.; Li, Y.; Yang, Y.; Zhang, H.; Shi, J. Molecular mechanisms associated with the antidepressant effects of the class I histone deacetylase inhibitor MS-275 in the rat ventrolateral orbital cortex. *Brain Res.,* **2012**, *1447*, 119-125. [http://dx.doi.org/10.1016/j.brainres.2012.01.053] [PMID: 22341874]

[51] Meylan, E.M.; Halfon, O.; Magistretti, P.J.; Cardinaux, J-R. The HDAC inhibitor SAHA improves depressive-like behavior of CRTC1-deficient mice: Possible relevance for treatment-resistant depression. *Neuropharmacology,* **2016**, *107*, 111-121. [http://dx.doi.org/10.1016/j.neuropharm.2016.03.012] [PMID: 26970016]

[52] Kv, A.; Madhana, R.M.; Js, I.C.; Lahkar, M.; Sinha, S.; Naidu, V.G.M. Antidepressant activity of vorinostat is associated with amelioration of oxidative stress and inflammation in a corticosterone-induced chronic stress model in mice. *Behav. Brain Res.,* **2018**, *344*, 73-84. [http://dx.doi.org/10.1016/j.bbr.2018.02.009] [PMID: 29452193]

[53] Hek, K.; Demirkan, A.; Lahti, J.; Terracciano, A.; Teumer, A.; Cornelis, M.C.; Amin, N.; Bakshis, E.; Baumert, J.; Ding, J.; Liu, Y.; Marciante, K.; Meirelles, O.; Nalls, M.A.; Sun, Y.V.; Vogelzangs, N.; Yu, L.; Bandinelli, S.; Benjamin, E.J.; Bennett, D.A.; Boomsma, D.; Cannas, A.; Coker, L.H.; de Geus, E.; De Jager, P.L.; Diez-Roux, A.V.; Purcell, S.; Hu, F.B.; Rimma, E.B.; Hunter, D.J.; Jensen, M.K.; Curhan, G.; Rice, K.; Penman, A.D.; Rotter, J.I.; Sotoodehnia, N.; Emeny, R.; Eriksson, J.G.; Evans, D.A.; Ferrucci, L.; Fornage, M.; Gudnason, V.; Hofman, A.; Illig, T.; Kardia, S.; Kelly-Hayes, M.; Koenen, K.; Kraft, P.; Kuningas, M.; Massaro, J.M.; Melzer, D.; Mulas, A.; Mulder, C.L.; Murray, A.; Oostra, B.A.; Palotie, A.; Penninx, B.; Petersmann, A.; Pilling, L.C.; Psaty, B.; Rawal, R.; Reiman, E.M.; Schulz, A.; Shulman, J.M.; Singleton, A.B.; Smith, A.V.; Sutin, A.R.; Uitterlinden, A.G.; Völzke, H.; Widen, E.; Yaffe, K.; Zonderman, A.B.; Cucca, F.; Harris, T.; Ladwig, K.H.; Llewellyn, D.J.; Räikkönen, K.; Tanaka, T.; van Duijn, C.M.; Grabe, H.J.; Launer, L.J.; Lunetta, K.L.; Mosley, T.H., Jr; Newman, A.B.; Tiemeier, H.; Murabito, J. A genome-wide association study of depressive symptoms. *Biol. Psychiatry,* **2013**, *73*(7), 667-678. [http://dx.doi.org/10.1016/j.biopsych.2012.09.033] [PMID: 23290196]

[54] Dunn, E.C.; Wiste, A.; Radmanesh, F.; Almli, L.M.; Gogarten, S.M.; Sofer, T.; Faul, J.D.; Kardia, S.L.; Smith, J.A.; Weir, D.R.; Zhao, W.; Soare, T.W.; Mirza, S.S.; Hek, K.; Tiemeier, H.; Goveas, J.S.; Sarto, G.E.; Snively, B.M.; Cornelis, M.; Koenen, K.C.; Kraft, P.; Purcell, S.; Ressler, K.J.; Rosand, J.; Wassertheil-

Smoller, S.; Smoller, J.W. Genome‐wide association study (GWAS) and genome‐wide by environment interaction study (GWEIS) of depressive symptoms in African American and Hispanic/Latina women. *Depress. Anxiety,* **2016**, *33*(4), 265-280. [http://dx.doi.org/10.1002/da.22484] [PMID: 27038408]

[55] Wray, N.; Sullivan, P. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, **2018**, *50*, 668-681. bioRxiv, URL https://www biorxiv org/content/early/2017/07/24/167577

[56] Bunney, B.G.; Li, J.Z.; Walsh, D.M.; Stein, R.; Vawter, M.P.; Cartagena, P.; Barchas, J.D.; Schatzberg, A.F.; Myers, R.M.; Watson, S.J.; Akil, H.; Bunney, W.E. Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. *Mol. Psychiatry,* **2015**, *20*(1), 48-55. [http://dx.doi.org/10.1038/mp.2014.138] [PMID: 25349171]

[57] Benedetti, F.; Serretti, A.; Colombo, C.; Barbini, B.; Lorenzi, C.; Campori, E.; Smeraldi, E. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.,* **2003**, *123B*(1), 23-26. [http://dx.doi.org/10.1002/ajmg.b.20038] [PMID: 14582141]

[58] Soria, V.; Martínez-Amorós, E.; Escaramís, G.; Valero, J.; Pérez-Egea, R.; García, C.; Gutiérrez-Zotes, A.; Puigdemont, D.; Bayés, M.; Crespo, J.M.; Martorell, L.; Vilella, E.; Labad, A.; Vallejo, J.; Pérez, V.; Menchón, J.M.; Estivill, X.; Gratacòs, M.; Urretavizcaya, M. Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. *Neuropsychopharmacology,* **2010**, *35*(6), 1279-1289. [http://dx.doi.org/10.1038/npp.2009.230] [PMID: 20072116]

[59] Utge, S.J.; Soronen, P.; Loukola, A.; Kronholm, E.; Ollila, H.M.; Pirkola, S.; Porkka-Heiskanen, T.; Partonen, T.; Paunio, T. Systematic analysis of circadian genes in a population-based sample reveals association of TIMELESS with depression and sleep disturbance. *PLoS One,* **2010**, *5*(2), e9259. [http://dx.doi.org/10.1371/journal.pone.0009259] [PMID: 20174623]

[60] Garriock, H.A.; Kraft, J.B.; Shyn, S.I.; Peters, E.J.; Yokoyama, J.S.; Jenkins, G.D.; Reinalda, M.S.; Slager, S.L.; McGrath, P.J.; Hamilton, S.P. A genomewide association study of citalopram response in major depressive disorder. *Biol. Psychiatry,* **2010**, *67*(2), 133-138. [http://dx.doi.org/10.1016/j.biopsych.2009.08.029] [PMID: 19846067]

[61] Smith, E.N.; Bloss, C.S.; Badner, J.A.; Barrett, T.; Belmonte, P.L.; Berrettini, W.; Byerley, W.; Coryell, W.; Craig, D.; Edenberg, H.J.; Eskin, E.; Foroud, T.; Gershon, E.; Greenwood, T.A.; Hipolito, M.; Koller, D.L.; Lawson, W.B.; Liu, C.; Lohoff, F.; McInnis, M.G.; McMahon, F.J.; Mirel, D.B.; Murray, S.S.; Nievergelt, C.; Nurnberger, J.; Nwulia, E.A.; Paschall, J.; Potash, J.B.; Rice, J.; Schulze, T.G.; Scheftner, W.; Panganiban, C.; Zaitlen, N.; Zandi, P.P.; Zöllner, S.; Schork, N.J.; Kelsoe, J.R. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol. Psychiatry,* **2009**, *14*(8), 755-763. [http://dx.doi.org/10.1038/mp.2009.43] [PMID: 19488044]

[62] Terracciano, A.; Tanaka, T.; Sutin, A.R.; Sanna, S.; Deiana, B.; Lai, S.; Uda, M.; Schlessinger, D.; Abecasis, G.R.; Ferrucci, L.; Costa, P.T., Jr. Genome-wide association scan of trait depression. *Biol. Psychiatry,* **2010**, *68*(9), 811-817. [http://dx.doi.org/10.1016/j.biopsych.2010.06.030] [PMID: 20800221]

[63] Landgraf, D.; McCarthy, M.J.; Welsh, D.K. Circadian clock and stress interactions in the molecular biology of psychiatric disorders. *Curr. Psychiatry Rep.,* **2014**, *16*(10), 483. [http://dx.doi.org/10.1007/s11920-014-0483-7] [PMID: 25135782]

[64] Mukherjee, S.; Coque, L.; Cao, J-L.; Kumar, J.; Chakravarty, S.; Asaithamby, A.; Graham, A.; Gordon, E.; Enwright, J.F., III; DiLeone, R.J.; Birnbaum, S.G.; Cooper, D.C.; McClung, C.A. Knockdown of Clock in the ventral tegmental area through RNA interference results in a mixed state of mania and depression-like behavior. *Biol. Psychiatry,* **2010**, *68*(6), 503-511. [http://dx.doi.org/10.1016/j.biopsych.2010.04.031] [PMID: 20591414]

[65] López León, S.; Croes, E.A.; Sayed-Tabatabaei, F.A.; Claes, S.; Van Broeckhoven, C.; van Duijn, C.M. The dopamine D4 receptor gene 48-base-pair-repeat polymorphism and mood disorders: a meta-analysis. *Biol. Psychiatry,* **2005**, *57*(9), 999-1003. [http://dx.doi.org/10.1016/j.biopsych.2005.01.030] [PMID: 15860340]

