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REVIEW ARTICLE

Role of Microglia in Psychostimulant Addiction

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Abstract: The use of psychostimulant drugs can modify brain function by inducing changes in the reward system, mainly due to alterations in dopaminergic and glutamatergic transmissions in the mesocorticolimbic pathway. However, the etiopathogenesis of addiction is a much more complex process. Previous data have suggested that microglia and other immune cells are involved in events associated with neuroplasticity and memory, which are phenomena that also occur in addiction. Nevertheless, how dependent is the development of addiction on the activity of these cells? Although the mechanisms are not known, some pathways may be involved. Recent data have shown psychoactive substances may act directly on immune cells, alter their functions and induce various inflammatory mediators that modulate synaptic activity. These could, in turn, be involved in the pathological alterations that occur in substance use disorder. Here, we extensively review the studies demonstrating how cocaine and amphetamines modulate microglial number, morphology, and function. We also describe the effect of these substances in the production of inflammatory mediators and a possible involvement of some molecular signaling pathways, such as the toll-like receptor 4. Although the literature in this field is scarce, this review compiles the knowledge on the neuroimmune axis that is involved in the pathogenesis of addiction, and suggests some pharmacological targets for the development of pharmacotherapy.

Keywords: Microglia, addiction, cocaine, amphetamine, cytokines, neuroinflammation, synaptic plasticity.

1. INTRODUCTION

Psychostimulants induce neuroplastic adaptations in memory and learning processes related to the positive reinforcement in the reward system, "hijacking" the neural adaptive motivational mechanisms and causing the dysfunctional pattern of behavior that characterizes drug addiction [1, 2]. Importantly, these neuroplastic changes that occur after drug exposure are robust; even after extended periods of abstinence, the reinforcing effects are still present, leading to high relapse rates [3]. Consequently, despite their deleterious effects and difficulty in treatment, psychostimulants remain extremely widely used [4]. This review will begin by discussing important dopaminergic and glutamatergic alterations involved in neuroplasticity induced by psychostimulant abuse. In addition, we will review the neurobiology of microglia and how these immune cells are important for synaptic plasticity. We will discuss the literature that shows alterations in microglial cells induced by psychostimulants. Finally, we will outline possible pathways through which microglia can mediate the neuroplasticity induced by psychostimulants.

2. GENERAL EFFECTS OF PSYCHOSTIMULANTS IN THE DOPAMINERGIC AND GLUTAMATERGIC PATHWAYS

Drug addiction is a chronic disease characterized by a compulsive drug-seeking behavior, lack of self-control during use, and negative physiological/psychological changes such as irritability, anxiety, and dysphoria in the absence of the substance [3, 5]. According to DSM-5, substance use disorder encompasses multiple distinct classes of drugs. Despite being divided into different categories and presenting different neuropharmacological properties, psychoactive substances can increase dopamine levels in the reward system associated with the development of addiction [5, 6].

Psychostimulants, such as cocaine, amphetamine, methamphetamine (METH), and methylene-dioxy-methamphetamine (MDMA; 'ecstasy') acutely increase the monoaminergic neurotransmission in this circuit by either blocking the membrane transporters involved in the reuptake of dopa-

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mine, norepinephrine, and serotonin, or competing with the uptake of monoamines albeit with different affinity [7]. Additionally, amphetamines can disrupt neurotransmitter storage by interacting with the vesicular monoamine transporters (VMAT2) [8] that underlie enhanced monoamine release *via* a reverse efflux transport mechanism [9-11]. Importantly, amphetamines increase dopamine transporter-induced sodium conductance, leading to neuronal depolarization and increased dopamine transmission [9, 10, 12-14].

The adaptive cellular responses in the CNS induced by prolonged exposure to psychoactive substances may occur due to the signaling pathways recruited by the dopamine receptors. For instance, activation of D_1 increases the cAMP levels that further activate protein kinase A (PKA) and extracellular signal-regulated kinase (ERK) [15]. This leads to the activation of transcription factors such as delta FosB (ΔFosB), transcription factor regulated by cAMP response element-binding protein (CREB), myocyte enhancing factor 2 (MEF2), and nuclear factor kappa B (NF-κB), which are related to changes in genes and proteins expression [16], receptor expression, cell morphology and neuronal excitability [17-20]. Thus, psychostimulants can modify signaling cascades related to neuroplasticity, which is crucial for psychostimulants' craving, drug seeking, and relapse [21, 22].

Apart from dopamine, acute and chronic psychostimulants exposure can also dysregulate glutamatergic synaptic activities that involve alterations in glutamate levels and their receptors expression, long-term potentiation (LTP), long-term depression (LTD), and modulation of synaptic connectivity strength in various brain regions involved in reward and reinforcement [23, 24]. These substances also alter the glutamatergic system of medium spiny neurons (MSN) in the nucleus accumbens (NAc), whose functions are driven by excitatory synapses arising from several cortical and subcortical projections [25].