[66] Jesulola, E.; Micalos, P.; Baguley, I.J. Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model - are we there yet? *Behav. Brain Res.,* **2018**, *341*, 79-90. [http://dx.doi.org/10.1016/j.bbr.2017.12.025] [PMID: 29284108]

[67] Poon, D.C-H.; Ho, Y-S.; Chiu, K.; Chang, R.C-C. Cytokines: how important are they in mediating sickness? *Neurosci. Biobehav. Rev.,* **2013**, *37*(1), 1-10. [http://dx.doi.org/10.1016/j.neubiorev.2012.11.001] [PMID: 23153795]

[68] Pralong, E.; Magistretti, P.; Stoop, R. Cellular perspectives on the glutamate-monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. *Prog. Neurobiol.,* **2002**, *67*(3), 173-202. [http://dx.doi.org/10.1016/S0301-0082(02)00017-5] [PMID: 12169296]

[69] Hurst, R.; Rollema, H.; Bertrand, D. Nicotinic acetylcholine receptors: from basic science to therapeutics. *Pharmacol. Ther.,* **2013**, *137*(1), 22-54. [http://dx.doi.org/10.1016/j.pharmthera.2012.08.012] [PMID: 22925690]

[70] Holmes, A. Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. *Neurosci. Biobehav. Rev.,* **2008**, *32*(7), 1293-1314. [http://dx.doi.org/10.1016/j.neubiorev.2008.03.006] [PMID: 18439676]

[71] Li, X.; Frye, M.A.; Shelton, R.C. Review of pharmacological treatment in mood disorders and future directions for drug development. *Neuropsychopharmacology,* **2012**, *37*(1), 77-101. [http://dx.doi.org/10.1038/npp.2011.198] [PMID: 21900884]

[72] Micale, V.; Tabiova, K.; Kucerova, J.; Drago, F. Role of the endocannabinoid system in depression: from preclinical to clinical evidence in Cannabinoid modulation of emotion, memory, and motivation; Springer, **2015**, pp. 97-129. [http://dx.doi.org/10.1007/978-1-4939-2294-9_5]

[73] Coppen, A. The biochemistry of affective disorders. *Br. J. Psychiatry,* **1967**, *113*(504), 1237-1264. [http://dx.doi.org/10.1192/bjp.113.504.1237] [PMID: 4169954]

[74] Maes, M. The serotonin hypothesis of depression Psychopharmacology: the fourth generation of progress, **1995**, 933-944.

[75] Blier, P.; de Montigny, C. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders. *Neuropsychopharmacology,* **1999**, *21*(2)(Suppl.), 91S-98S. [http://dx.doi.org/10.1016/S0893-133X(99)00036-6] [PMID: 10432494]

[76] Ressler, K.J.; Nemeroff, C.B. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress. Anxiety,* **2000**, *12*(Suppl. 1), 2-19. [http://dx.doi.org/10.1002/1520-6394(2000)12:1+<2::AID-DA2>3.0.CO;2-4] [PMID: 11098410]

[77] Svenningsson, P.; Kim, Y.; Warner-Schmidt, J.; Oh, Y-S.; Greengard, P. p11 and its role in depression and therapeutic responses to antidepressants. *Nat. Rev. Neurosci.,* **2013**, *14*(10), 673-680. [http://dx.doi.org/10.1038/nrn3564] [PMID: 24002251]

[78] Albert, P.R.; Benkelfat, C.; Descarries, L. The neurobiology of depression—revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2012**, *367*, 1601. [http://dx.doi.org/10.1098/rstb.2012.0190]

[79] Hervás, I.; Artigas, F. Effect of fluoxetine on extracellular 5-hydroxytryptamine in rat brain. Role of 5-HT autoreceptors. *Eur. J. Pharmacol.,* **1998**, *358*(1), 9-18. [http://dx.doi.org/10.1016/S0014-2999(98)00579-2] [PMID: 9809863]

[80] Lambert, G.; Johansson, M.; Ågren, H.; Friberg, P. Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. *Arch. Gen. Psychiatry,* **2000**, *57*(8), 787-793. [http://dx.doi.org/10.1001/archpsyc.57.8.787] [PMID: 10920468]

[81] Leggio, G.M.; Salomone, S.; Bucolo, C.; Platania, C.; Micale, V.; Caraci, F.; Drago, F. Dopamine D(3) receptor as a new pharmacol-

ogical target for the treatment of depression. *Eur. J. Pharmacol.,* **2013**, *719*(1-3), 25-33.
[http://dx.doi.org/10.1016/j.ejphar.2013.07.022] [PMID: 23872400]

[82] Diaz, M.R.; Chappell, A.M.; Christian, D.T.; Anderson, N.J.; McCool, B.A. Dopamine D3-like receptors modulate anxiety-like behavior and regulate GABAergic transmission in the rat lateral/basolateral amygdala. *Neuropsychopharmacology,* **2011**, *36*(5), 1090-1103.
[http://dx.doi.org/10.1038/npp.2010.246] [PMID: 21270771]

[83] Garattini, S. Pharmacology of amineptine, an antidepressant agent acting on the dopaminergic system: a review. *Int. Clin. Psychopharmacol.,* **1997**, *12*(Suppl. 3), S15-S19.
[http://dx.doi.org/10.1097/00004850-199707003-00003] [PMID: 9347388]

[84] Foley, K.F.; DeSanty, K.P.; Kast, R.E. Bupropion: pharmacology and therapeutic applications. *Expert Rev. Neurother.,* **2006**, *6*(9), 1249-1265.
[http://dx.doi.org/10.1586/14737175.6.9.1249] [PMID: 17009913]

[85] Katz, N.S.; Guiard, B.P.; El Mansari, M.; Blier, P. Effects of acute and sustained administration of the catecholamine reuptake inhibitor nomifensine on the firing activity of monoaminergic neurons. *J. Psychopharmacol. (Oxford),* **2010**, *24*(8), 1223-1235.
[http://dx.doi.org/10.1177/0269881109348178] [PMID: 19939862]

[86] Tadori, Y.; Forbes, R.A.; McQuade, R.D.; Kikuchi, T. *In vitro* pharmacology of aripiprazole, its metabolite and experimental dopamine partial agonists at human dopamine D2 and D3 receptors. *Eur. J. Pharmacol.,* **2011**, *668*(3), 355-365.
[http://dx.doi.org/10.1016/j.ejphar.2011.07.020] [PMID: 21816144]

[87] Pae, C-U.; Forbes, A.; Patkar, A.A. Aripiprazole as adjunctive therapy for patients with major depressive disorder: overview and implications of clinical trial data. *CNS Drugs,* **2011**, *25*(2), 109-127.
[http://dx.doi.org/10.2165/11538980-000000000-00000] [PMID: 21254788]

[88] Kiss, B.; Horváth, A.; Némethy, Z.; Schmidt, E.; Laszlovszky, I.; Bugovics, G.; Fazekas, K.; Hornok, K.; Orosz, S.; Gyertyán, I.; Agai-Csongor, E.; Domány, G.; Tihanyi, K.; Adham, N.; Szombathelyi, Z. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: *in vitro* and neurochemical profile. *J. Pharmacol. Exp. Ther.,* **2010**, *333*(1), 328-340.
[http://dx.doi.org/10.1124/jpet.109.160432] [PMID: 20093397]

[89] Willner, P.; Hale, A.S.; Argyropoulos, S. Dopaminergic mechanism of antidepressant action in depressed patients. *J. Affect. Disord.,* **2005**, *86*(1), 37-45.
[http://dx.doi.org/10.1016/j.jad.2004.12.010] [PMID: 15820269]

[90] Gobert, A.; Rivet, J.M.; Cistarelli, L.; Melon, C.; Millan, M.J. α2-adrenergic receptor blockade markedly potentiates duloxetine- and fluoxetine-induced increases in noradrenaline, dopamine, and serotonin levels in the frontal cortex of freely moving rats. *J. Neurochem.,* **1997**, *69*(6), 2616-2619.
[http://dx.doi.org/10.1046/j.1471-4159.1997.69062616.x] [PMID: 9375697]

[91] Dremencov, E.; Gispan-Herman, I.; Rosenstein, M.; Mendelman, A.; Overstreet, D.H.; Zohar, J.; Yadid, G. The serotonin-dopamine interaction is critical for fast-onset action of antidepressant treatment: *in vivo* studies in an animal model of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2004**, *28*(1), 141-147.
[http://dx.doi.org/10.1016/j.pnpbp.2003.09.030] [PMID: 14687868]

[92] Guillin, O.; Diaz, J.; Carroll, P.; Griffon, N.; Schwartz, J-C.; Sokoloff, P. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. *Nature,* **2001**, *411*(6833), 86-89.
[http://dx.doi.org/10.1038/35075076] [PMID: 11333982]

[93] Leggio, G.M.; Bucolo, C.; Platania, C.B.M.; Salomone, S.; Drago, F. Current drug treatments targeting dopamine D3 receptor. *Pharmacol. Ther.,* **2016**, *165*, 164-177.
[http://dx.doi.org/10.1016/j.pharmthera.2016.06.007] [PMID: 27343365]

[94] Sanacora, G.; Treccani, G.; Popoli, M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology,* **2012**, *62*(1), 63-77.
[http://dx.doi.org/10.1016/j.neuropharm.2011.07.036] [PMID: 21827775]

[95] Luscher, B.; Shen, Q.; Sahir, N. The GABAergic deficit hypothesis of major depressive disorder. *Mol. Psychiatry,* **2011**, *16*(4), 383-406.
[http://dx.doi.org/10.1038/mp.2010.120] [PMID: 21079608]

[96] Miller, A.H. Conceptual confluence: the kynurenine pathway as a common target for ketamine and the convergence of the inflammation and glutamate hypotheses of depression. *Neuropsychopharmacology,* **2013**, *38*(9), 1607-1608.
[http://dx.doi.org/10.1038/npp.2013.140] [PMID: 23857540]

[97] Luscher, B.; Fuchs, T. *GABAergic control of depression-related brain states in Advances in pharmacology*; Elsevier, **2015**, pp. 97-144.

[98] Zarate, C.A., Jr; Singh, J.B.; Carlson, P.J.; Brutsche, N.E.; Ameli, R.; Luckenbaugh, D.A.; Charney, D.S.; Manji, H.K. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry,* **2006**, *63*(8), 856-864.
[http://dx.doi.org/10.1001/archpsyc.63.8.856] [PMID: 16894061]

[99] Li, N.; Liu, R-J.; Dwyer, J.M.; Banasr, M.; Lee, B.; Son, H.; Li, X-Y.; Aghajanian, G.; Duman, R.S. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol. Psychiatry,* **2011**, *69*(8), 754-761.
[http://dx.doi.org/10.1016/j.biopsych.2010.12.015] [PMID: 21292242]

[100] Harraz, M.M.; Tyagi, R.; Cortés, P.; Snyder, S.H. Antidepressant action of ketamine *via* mTOR is mediated by inhibition of nitrergic Rheb degradation. *Mol. Psychiatry,* **2016**, *21*(3), 313-319.
[http://dx.doi.org/10.1038/mp.2015.211] [PMID: 26782056]

[101] Preskorn, S.; Macaluso, M.; Mehra, D.O.; Zammit, G.; Moskal, J.R.; Burch, R.M. Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. *J. Psychiatr. Pract.,* **2015**, *21*(2), 140-149.
[http://dx.doi.org/10.1097/01.pra.0000462606.17725.93] [PMID: 25782764]

[102] Hillard, C.J.; Liu, Q.S. Endocannabinoid signaling in the etiology and treatment of major depressive illness. *Curr. Pharm. Des.,* **2014**, *20*(23), 3795-3811.
[http://dx.doi.org/10.2174/1381612811319666073 5] [PMID: 24180398]

[103] Häring, M.; Marsicano, G.; Lutz, B.; Monory, K. Identification of the cannabinoid receptor type 1 in serotonergic cells of raphe nuclei in mice. *Neuroscience,* **2007**, *146*(3), 1212-1219.
[http://dx.doi.org/10.1016/j.neuroscience.2007.02.021] [PMID: 17383106]

[104] Oropeza, V.C.; Mackie, K.; Van Bockstaele, E.J. Cannabinoid receptors are localized to noradrenergic axon terminals in the rat frontal cortex. *Brain Res.,* **2007**, *1127*(1), 36-44.
[http://dx.doi.org/10.1016/j.brainres.2006.09.110] [PMID: 17113043]

[105] Marsicano, G.; Lutz, B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. *Eur. J. Neurosci.,* **1999**, *11*(12), 4213-4225.
[http://dx.doi.org/10.1046/j.1460-9568.1999.00847.x] [PMID: 10594647]

[106] Navarria, A.; Tamburella, A.; Iannotti, F.A.; Micale, V.; Camillieri, G.; Gozzo, L.; Verde, R.; Imperatore, R.; Leggio, G.M.; Drago, F.; Di Marzo, V. The dual blocker of FAAH/TRPV1 N-arachidonoylserotonin reverses the behavioral despair induced by stress in rats and modulates the HPA-axis. *Pharmacol. Res.,* **2014**, *87*, 151-159.
[http://dx.doi.org/10.1016/j.phrs.2014.04.014] [PMID: 24861565]

[107] Carney, R.M.; Freedland, K.E.; Miller, G.E.; Jaffe, A.S. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J. Psychosom. Res.,* **2002**, *53*(4), 897-902.
[http://dx.doi.org/10.1016/S0022-3999(02)00311-2] [PMID: 12377300]

[108] Pittenger, C.; Duman, R.S. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology,* **2008**, *33*(1), 88-109.
[http://dx.doi.org/10.1038/sj.npp.1301574] [PMID: 17851537]

[109] Duman, R.S.; Monteggia, L.M. A neurotrophic model for stress-related mood disorders. *Biol. Psychiatry,* **2006**, *59*(12), 1116-1127.

[http://dx.doi.org/10.1016/j.biopsych.2006.02.013] [PMID: 16631126]

[110] Monteggia, L.M.; Barrot, M.; Powell, C.M.; Berton, O.; Galanis, V.; Gemelli, T.; Meuth, S.; Nagy, A.; Greene, R.W.; Nestler, E.J. Essential role of brain-derived neurotrophic factor in adult hippocampal function. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(29), 10827-10832. [http://dx.doi.org/10.1073/pnas.0402141101] [PMID: 15249684]

[111] Krishnan, V.; Nestler, E.J. The molecular neurobiology of depression. *Nature,* **2008**, *455*(7215), 894-902. [http://dx.doi.org/10.1038/nature07455] [PMID: 18923511]

[112] Zhang, X.; Li, J.; Sha, W.; Bu, R. Neurotrophic factors and major depressive disorder, Major Depressive Disorder-Cognitive and Neurobiological Mechanisms, IntechOpen, **2015**. Available from: https://www.intechopen.com/books/major-depressive-disorder-cognitive-and-neurobiological-mechanisms/neurotrophic-factors-and-major-depressive-disorder.

[113] Kotyuk, E.; Keszler, G.; Nemeth, N.; Ronai, Z.; Sasvari-Szekely, M.; Szekely, A. Glial cell line-derived neurotrophic factor (GDNF) as a novel candidate gene of anxiety. *PLoS One,* **2013**, *8*(12), e80613. [http://dx.doi.org/10.1371/journal.pone.0080613] [PMID: 24324616]

[114] Ambrée, O.; Bergink, V.; Grosse, L.; Alferink, J.; Drexhage, H.A.; Rothermundt, M.; Arolt, V.; Birkenhäger, T.K. S100B serum levels predict treatment response in patients with melancholic depression. *Int. J. Neuropsychopharmacol.,* **2015**, *19*(3), pyv103. [http://dx.doi.org/10.1093/ijnp/pyv103] [PMID: 26364276]

[115] Numakawa, T.; Adachi, N.; Richards, M.; Chiba, S.; Kunugi, H. Brain-derived neurotrophic factor and glucocorticoids: reciprocal influence on the central nervous system. *Neuroscience,* **2013**, *239*, 157-172. [http://dx.doi.org/10.1016/j.neuroscience.2012.09.073] [PMID: 23069755]

[116] Ichim, G.; Tauszig-Delamasure, S.; Mehlen, P. Neurotrophins and cell death. *Exp. Cell Res.,* **2012**, *318*(11), 1221-1228. [http://dx.doi.org/10.1016/j.yexcr.2012.03.006] [PMID: 22465479]

[117] Numakawa, T.; Richards, M.; Nakajima, S.; Adachi, N.; Furuta, M.; Odaka, H.; Kunugi, H. The role of brain-derived neurotrophic factor in comorbid depression: possible linkage with steroid hormones, cytokines, and nutrition. *Front. Psychiatry,* **2014**, *5*, 136. [http://dx.doi.org/10.3389/fpsyt.2014.00136] [PMID: 25309465]

[118] Calabrese, F.; Rossetti, A.C.; Racagni, G.; Gass, P.; Riva, M.A.; Molteni, R. Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. *Front. Cell. Neurosci.,* **2014**, *8*, 430. [http://dx.doi.org/10.3389/fncel.2014.00430] [PMID: 25565964]

[119] Takebayashi, M.; Hisaoka, K.; Nishida, A.; Tsuchioka, M.; Miyoshi, I.; Kozuru, T.; Hikasa, S.; Okamoto, Y.; Shinno, H.; Morinobu, S.; Yamawaki, S. Decreased levels of whole blood glial cell line-derived neurotrophic factor (GDNF) in remitted patients with mood disorders. *Int. J. Neuropsychopharmacol.,* **2006**, *9*(5), 607-612. [http://dx.doi.org/10.1017/S1461145705006085] [PMID: 16191208]

[120] Hosang, G.M.; Shiles, C.; Tansey, K.E.; McGuffin, P.; Uher, R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. *BMC Med.,* **2014**, *12*, 7. [http://dx.doi.org/10.1186/1741-7015-12-7] [PMID: 24433458]

[121] Klinedinst, N.J.; Resnick, B.; Yerges-Armstrong, L.M.; Dorsey, S.G. The interplay of genetics, behavior, and pain with depressive symptoms in the elderly. *Gerontologist,* **2015**, *55*(Suppl. 1), S67-S77. [http://dx.doi.org/10.1093/geront/gnv015] [PMID: 26055783]

[122] Bramham, C.R.; Messaoudi, E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog. Neurobiol.,* **2005**, *76*(2), 99-125. [http://dx.doi.org/10.1016/j.pneurobio.2005.06.003] [PMID: 16099088]