Recently, it has been shown that some of these molecular mechanisms could be regulated by microglial cells. For example, microglia can alter the morphology and functionality of dopaminergic neurons by modifying the expression of the receptors, dopamine transporter (DAT) and tyrosine hydroxylase (TH) [26-29]. These cells are also involved in glutamatergic-induced synaptic alterations by changing AMPA receptor expression, AMPAR/NMDAR ratio, and glutamate release [30-33]. Finally, both dopaminergic and glutamatergic neurotransmissions also modulate microglial activity [34, 35], including in the context of psychostimulant abuse [36, 37]. Thus, this places these cells as an essential factor in the pathogenesis of substance use disorder. In the following sections, we will revise the current knowledge on the effects of microglia and inflammatory mediators in the brain alterations induced by cocaine and amphetamines.

3. THE INVOLVEMENT OF MICROGLIA IN DRUG ADDICTION

3.1. Overview of the History and Neurobiology of Microglial Cells

Microglia were first studied by Nissl in 1899, who described them as a distinct cellular entity with migratory and phagocytic capacity, called *Stäbchenzellen*, or rod cells, due to the shape of their nuclei. In 1913, Rámon y Cajal named microglia, together with oligodendrocytes, "third element", with neurons and astrocytes being the first and second elements. However, microglia were still unknown, and only in 1932 Pío del Rio-Hortega introduced the term “microglia" and characterized them phenotypically [38, 39]. He described the microglia as cells with ameboid morphology from the mesoderm, which enter all brain regions during early development. In the mature brain, they present a ramified morphological phenotype in the homeostatic state but acquire an ameboid morphology during pathological events, with an increased phagocytic activity [38-40].

Microglia are resident cells of the immune system that consist of about 5-10% of brain cells. They are present in the cerebral parenchyma, interacting with neurons, astrocytes, and oligodendrocytes, and together with perivascular macrophages, they occupy strategic niches, covering the entire central nervous system (CNS) [40]. Additionally, microglia numbers and their spatial distribution are heterogeneous under physiological conditions, with main differences in some regions such as the striatum, hippocampus, and cortex [41].

Microglia detect changes in the brain mainly through pattern recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering an inflammatory response [42]. In this process, microglia exert a neuroprotective function to reestablish homeostasis [43, 44]. Their homeostatic state is characterized by a highly branched morphology and a small cell body. However, once exposed to pathogens or tissue debris, these cells become polarized in a reactive phenotype with high phagocytic activity, characterized by a larger cell body and a rounded shape, shorter and thicker branches [45, 46]. In addition, there is an increase in molecules such as cytokines and the major histocompatibility complex (MHC) [43]. These morphological characteristics and specific secretory profiles occur due to the microglia's ability to perform functions such as phagocytosis of apoptotic neurons and cellular debris, protection of the brain against infections, elimination of the pathogen and tissue repair [47, 48].

These cells produce a variety of mediators depending on the stimuli they are exposed to. For example, when stimulated with lipopolysaccharide (LPS) or interferon-gamma (IFN-γ), microglia produce more pro-inflammatory or “toxic” mediators, such as tumor necrosis factor (TNF), interleukin (IL)-1β and nitric oxide (NO). On the other hand, their stimulation with IL-4 or IL-13 leads to the production of anti-inflammatory or “protective” mediators like IL-10 and arginase-1 [49-52]. However, these stimuli lead to different alterations in gene expression, electrophysiological properties, neurotransmitter receptors and microglial cell morphology and motility, allowing functional changes according to stimuli and environmental conditions. Thus, this broad spectrum of microglia activation gives them the versatility to participate in different brain processes [53] such as neural network development, neuronal survival, neurogenesis, axonal outgrowth, and synaptogenesis [54].

3.2. Microglia Regulate Synaptic Plasticity

Microglia were initially considered static cells in healthy environments. However, this view has evolved, with studies increasingly focusing on their physiological roles in the healthy brain [55, 56]. In this context, in addition to its neuroinflammatory function as a response to tissue damage, microglia may modulate the establishment and remodeling of neuronal circuits, actively participating in processes such as neurogenesis, programmed cell death, cell survival, and proliferation. Therefore, since microglia may be involved in modeling the central nervous system throughout life, microglia malfunction may be involved in neurodevelopment and CNS diseases [57-59].

Microglia have also been recognized as important regulators of synaptic plasticity due to their ability to change pre- and postsynaptic elements that alter the synaptic morphology. This is made through the release of trophic factors or microglia-neuron contact.