[123] Chen, A.; Xiong, L-J.; Tong, Y.; Mao, M. The neuroprotective roles of BDNF in hypoxic ischemic brain injury. *Biomed. Rep.,* **2013**, *1*(2), 167-176. [http://dx.doi.org/10.3892/br.2012.48] [PMID: 24648914]

[124] Fargali, S.; Sadahiro, M.; Jiang, C.; Frick, A.L.; Indall, T.; Cogliani, V.; Welagen, J.; Lin, W-J.; Salton, S.R. Role of neurotrophins in the development and function of neural circuits that regulate energy homeostasis. *J. Mol. Neurosci.,* **2012**, *48*(3), 654-659. [http://dx.doi.org/10.1007/s12031-012-9790-9] [PMID: 22581449]

[125] Pruunsild, P.; Kazantseva, A.; Aid, T.; Palm, K.; Timmusk, T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics,* **2007**, *90*(3), 397-406. [http://dx.doi.org/10.1016/j.ygeno.2007.05.004] [PMID: 17629449]

[126] Groves, J.O. Is it time to reassess the BDNF hypothesis of depression? *Mol. Psychiatry,* **2007**, *12*(12), 1079-1088. [http://dx.doi.org/10.1038/sj.mp.4002075] [PMID: 17700574]

[127] Ibáñez, C.F. Neurotrophic factors: from structure-function studies to designing effective therapeutics. *Trends Biotechnol.,* **1995**, *13*(6), 217-227. [http://dx.doi.org/10.1016/S0167-7799(00)88949-0] [PMID: 7598845]

[128] Clelland, C.D.; Choi, M.; Romberg, C.; Clemenson, G.D., Jr; Fragniere, A.; Tyers, P.; Jessberger, S.; Saksida, L.M.; Barker, R.A.; Gage, F.H.; Bussey, T.J. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science,* **2009**, *325*(5937), 210-213. [http://dx.doi.org/10.1126/science.1173215] [PMID: 19590004]

[129] Sahay, A.; Scobie, K.N.; Hill, A.S.; O'Carroll, C.M.; Kheirbek, M.A.; Burghardt, N.S.; Fenton, A.A.; Dranovsky, A.; Hen, R. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature,* **2011**, *472*(7344), 466-470. [http://dx.doi.org/10.1038/nature09817] [PMID: 21460835]

[130] Denny, C.A.; Kheirbek, M.A.; Alba, E.L.; Tanaka, K.F.; Brachman, R.A.; Laughman, K.B.; Tomm, N.K.; Turi, G.F.; Losonczy, A.; Hen, R. Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis. *Neuron,* **2014**, *83*(1), 189-201. [http://dx.doi.org/10.1016/j.neuron.2014.05.018] [PMID: 24991962]

[131] Ming, G.L.; Song, H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron,* **2011**, *70*(4), 687-702. [http://dx.doi.org/10.1016/j.neuron.2011.05.001] [PMID: 21609825]

[132] Banasr, M.; Soumier, A.; Hery, M.; Mocaër, E.; Daszuta, A. Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. *Biol. Psychiatry,* **2006**, *59*(11), 1087-1096. [http://dx.doi.org/10.1016/j.biopsych.2005.11.025] [PMID: 16499883]

[133] Dranovsky, A.; Hen, R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol. Psychiatry,* **2006**, *59*(12), 1136-1143. [http://dx.doi.org/10.1016/j.biopsych.2006.03.082] [PMID: 16797263]

[134] Fava, M.; Johe, K.; Ereshefsky, L.; Gertsik, L.G.; English, B.A.; Bilello, J.A.; Thurmond, L.M.; Johnstone, J.; Dickerson, B.C.; Makris, N.; Hoeppner, B.B.; Flynn, M.; Mischoulon, D.; Kinrys, G.; Freeman, M.P. A Phase 1B, randomized, double blind, placebo controlled, multiple-dose escalation study of NSI-189 phosphate, a neurogenic compound, in depressed patients. *Mol. Psychiatry,* **2016**, *21*(10), 1372-1380. [http://dx.doi.org/10.1038/mp.2015.178] [PMID: 26643541]

[135] Perera, T.D.; Coplan, J.D.; Lisanby, S.H.; Lipira, C.M.; Arif, M.; Carpio, C.; Spitzer, G.; Santarelli, L.; Scharf, B.; Hen, R.; Rosoklija, G.; Sackeim, H.A.; Dwork, A.J. Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. *J. Neurosci.,* **2007**, *27*(18), 4894-4901. [http://dx.doi.org/10.1523/JNEUROSCI.0237-07.2007] [PMID: 17475797]

[136] Ueyama, E.; Ukai, S.; Ogawa, A.; Yamamoto, M.; Kawaguchi, S.; Ishii, R.; Shinosaki, K. Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats. *Psychiatry Clin. Neurosci.,* **2011**, *65*(1), 77-81. [http://dx.doi.org/10.1111/j.1440-1819.2010.02170.x] [PMID: 21265939]

[137] Glasper, E.R.; Llorens-Martin, M.V.; Leuner, B.; Gould, E.; Trejo, J.L. Blockade of insulin-like growth factor-I has complex effects on structural plasticity in the hippocampus. *Hippocampus,* **2010**, *20*(6), 706-712. [PMID: 19603528]

[138] Kiuchi, T.; Lee, H.; Mikami, T. Regular exercise cures depression-like behavior *via* VEGF-Flk-1 signaling in chronically stressed mice. *Neuroscience,* **2012**, *207*, 208-217.

[http://dx.doi.org/10.1016/j.neuroscience.2012.01.023] [PMID: 22306286]

[139] Brunoni, A.R.; Machado-Vieira, R.; Zarate, C.A., Jr; Vieira, E.L.; Valiengo, L.; Benseñor, I.M.; Lotufo, P.A.; Gattaz, W.F.; Teixeira, A.L. Assessment of non-BDNF neurotrophins and GDNF levels after depression treatment with sertraline and transcranial direct current stimulation in a factorial, randomized, sham-controlled trial (SELECT-TDCS): an exploratory analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2015**, *56*, 91-96. [http://dx.doi.org/10.1016/j.pnpbp.2014.08.009] [PMID: 25172025]

[140] Autry, A.E.; Monteggia, L.M. Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacol. Rev.,* **2012**, *64*(2), 238-258. [http://dx.doi.org/10.1124/pr.111.005108] [PMID: 22407616]

[141] Lupien, S.J.; McEwen, B.S.; Gunnar, M.R.; Heim, C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat. Rev. Neurosci.,* **2009**, *10*(6), 434-445. [http://dx.doi.org/10.1038/nrn2639] [PMID: 19401723]

[142] Carroll, B.J. *Dexamethasone suppression test in depression in Handbook of Psychiatric Diagnostic Procedures*; Springer, **1980**.

[143] Hauger, R.L.; Dautzenberg, F.M. *Regulation of the stress response by corticotropin-releasing factor receptors in Neuroendocrinology in physiology and medicine*; Springer, **2000**, pp. 261-286.

[144] Herbert, J.; Goodyer, I.M.; Grossman, A.B.; Hastings, M.H.; de Kloet, E.R.; Lightman, S.L.; Lupien, S.J.; Roozendaal, B.; Seckl, J.R. Do corticosteroids damage the brain? *J. Neuroendocrinol.,* **2006**, *18*(6), 393-411. [http://dx.doi.org/10.1111/j.1365-2826.2006.01429.x] [PMID: 16684130]

[145] Gutman, D.A.; Musselman, D.L.; Nemeroff, C.B. Neuropeptide alterations in depression and anxiety disorders. *Medical Psychiatry,* **2003**, *21*, 229-266.

[146] Aguilera, G.; Subburaju, S.; Young, S.; Chen, J. The parvocellular vasopressinergic system and responsiveness of the hypothalamic pituitary adrenal axis during chronic stress. *Prog. Brain Res.,* **2008**, *170*, 29-39. [http://dx.doi.org/10.1016/S0079-6123(08)00403-2] [PMID: 18655869]

[147] Ranabir, S.; Reetu, K. Stress and hormones. *Indian J. Endocrinol. Metab.,* **2011**, *15*(1), 18-22. [http://dx.doi.org/10.4103/2230-8210.77573] [PMID: 21584161]

[148] Smith, S.M.; Vale, W.W. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin. Neurosci.,* **2006**, *8*(4), 383-395. [PMID: 17290797]

[149] Reul, J.M.; de Kloet, E.R. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology,* **1985**, *117*(6), 2505-2511. [http://dx.doi.org/10.1210/endo-117-6-2505] [PMID: 2998738]

[150] Reul, J.M.; de Kloet, E.R.; van Sluijs, F.J.; Rijnberk, A.; Rothuizen, J. Binding characteristics of mineralocorticoid and glucocorticoid receptors in dog brain and pituitary. *Endocrinology,* **1990**, *127*(2), 907-915. [http://dx.doi.org/10.1210/endo-127-2-907] [PMID: 2164924]

[151] Stavreva, D.A.; Wiench, M.; John, S.; Conway-Campbell, B.L.; McKenna, M.A.; Pooley, J.R.; Johnson, T.A.; Voss, T.C.; Lightman, S.L.; Hager, G.L. Ultradian hormone stimulation induces glucocorticoid receptor-mediated pulses of gene transcription. *Nat. Cell Biol.,* **2009**, *11*(9), 1093-1102. [http://dx.doi.org/10.1038/ncb1922] [PMID: 19684579]

[152] Palazidou, E. The neurobiology of depression. *Br. Med. Bull.,* **2012**, *101*, 127-145. [http://dx.doi.org/10.1093/bmb/lds004] [PMID: 22334281]

[153] Pariante, C.M.; Lightman, S.L. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci.,* **2008**, *31*(9), 464-468. [http://dx.doi.org/10.1016/j.tins.2008.06.006] [PMID: 18675469]

[154] Carroll, B.J. The dexamethasone suppression test for melancholia. *Br. J. Psychiatry,* **1982**, *140*, 292-304. [http://dx.doi.org/10.1192/bjp.140.3.292] [PMID: 7093598]

[155] Nemeroff, C.B.; Vale, W.W. The neurobiology of depression: inroads to treatment and new drug discovery. *J. Clin. Psychiatry,* **2005**, *66*(Suppl. 7), 5-13. [PMID: 16124836]

[156] Schatzberg, A.F.; Keller, J.; Tennakoon, L.; Lembke, A.; Williams, G.; Kraemer, F.B.; Sarginson, J.E.; Lazzeroni, L.C.; Murphy, G.M. HPA axis genetic variation, cortisol and psychosis in major depression. *Mol. Psychiatry,* **2014**, *19*(2), 220-227. [http://dx.doi.org/10.1038/mp.2013.129] [PMID: 24166410]

[157] Lee, S.; Ng, K.L.; Tsang, A. Prevalence and correlates of depression with atypical symptoms in Hong Kong. *Aust. N. Z. J. Psychiatry,* **2009**, *43*(12), 1147-1154. [http://dx.doi.org/10.3109/00048670903279895] [PMID: 20001414]

[158] Zhao, Y.; Ma, R.; Shen, J.; Su, H.; Xing, D.; Du, L. A mouse model of depression induced by repeated corticosterone injections. *Eur. J. Pharmacol.,* **2008**, *581*(1-2), 113-120. [http://dx.doi.org/10.1016/j.ejphar.2007.12.005] [PMID: 18184609]

[159] Ali, S.H.; Madhana, R.M.; K v, A.; Kasala, E.R.; Bodduluru, L.N.; Pitta, S.; Mahareddy, J.R.; Lahkar, M. Resveratrol ameliorates depressive-like behavior in repeated corticosterone-induced depression in mice. *Steroids,* **2015**, *101*, 37-42. [http://dx.doi.org/10.1016/j.steroids.2015.05.010] [PMID: 26048446]

[160] Freitas, A.E.; Egea, J.; Buendia, I.; Gómez-Rangel, V.; Parada, E.; Navarro, E.; Casas, A.I.; Wojnicz, A.; Ortiz, J.A.; Cuadrado, A.; Ruiz-Nuño, A.; Rodrigues, A.L.S.; Lopez, M.G. Agmatine, by improving neuroplasticity markers and inducing Nrf2, prevents corticosterone-induced depressive-like behavior in mice. *Mol. Neurobiol.,* **2016**, *53*(5), 3030-3045. [http://dx.doi.org/10.1007/s12035-015-9182-6] [PMID: 25966970]

[161] McEwen, B.S. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol. Rev.,* **2007**, *87*(3), 873-904. [http://dx.doi.org/10.1152/physrev.00041.2006] [PMID: 17615391]

[162] Dekker, M.J.; Tiemeier, H.; Luijendijk, H.J.; Kuningas, M.; Hofman, A.; de Jong, F.H.; Stewart, P.M.; Koper, J.W.; Lamberts, S.W. The effect of common genetic variation in 11β-hydroxysteroid dehydrogenase type 1 on hypothalamic-pituitary-adrenal axis activity and incident depression. *J. Clin. Endocrinol. Metab.,* **2012**, *97*(2), E233-E237. [http://dx.doi.org/10.1210/jc.2011-0601] [PMID: 22112815]

[163] Maes, M.; Bosmans, E.; Suy, E.; Vandervorst, C.; De Jonckheere, C.; Raus, J. Immune disturbances during major depression: upregulated expression of interleukin-2 receptors. *Neuropsychobiology,* **1990-1991**, *24*(3), 115-120. [http://dx.doi.org/10.1159/000119472] [PMID: 2135065]

[164] Maes, M.; Bosmans, E.; Suy, E.; Vandervorst, C.; DeJonckheere, C.; Raus, J. Depression-related disturbances in mitogen-induced lymphocyte responses and interleukin-1 β and soluble interleukin-2 receptor production. *Acta Psychiatr. Scand.,* **1991**, *84*(4), 379-386. [http://dx.doi.org/10.1111/j.1600-0447.1991.tb03163.x] [PMID: 1746291]

[165] Maes, M.; Scharpé, S.; Meltzer, H.Y.; Bosmans, E.; Suy, E.; Calabrese, J.; Cosyns, P. Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. *Psychiatry Res.,* **1993**, *49*(1), 11-27. [http://dx.doi.org/10.1016/0165-1781(93)90027-E] [PMID: 7511248]

[166] Maes, M.; Bosmans, E.; Meltzer, H.Y. Immunoendocrine aspects of major depression. Relationships between plasma interleukin-6 and soluble interleukin-2 receptor, prolactin and cortisol. *Eur. Arch. Psychiatry Clin. Neurosci.,* **1995**, *245*(3), 172-178. [http://dx.doi.org/10.1007/BF02193091] [PMID: 7669825]

[167] Smith, R.S. The macrophage theory of depression. *Med. Hypotheses,* **1991**, *35*(4), 298-306. [http://dx.doi.org/10.1016/0306-9877(91)90272-Z] [PMID: 1943879]

[168] Maes, M. Evidence for an immune response in major depression: a review and hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **1995**, *19*(1), 11-38. [http://dx.doi.org/10.1016/0278-5846(94)00101-M] [PMID: 7708925]

[169] Darko, D.F.; Lucas, A.H.; Gillin, J.C.; Risch, S.C.; Golshan, S.; Hamburger, R.N.; Silverman, M.B.; Janowsky, D.S. Cellular immunity and the hypothalamic-pituitary axis in major affective disorder: a preliminary study. *Psychiatry Res.,* **1988**, *25*(1), 1-9. [http://dx.doi.org/10.1016/0165-1781(88)90152-7] [PMID: 2905815]

[170] Tondo, L.; Pani, P.; Pellegrini-Bettoli, R.; Milia, G. T-lymphocytes in depressive disorder. *Med. Sci. Res.,* **1988**, *16*, 867-868.

[171] Maes, M.; Lambrechts, J.; Bosmans, E.; Jacobs, J.; Suy, E.; Vandervorst, C.; de Jonckheere, C.; Minner, B.; Raus, J. Evidence for a systemic immune activation during depression: results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining. *Psychol. Med.,* **1992**, *22*(1), 45-53. [http://dx.doi.org/10.1017/S0033291700032712] [PMID: 1574566]

[172] Liu, Y.; Ho, R.C-M.; Mak, A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J. Affect. Disord.,* **2012**, *139*(3), 230-239. [http://dx.doi.org/10.1016/j.jad.2011.08.003] [PMID: 21872339]

[173] Maes, M.; Stevens, W.J.; DeClerck, L.S.; Bridts, C.H.; Peeters, D.; Schotte, C.; Cosyns, P. A significantly increased number and percentage of B cells in depressed subjects: results of flow cytometric measurements. *J. Affect. Disord.,* **1992**, *24*(3), 127-134. [http://dx.doi.org/10.1016/0165-0327(92)90060-J] [PMID: 1573121]

[174] Robertson, M.J.; Schacterle, R.S.; Mackin, G.A.; Wilson, S.N.; Bloomingdale, K.L.; Ritz, J.; Komaroff, A.L. Lymphocyte subset differences in patients with chronic fatigue syndrome, multiple sclerosis and major depression. *Clin. Exp. Immunol.,* **2005**, *141*(2), 326-332. [http://dx.doi.org/10.1111/j.1365-2249.2005.02833.x] [PMID: 15996197]

[175] Li, Y.; Xiao, B.; Qiu, W.; Yang, L.; Hu, B.; Tian, X.; Yang, H. Altered expression of $CD4^{(+)}CD25^{(+)}$ regulatory T cells and its 5-HT(1a) receptor in patients with major depression disorder. *J. Affect. Disord.,* **2010**, *124*(1-2), 68-75. [http://dx.doi.org/10.1016/j.jad.2009.10.018] [PMID: 19900711]

[176] Ronaldson, A.; Gazali, A.M.; Zalli, A.; Kaiser, F.; Thompson, S.J.; Henderson, B.; Steptoe, A.; Carvalho, L. Increased percentages of regulatory T cells are associated with inflammatory and neuroendocrine responses to acute psychological stress and poorer health status in older men and women. *Psychopharmacology (Berl.),* **2016**, *233*(9), 1661-1668. [http://dx.doi.org/10.1007/s00213-015-3876-3] [PMID: 25678193]

[177] Musselman, D.L.; Lawson, D.H.; Gumnick, J.F.; Manatunga, A.K.; Penna, S.; Goodkin, R.S.; Greiner, K.; Nemeroff, C.B.; Miller, A.H. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.,* **2001**, *344*(13), 961-966. [http://dx.doi.org/10.1056/NEJM200103293441303] [PMID: 11274622]