3.2.1. Cell-to-Cell Communication

Microglia-neuron communication through the CX_3CL_1, released by neurons, and CX_3CR_1 receptors, expressed by microglia, are important for neuronal excitability [60, 61]. IL-1β release by stimulation of CX_3CR_1 increases glutamate release, leading to postsynaptic NMDA receptor activation. TNF, another important cytokine released by microglia, regulates homeostatic synaptic scaling of AMPA receptors and may boost glutamatergic neurotransmission. Inhibitory neurotransmission in the cortex is reduced by activated microglia, which displaces GABAergic synapses [62-64] Thus, these cells can either remodel neuronal networks or control the synaptic properties.

The synaptic remodeling mediated by microglia involves the CX_3CR_1 (fractalkine receptor) and other receptors like the CR_3 complement and purinergic receptors. Microglia phagocytize dendritic spines and trogocyte small portions of axons by these different pathways. In fact, both pre- and postsynaptic (SNAP25 and PDS95, respectively) components were found inside the microglia lysosomes [65, 66]. The attraction of the microglial process to dendrites to provide contact with neurons is mediated by $P2Y_{12}$ receptors. In this sense, complement C1q, C3, and C4 components which are expressed by neurons, function as targets for microglia. Indeed, synapses may be eliminated by recognizing synaptical C3 by the microglial CR_3. Depleting these glial cells or inhibiting the complement system in the adult mouse brain affects memory removal in the contextual fear test [67]. On the other hand, CD47 and its receptor SIRP mediate the "do not eat me" signaling, since their deletion causes an increase in synaptic phagocytosis by microglia and a decrease in functional synapses [68]. Furthermore, modulation of neuronal connection by these cells can also occur by forming functional synapses. Microglial processes contacting the dendrite can increase calcium concentrations and actin accumulation. They can engulf the extracellular matrix and trogocyte presynaptic structures and induce filopodia formation and extension [55].

The clusters of differentiation (CD) are important signaling that control microglia homeostasis [69]. The CD200 is a neuronal glycoprotein that binds to the microglial receptor CD200r and controls the inflammatory activity of the cells by maintaining them in an homeostatic state [70, 71]. Disruption of this signaling can lead to synaptic deficits and cognitive impairment [71]. The CD22-CD45 pathway also works as a "negative regulator" of the neuroinflammatory processes. CD45 is a transmembrane protein-tyrosine phosphatase expressed by microglial cells, while neurons express their ligand CD22 [72, 73]. Upregulation of CD22 pathway is related to impaired microglia phagocytic activity and surveillance, as well as cognitive impairment in aged mice [72, 74]. Finally, the CD95 (Fas) and CD95 (Fas ligand) is a pathway that can drive homeostatic microglia to a more activated state [75] and mediate synaptic plasticity [76, 77].

3.2.2. Soluble Factors (Non-Contact Dependent)

Synaptic remodeling can also occur by microglia release of trophic factors that induce cell proliferation and survival, involving IL-9, IL-10, BDNF, and insulin-like growth factor type 1 (IGF-1) [78-80], among others. In addition, signals that involve TNF-α and IFN-γ can regulate synaptic pruning, eliminating the excess of immature synapses [81, 82].

Various substances secreted from neurons, such as neurotransmitters, may control the microglia's ability to change the synapses' morphology. This is achieved by different receptors expressed on glial cells, including metabotropic and ionotropic receptors. For example, IL-33 released from neurons acts on microglia and is important for dendritic spine plasticity and, possibly, memory consolidation [55]. Furthermore, microglial $P2Y_{12}$ purinergic and β-adrenergic receptors control cytokine release and alter the visual cortex's synaptic plasticity [83, 84].

Finally, it's important to emphasize that microglia release factors that modulate the activity of other glial cells, which could exert roles in synaptic plasticity. For example, ATP and TNF released by microglia increase glutamate release by astrocytes *via* $P2Y_1$ and TNF receptors, which alters the synaptic transmission [85]. The release of ATP by astrocytes may also attract microglia processes to these regions. Additionally, microglial BDNF can bind on TrkB in OPCs, which is important for activity-regulated myelination and memory [86]. Thus, glia-glia interaction is an essential communication for regulating neuroinflammation and acting as sculptors of synaptic plasticity.

3.2.3. Microglia as a Source of BDNF for Synaptic Plasticity

BDNF is the most abundant neurotrophic factor in the brain and, together with its receptor TrkB, is expressed in brain regions involved in learning and memory processes. In the CNS, BDNF is stored and released from axonal and dendritic compartments and other neural cells, such as the microglia and the astrocytes [87].