[178] Capuron, L.; Raison, C.L.; Musselman, D.L.; Lawson, D.H.; Nemeroff, C.B.; Miller, A.H. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am. J. Psychiatry,* **2003**, *160*(7), 1342-1345. [http://dx.doi.org/10.1176/appi.ajp.160.7.1342] [PMID: 12832253]

[179] Felger, J.C.; Lotrich, F.E. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience,* **2013**, *246*, 199-229. [http://dx.doi.org/10.1016/j.neuroscience.2013.04.060] [PMID: 23644052]

[180] Maes, M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. *Neuroendocrinol. Lett.,* **2008**, *29*(3), 287-291. [PMID: 18580840]

[181] Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W.; Kelley, K.W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.,* **2008**, *9*(1), 46-56. [http://dx.doi.org/10.1038/nrn2297] [PMID: 18073775]

[182] Capuron, L.; Miller, A.H. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol. Ther.,* **2011**, *130*(2), 226-238. [http://dx.doi.org/10.1016/j.pharmthera.2011.01.014] [PMID: 21334376]

[183] Loftis, J.M.; Huckans, M.; Morasco, B.J. Neuroimmune mechanisms of cytokine-induced depression: current theories and novel treatment strategies. *Neurobiol. Dis.,* **2010**, *37*(3), 519-533. [http://dx.doi.org/10.1016/j.nbd.2009.11.015] [PMID: 19944762]

[184] Valentine, A.D.; Meyers, C.A. Neurobehavioral effects of interferon therapy. *Curr. Psychiatry Rep.,* **2005**, *7*(5), 391-395. [http://dx.doi.org/10.1007/s11920-005-0042-3] [PMID: 16216160]

[185] Wichers, M.C.; Kenis, G.; Koek, G.H.; Robaeys, G.; Nicolson, N.A.; Maes, M. Interferon-α-induced depressive symptoms are related to changes in the cytokine network but not to cortisol. *J. Psychosom. Res.,* **2007**, *62*(2), 207-214. [http://dx.doi.org/10.1016/j.jpsychores.2006.09.007] [PMID: 17270579]

[186] Haapakoski, R.; Ebmeier, K.P.; Alenius, H.; Kivimäki, M. Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2016**, *66*, 63-72. [http://dx.doi.org/10.1016/j.pnpbp.2015.11.012] [PMID: 26631274]

[187] Uher, R.; Tansey, K.E.; Dew, T.; Maier, W.; Mors, O.; Hauser, J.; Dernovsek, M.Z.; Henigsberg, N.; Souery, D.; Farmer, A.; McGuffin, P. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am. J. Psychiatry,* **2014**, *171*(12), 1278-1286. [http://dx.doi.org/10.1176/appi.ajp.2014.14010094] [PMID: 25017001]

[188] Grosse, L.; Carvalho, L.A.; Birkenhager, T.K.; Hoogendijk, W.J.; Kushner, S.A.; Drexhage, H.A.; Bergink, V. Circulating cytotoxic T cells and natural killer cells as potential predictors for antidepressant response in melancholic depression. Restoration of T regulatory cell populations after antidepressant therapy. *Psychopharmacology (Berl.),* **2016**, *233*(9), 1679-1688. [http://dx.doi.org/10.1007/s00213-015-3943-9] [PMID: 25953327]

[189] Miller, A.H. Depression and immunity: a role for T cells? *Brain Behav. Immun.,* **2010**, *24*(1), 1-8. [http://dx.doi.org/10.1016/j.bbi.2009.09.009] [PMID: 19818725]

[190] Grosse, L.; Carvalho, L.A.; Wijkhuijs, A.J.; Bellingrath, S.; Ruland, T.; Ambrée, O.; Alferink, J.; Ehring, T.; Drexhage, H.A.; Arolt, V. Clinical characteristics of inflammation-associated depression: Monocyte gene expression is age-related in major depressive disorder. *Brain Behav. Immun.,* **2015**, *44*, 48-56. [http://dx.doi.org/10.1016/j.bbi.2014.08.004] [PMID: 25150007]

[191] Grosse, L.; Hoogenboezem, T.; Ambrée, O.; Bellingrath, S.; Jörgens, S.; de Wit, H.J.; Wijkhuijs, A.M.; Arolt, V.; Drexhage, H.A. Deficiencies of the T and natural killer cell system in major depressive disorder: T regulatory cell defects are associated with inflammatory monocyte activation. *Brain Behav. Immun.,* **2016**, *54*, 38-44. [http://dx.doi.org/10.1016/j.bbi.2015.12.003] [PMID: 26674997]

[192] Jansen, R.; Penninx, B.W.; Madar, V.; Xia, K.; Milaneschi, Y.; Hottenga, J.J.; Hammerschlag, A.R.; Beekman, A.; van der Wee, N.; Smit, J.H.; Brooks, A.I.; Tischfield, J.; Posthuma, D.; Schoevers, R.; van Grootheest, G.; Willemsen, G.; de Geus, E.J.; Boomsma, D.I.; Wright, F.A.; Zou, F.; Sun, W.; Sullivan, P.F. Gene expression in major depressive disorder. *Mol. Psychiatry,* **2016**, *21*(3), 339-347. [http://dx.doi.org/10.1038/mp.2015.57] [PMID: 26008736]

[193] Dean, J.; Keshavan, M. The neurobiology of depression: An integrated view. *Asian J. Psychiatr.,* **2017**, *27*, 101-111. [http://dx.doi.org/10.1016/j.ajp.2017.01.025] [PMID: 28558878]

[194] Fallarino, F.; Grohmann, U.; Vacca, C.; Orabona, C.; Spreca, A.; Fioretti, M.C.; Puccetti, P. *T cell apoptosis by kynurenines in Developments in tryptophan and serotonin metabolism*; Springer, **2003**, pp. 183-190. [http://dx.doi.org/10.1007/978-1-4615-0135-0_21]

[195] Terness, P.; Bauer, T.M.; Röse, L.; Dufter, C.; Watzlik, A.; Simon, H.; Opelz, G. Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: mediation of suppression by tryptophan metabolites. *J. Exp. Med.,* **2002**, *196*(4), 447-457. [http://dx.doi.org/10.1084/jem.20020052] [PMID: 12186837]

[196] Morris, G.; Carvalho, A.F.; Anderson, G.; Galecki, P.; Maes, M. The many neuroprogressive actions of tryptophan catabolites (TRYCATs) that may be associated with the pathophysiology of neuro-immune disorders. *Curr. Pharm. Des.,* **2016**, *22*(8), 963-977. [http://dx.doi.org/10.2174/1381612822666151215102420] [PMID: 26667000]

[197] Maes, M.; Leonard, B.E.; Myint, A.M.; Kubera, M.; Verkerk, R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental

tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 702-721.
[http://dx.doi.org/10.1016/j.pnpbp.2010.12.017] [PMID: 21185346]

[198] Maes, M.; Galecki, P.; Verkerk, R.; Rief, W. Somatization, but not depression, is characterized by disorders in the tryptophan catabolite (TRYCAT) pathway, indicating increased indoleamine 2,3-dioxygenase and lowered kynurenine aminotransferase activity. *Neuroendocrinol. Lett.,* **2011**, *32*(3), 264-273.
[PMID: 21712776]

[199] Maes, M.; Wauters, A.; Verkerk, R.; Demedts, P.; Neels, H.; Van Gastel, A.; Cosyns, P.; Scharpé, S.; Desnyder, R. Lower serum L-tryptophan availability in depression as a marker of a more generalized disorder in protein metabolism. *Neuropsychopharmacology,* **1996**, *15*(3), 243-251.
[http://dx.doi.org/10.1016/0893-133X(95)00181-C] [PMID: 8873107]

[200] Maes, M.; Mihaylova, I.; Ruyter, M.D.; Kubera, M.; Bosmans, E. The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation. *Neuroendocrinol. Lett.,* **2007**, *28*(6), 826-831.
[PMID: 18063923]

[201] Setiawan, E.; Wilson, A.A.; Mizrahi, R.; Rusjan, P.M.; Miler, L.; Rajkowska, G.; Suridjan, I.; Kennedy, J.L.; Rekkas, P.V.; Houle, S.; Meyer, J.H. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry,* **2015**, *72*(3), 268-275.
[http://dx.doi.org/10.1001/jamapsychiatry.2014.2427] [PMID: 25629589]

[202] Réus, G.Z.; Fries, G.R.; Stertz, L.; Badawy, M.; Passos, I.C.; Barichello, T.; Kapczinski, F.; Quevedo, J. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience,* **2015**, *300*, 141-154.
[http://dx.doi.org/10.1016/j.neuroscience.2015.05.018] [PMID: 25981208]

[203] Ransohoff, R.M.; Cardona, A.E. The myeloid cells of the central nervous system parenchyma. *Nature,* **2010**, *468*(7321), 253-262.
[http://dx.doi.org/10.1038/nature09615] [PMID: 21068834]

[204] Maccioni, R.B.; Rojo, L.E.; Fernández, J.A.; Kuljis, R.O. The role of neuroimmunomodulation in Alzheimer's disease. *Ann. N. Y. Acad. Sci.,* **2009**, *1153*, 240-246.
[http://dx.doi.org/10.1111/j.1749-6632.2008.03972.x] [PMID: 19236346]

[205] Martinon, F.; Burns, K.; Tschopp, J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-β. *Mol. Cell,* **2002**, *10*(2), 417-426.
[http://dx.doi.org/10.1016/S1097-2765(02)00599-3] [PMID: 12191486]

[206] Leemans, J.C.; Cassel, S.L.; Sutterwala, F.S. Sensing damage by the NLRP3 inflammasome. *Immunol. Rev.,* **2011**, *243*(1), 152-162.
[http://dx.doi.org/10.1111/j.1600-065X.2011.01043.x] [PMID: 21884174]

[207] Hornung, V.; Latz, E. Critical functions of priming and lysosomal damage for NLRP3 activation. *Eur. J. Immunol.,* **2010**, *40*(3), 620-623.
[http://dx.doi.org/10.1002/eji.200940185] [PMID: 20201015]

[208] Martinon, F.; Mayor, A.; Tschopp, J. The inflammasomes: guardians of the body. *Annu. Rev. Immunol.,* **2009**, *27*, 229-265.
[http://dx.doi.org/10.1146/annurev.immunol.021908.132715] [PMID: 19302040]

[209] Church, L.D.; Cook, G.P.; McDermott, M.F. Primer: inflammasomes and interleukin 1β in inflammatory disorders. *Nat. Clin. Pract. Rheumatol.,* **2008**, *4*(1), 34-42.
[http://dx.doi.org/10.1038/ncprheum0681] [PMID: 18172447]

[210] Walsh, J.G.; Muruve, D.A.; Power, C. Inflammasomes in the CNS. *Nat. Rev. Neurosci.,* **2014**, *15*(2), 84-97.
[http://dx.doi.org/10.1038/nrn3638] [PMID: 24399084]

[211] Alcocer-Gómez, E.; de Miguel, M.; Casas-Barquero, N.; Núñez-Vasco, J.; Sánchez-Alcazar, J.A.; Fernández-Rodríguez, A.; Cordero, M.D. NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. *Brain Behav. Immun.,* **2014**, *36*, 111-117.
[http://dx.doi.org/10.1016/j.bbi.2013.10.017] [PMID: 24513871]

[212] Raz, E. Organ-specific regulation of innate immunity. *Nat. Immunol.,* **2007**, *8*(1), 3-4.
[http://dx.doi.org/10.1038/ni0107-3] [PMID: 17179960]

[213] Marino, F.; Cosentino, M. Adrenergic modulation of immune cells: an update. *Amino Acids,* **2013**, *45*(1), 55-71.
[http://dx.doi.org/10.1007/s00726-011-1186-6] [PMID: 22160285]

[214] Amsterdam, A.; Tajima, K.; Sasson, R. Cell-specific regulation of apoptosis by glucocorticoids: implication to their anti-inflammatory action. *Biochem. Pharmacol.,* **2002**, *64*(5-6), 843-850.
[http://dx.doi.org/10.1016/S0006-2952(02)01147-4] [PMID: 12213578]

[215] Tracey, K.J. Reflex control of immunity. *Nat. Rev. Immunol.,* **2009**, *9*(6), 418-428.
[http://dx.doi.org/10.1038/nri2566] [PMID: 19461672]

[216] Hodes, G.E.; Kana, V.; Menard, C.; Merad, M.; Russo, S.J. Neuroimmune mechanisms of depression. *Nat. Neurosci.,* **2015**, *18*(10), 1386-1393.
[http://dx.doi.org/10.1038/nn.4113] [PMID: 26404713]

[217] Manz, M.G.; Boettcher, S. Emergency granulopoiesis. *Nat. Rev. Immunol.,* **2014**, *14*(5), 302-314.
[http://dx.doi.org/10.1038/nri3660] [PMID: 24751955]

[218] Belarbi, K.; Arellano, C.; Ferguson, R.; Jopson, T.; Rosi, S. Chronic neuroinflammation impacts the recruitment of adult-born neurons into behaviorally relevant hippocampal networks. *Brain Behav. Immun.,* **2012**, *26*(1), 18-23.
[http://dx.doi.org/10.1016/j.bbi.2011.07.225] [PMID: 21787860]

[219] Walter, J.; Honsek, S.D.; Illes, S.; Wellen, J.M.; Hartung, H-P.; Rose, C.R.; Dihné, M. A new role for interferon gamma in neural stem/precursor cell dysregulation. *Mol. Neurodegener.,* **2011**, *6*, 18.
[http://dx.doi.org/10.1186/1750-1326-6-18] [PMID: 21371330]

[220] Hritcu, L.; Gorgan, L.D. Intranigral lipopolysaccharide induced anxiety and depression by altered BDNF mRNA expression in rat hippocampus. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2014**, *51*, 126-132.
[http://dx.doi.org/10.1016/j.pnpbp.2014.01.016] [PMID: 24508447]

[221] Di Filippo, M.; Chiasserini, D.; Gardoni, F.; Viviani, B.; Tozzi, A.; Giampà, C.; Costa, C.; Tantucci, M.; Zianni, E.; Boraso, M.; Siliquini, S.; de Iure, A.; Ghiglieri, V.; Colcelli, E.; Baker, D.; Sarchielli, P.; Fusco, F.R.; Di Luca, M.; Calabresi, P. Effects of central and peripheral inflammation on hippocampal synaptic plasticity. *Neurobiol. Dis.,* **2013**, *52*, 229-236.
[http://dx.doi.org/10.1016/j.nbd.2012.12.009] [PMID: 23295855]

[222] Galic, M.A.; Riazi, K.; Pittman, Q.J. Cytokines and brain excitability. *Front. Neuroendocrinol.,* **2012**, *33*(1), 116-125.
[http://dx.doi.org/10.1016/j.yfrne.2011.12.002] [PMID: 22214786]

[223] Maes, M.; Galecki, P.; Chang, Y.S.; Berk, M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 676-692.
[http://dx.doi.org/10.1016/j.pnpbp.2010.05.004] [PMID: 20471444]

[224] Black, C.N.; Bot, M.; Scheffer, P.G.; Cuijpers, P.; Penninx, B.W. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology,* **2015**, *51*, 164-175.
[http://dx.doi.org/10.1016/j.psyneuen.2014.09.025] [PMID: 25462890]

[225] Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: markers that further explain the higher incidence of neurodegeneration and coronary artery disease. *J. Affect. Disord.,* **2010**, *125*(1-3), 287-294.
[http://dx.doi.org/10.1016/j.jad.2009.12.014] [PMID: 20083310]

[226] Katalinic, V.; Modun, D.; Music, I.; Boban, M. Gender differences in antioxidant capacity of rat tissues determined by 2,2′-azinobis (3-ethylbenzothiazoline 6-sulfonate; ABTS) and ferric reducing antioxidant power (FRAP) assays. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.,* **2005**, *140*(1), 47-52.
[http://dx.doi.org/10.1016/j.cca.2005.01.005] [PMID: 15792622]

[227] Bakunina, N.; Pariante, C.M.; Zunszain, P.A. Immune mechanisms linked to depression *via* oxidative stress and neuroprogression. *Immunology,* **2015**, *144*(3), 365-373.
[http://dx.doi.org/10.1111/imm.12443] [PMID: 25580634]

[228] Gardner, A.; Johansson, A.; Wibom, R.; Nennesmo, I.; von Döbeln, U.; Hagenfeldt, L.; Hällström, T. Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients. *J. Affect. Disord.,* **2003**, *76*(1-3), 55-68. [http://dx.doi.org/10.1016/S0165-0327(02)00067-8] [PMID: 12943934]

[229] Gong, Y.; Chai, Y.; Ding, J-H.; Sun, X-L.; Hu, G. Chronic mild stress damages mitochondrial ultrastructure and function in mouse brain. *Neurosci. Lett.,* **2011**, *488*(1), 76-80. [http://dx.doi.org/10.1016/j.neulet.2010.11.006] [PMID: 21070835]

[230] Gandhi, S.; Abramov, A. Y. Mechanism of oxidative stress in neurodegeneration. *Oxidative Medicine and Cellular Longevity,* **2012**, *2012*. 1-11. [http://dx.doi.org/10.1155/2012/428010]

[231] Bakunina, N.; Pariante, C.; Zunszain, P. Modulation of oxidative stress in human hippocampal progenitor cells: a model to study underlying mechanisms of depression. *Free Radic. Biol. Med.,* **2015**, *86*, S19. [http://dx.doi.org/10.1016/j.freeradbiomed.2015.07.077]

[232] Djordjevic, J.; Djordjevic, A.; Adzic, M.; Mitic, M.; Lukic, I.; Radojcic, M.B. Alterations in the Nrf2-Keap1 signaling pathway and its downstream target genes in rat brain under stress. *Brain Res.,* **2015**, *1602*, 20-31. [http://dx.doi.org/10.1016/j.brainres.2015.01.010] [PMID: 25598205]

[233] Neurauter, G.; Schröcksnadel, K.; Scholl-Bürgi, S.; Sperner-Unterweger, B.; Schubert, C.; Ledochowski, M.; Fuchs, D. Chronic immune stimulation correlates with reduced phenylalanine turnover. *Curr. Drug Metab.,* **2008**, *9*(7), 622-627. [http://dx.doi.org/10.2174/138920008785821738] [PMID: 18781914]

[234] Kitagishi, Y.; Kobayashi, M.; Kikuta, K.; Matsuda, S. Roles of PI3K/AKT/GSK3/mTOR pathway in cell signaling of mental illnesses *Depression Res. Treat.,* **2012**, *2012*. 1-8.

[235] Hayashi, T. Conversion of psychological stress into cellular stress response: roles of the sigma-1 receptor in the process. *Psychiatry Clin. Neurosci.,* **2015**, *69*(4), 179-191. [http://dx.doi.org/10.1111/pcn.12262] [PMID: 25495202]

[236] Hotamisligil, G.S. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell,* **2010**, *140*(6), 900-917. [http://dx.doi.org/10.1016/j.cell.2010.02.034] [PMID: 20303879]

[237] Gold, P.W.; Licinio, J.; Pavlatou, M.G. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-γ systems. *Mol. Psychiatry,* **2013**, *18*(2), 154-165. [http://dx.doi.org/10.1038/mp.2012.167] [PMID: 23183489]

[238] Schröder, M.; Kaufman, R.J. The mammalian unfolded protein response. *Annu. Rev. Biochem.,* **2005**, *74*, 739-789. [http://dx.doi.org/10.1146/annurev.biochem.73.011303.074134] [PMID: 15952902]

[239] Smith, M.H.; Ploegh, H.L.; Weissman, J.S. Road to ruin: targeting proteins for degradation in the endoplasmic reticulum. *Science,* **2011**, *334*(6059), 1086-1090. [http://dx.doi.org/10.1126/science.1209235] [PMID: 22116878]

[240] Nevell, L.; Zhang, K.; Aiello, A.E.; Koenen, K.; Galea, S.; Soliven, R.; Zhang, C.; Wildman, D.E.; Uddin, M. Elevated systemic expression of ER stress related genes is associated with stress-related mental disorders in the Detroit Neighborhood Health Study. *Psychoneuroendocrinology,* **2014**, *43*, 62-70. [http://dx.doi.org/10.1016/j.psyneuen.2014.01.013] [PMID: 24703171]

[241] Timberlake, M.A., II; Dwivedi, Y. Altered expression of endoplasmic reticulum stress associated genes in hippocampus of learned helpless rats: relevance to depression pathophysiology. *Front. Pharmacol.,* **2016**, *6*, 319. [http://dx.doi.org/10.3389/fphar.2015.00319] [PMID: 26793110]

[242] Gardner, A.; Boles, R.G. Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 730-743. [http://dx.doi.org/10.1016/j.pnpbp.2010.07.030] [PMID: 20691744]

[243] Karry, R.; Klein, E.; Ben Shachar, D. Mitochondrial complex I subunits expression is altered in schizophrenia: a postmortem study. *Biol. Psychiatry,* **2004**, *55*(7), 676-684. [http://dx.doi.org/10.1016/j.biopsych.2003.12.012] [PMID: 15038995]

[244] Shao, L.; Martin, M.V.; Watson, S.J.; Schatzberg, A.; Akil, H.; Myers, R.M.; Jones, E.G.; Bunney, W.E.; Vawter, M.P. Mitochondrial involvement in psychiatric disorders. *Ann. Med.,* **2008**, *40*(4), 281-295. [http://dx.doi.org/10.1080/07853890801923753] [PMID: 18428021]

[245] Andreazza, A.C.; Shao, L.; Wang, J-F.; Young, L.T. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. *Arch. Gen. Psychiatry,* **2010**, *67*(4), 360-368. [http://dx.doi.org/10.1001/archgenpsychiatry.2010.22] [PMID: 20368511]

[246] Réus, G. Z.; Stringari, R. B.; Gonçalves, C. L.; Scaini, G.; Carvalho-Silva, M.; Jeremias, G. C.; Jeremias, I. C.; Ferreira, G. K.; Streck, E. L.; Hallak, J. E. Administration of harmine and imipramine alters creatine kinase and mitochondrial respiratory chain activities in the rat brain. *Depression Res. Treat.,* **2012**, *2012*. [http://dx.doi.org/10.1155/2012/987397]

[247] Kormos, V.; Gaszner, B. Role of neuropeptides in anxiety, stress, and depression: from animals to humans. *Neuropeptides,* **2013**, *47*(6), 401-419. [http://dx.doi.org/10.1016/j.npep.2013.10.014] [PMID: 24210138]

[248] Westrich, L.; Sprouse, J. Circadian rhythm dysregulation in bipolar disorder. *Curr. Opinion Investig. Drugs (London, England: 2000),,* **2010**, *11*, 779-787.

[249] Quera, A.; Salva, M. Hartley, S.; Barbot, F.; C Alvarez, J.; Lofaso, F.; Guilleminault, C. Circadian rhythms, melatonin and depression. *Curr. Pharm. Des.,* **2011**, *17*, 1459-1470.

[250] Orozco-Solis, R.; Montellier, E.; Aguilar-Arnal, L.; Sato, S.; Vawter, M.P.; Bunney, B.G.; Bunney, W.E.; Sassone-Corsi, P. A circadian genomic signature common to ketamine and sleep deprivation in the anterior cingulate cortex. *Biol. Psychiatry,* **2017**, *82*(5), 351-360. [http://dx.doi.org/10.1016/j.biopsych.2017.02.1176] [PMID: 28395871]

[251] Grosso, G.; Pajak, A.; Marventano, S.; Castellano, S.; Galvano, F.; Bucolo, C.; Drago, F.; Caraci, F. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One,* **2014**, *9*(5), e96905. [http://dx.doi.org/10.1371/journal.pone.0096905] [PMID: 24805797]

[252] Grosso, G.; Galvano, F.; Marventano, S.; Malaguarnera, M.; Bucolo, C.; Drago, F.; Caraci, F. Omega-3 fatty acids and depression: scientific evidence and biological mechanisms. *Oxidative Medicine and Cellular Longevity,* **2014**, *2014*, 1-16. [http://dx.doi.org/10.1155/2014/313570]

[253] Karisetty, B.C.; Joshi, P.C.; Kumar, A.; Chakravarty, S. Sex differences in the effect of chronic mild stress on mouse prefrontal cortical BDNF levels: A role of major ovarian hormones. *Neuroscience,* **2017**, *356*, 89-101. [http://dx.doi.org/10.1016/j.neuroscience.2017.05.020] [PMID: 28527954]

[254] Papakostas, G.I.; Ionescu, D.F. Towards new mechanisms: an update on therapeutics for treatment-resistant major depressive disorder. *Mol. Psychiatry,* **2015**, *20*(10), 1142-1150. [http://dx.doi.org/10.1038/mp.2015.92] [PMID: 26148812]

[255] Ramaker, M.J.; Dulawa, S.C. Identifying fast-onset antidepressants using rodent models. *Mol. Psychiatry,* **2017**, *22*(5), 656-665. [http://dx.doi.org/10.1038/mp.2017.36] [PMID: 28322276]

[256] Kocsis, J.H.; Gelenberg, A.J.; Rothbaum, B.O.; Klein, D.N.; Trivedi, M.H.; Manber, R.; Keller, M.B.; Leon, A.C.; Wisniewski, S.R.; Arnow, B.A.; Markowitz, J.C.; Thase, M.E. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP Trial. *Arch. Gen. Psychiatry,* **2009**, *66*(11), 1178-1188. [http://dx.doi.org/10.1001/archgenpsychiatry.2009.144] [PMID: 19884606]

[257] Bewernick, B.H.; Kayser, S.; Sturm, V.; Schlaepfer, T.E. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. *Neuropsychopharmacology,* **2012**, *37*(9), 1975-1985. [http://dx.doi.org/10.1038/npp.2012.44] [PMID: 22473055]

[258] McGrath, C.L.; Kelley, M.E.; Holtzheimer, P.E.; Dunlop, B.W.; Craighead, W.E.; Franco, A.R.; Craddock, R.C.; Mayberg, H.S. Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry,* **2013**, *70*(8), 821-829. [http://dx.doi.org/10.1001/jamapsychiatry.2013.143] [PMID: 23760393]

[259] Nassan, M.; Nicholson, W.T.; Elliott, M.A.; Vitek, C.R.R.; Black, J.L.; Frye, M.A. Pharmacokinetic pharmacogenetic prescribing guidelines for antidepressants: a template for psychiatric precision medicine. *Mayo Clinic Proceedings,* **2016**, *91*, 897-907. [http://dx.doi.org/10.1016/j.mayocp.2016.02.023]

[260] Sanchez, C.; Asin, K.E.; Artigas, F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol. Ther.,* **2015**, *145*, 43-57. [http://dx.doi.org/10.1016/j.pharmthera.2014.07.001] [PMID: 25016186]

[261] Ribas, L.A.A.; de Aguiar, P.H.P.; dos Santos Camargo, A.T.; Ferreira, J.J.C.; Lopes, V.H.; Simis, A.; Cottin, S.C.; Galani, N.; Simis, S. Deep brain stimulation versus vagus nerve stimulation in the treatment of therapy-resistant depression: A systematic review and meta-analysis. *Revista Chilena de Neurocirugia,* **2018**, *44*, 69.

[262] Khan, A.M.; Ahmed, R.; Kotapati, V.P.; Dar, S.K.; Qamar, I.; Jafri, A.; Ibrahim, M.; Kumar, P.; Begum, G. Vagus Nerve Stimulation (VNS) *vs*. Deep Brain Stimulation (DBS) Treatment for Major Depressive Disorder and Bipolar Depression: A Comparative Meta-analytic Review. *Int. J. Med. Public Health,* **2018**, 8. [http://dx.doi.org/10.5530/ijmedph.2018.3.26]

[263] Elliott, W.; Chan, J. *Esketamine Nasal Spray (Spravato) CIII*; *Internal Medicine Alert*, **2019**, 41.