Recently, studies have shown the importance of the BDNF released from microglial cells in physiological and pathological conditions. Parkhurst *et al.* (2013) demonstrated that animals with a specific depletion of the microglial BDNF had impaired spine formation and, consequently, impaired motor task learning [78]. On the other hand, although the specific genetic ablation of microglial BDNF had no ef-

fects on the morphology of the dendritic spine of adult-born neurons under physiological conditions, it impacted microglial proliferation and hippocampal neurogenesis [88]. Besides, in neuroinflammatory conditions induced by LPS or traumatic brain injury, the specific microglial BDNF ablation increased the generation and survival of immature neurons, and also reduced the activation of these glial cells [88]. Finally, specific microglial BDNF modulation was also important in other conditions such as neuropathic pain [89], withdrawal, and hyperalgesia induced by morphine [90, 91], and after cocaine exposure [92]. Recent studies showed the role of the microglia in synaptic plasticity, besides the importance of the BDNF-TrkB pathway in conditions where microglial cells are activated [93, 94]. Activation of the phosphatidylinositol 3-kinase (PI3K)/Akt or Ca^{2+}/calmodulin dependent kinase 2a (CAMK2A)/CREB in BV-2 microglial cells increased the expression of BDNF and led to alterations in neuronal LTP and synaptic plasticity [95, 96]. In this sense, microglia activation is necessary for functional and structural plasticity in a model of chronic pain induced by high-frequency stimulus (HFS). Besides, specific ablation of the microglia or ablation of the microglial BDNF prevented the LTP induced by the HFS [97]. In another model of chronic pain, activation of the microglial receptor $P2X_4$ induced BDNF release from microglia that, consequently, mediated the plastic changes that occur in central sensitization induced by nitroglycerin (NTG) [98], and NTG associated with nicotine [99, 100]. Besides, increased BDNF levels induced by $P2X_4$ activation were also observed after alcohol exposure, which was prevented by the 5-BDBD - a $P2X_4$ antagonist - suggesting the $P2X_4$ signaling as an essential modulator of the microglia in neuroplastic functions in the context of alcohol [101-103]. In sum, given the interaction of the microglia and BDNF in synaptic plasticity in different conditions, both could act as key players in neural plasticity induced by psychostimulants.

4. RESPONSES OF MICROGLIA TO PSYCHOSTIMULANTS

Although alterations in the dopaminergic and glutamatergic systems are considered the key to neurobiological changes that regulate motivated behavior, it is well known that psychoactive substances can also alter other neurotransmitter systems such as glutamatergic, serotonergic, GABAergic, and also modulate different molecular pathways, including the neurotrophic factor and cytokines levels [104-106]. In addition, microglial cells express ion channels and neurotransmitter receptors that are also expressed in neurons; therefore, they can respond to neurochemical changes induced by psychoactive substances. Interestingly, microglial activation has been shown to modulate the reward system [29, 107], mainly because dopaminergic neurons present high liability to neuroinflammatory signals [108]. For example, in the mesolimbic pathway, D_3 knockout or D_3 inhibition showed increased BDNF levels, microglial activation, and synaptic density, which was prevented by the microglia inhibitor minocycline [109, 110].

4.1. Microglia and Cocaine

Preclinical studies have demonstrated that cocaine increases the expression of the classical microglial marker Iba-1 in the hippocampus, frontal cortex, and NAc [36, 92, 111, 112], as well as in sections encompassing the entire brain [112, 113] of mice and rats. In addition, cocaine increased the CD11 expression in the ventral tegmental area (VTA), striatum, and cortical regions [114-116]. Interestingly, Brown *et al.* (2018) found that acute cocaine injection only increases CD11 expression in mice with self-administration history [115]. Furthermore, cocaine also increased the expression of CD68 - a transmembrane glycoprotein expressed by the microglia that suggests increased phagocytic activity [117, 118]. In addition to altering protein expression in microglial cells, cocaine also alters their number and morphology. For example, Thangaraj *et al.* (2020) found an increased number of cells expressing AIF1 after cocaine treatment for seven consecutive days [119]. Moreover, Lewitus *et al.* (2016), Cotto *et al.* (2018), Silva *et al.* (2020), and Burkovetskaya *et al.* (2021) demonstrated that cocaine exposure increases the microglial cell body size and reduces the microglial branches [36, 92, 118, 120]. In other words, cocaine induces morphologic alterations, which may be related to increased microglial activation.

In non-human primates, striatal sections from monkeys subjected to the cocaine self-administration paradigm for approximately 15 months presented a greater binding of [3H]PK11195 - a marker for the microglial 18-kDa translocator protein (TSPO) in the autoradiography [121]. A study that evaluated cocaine users during abstinence did not observe any alteration in TSPO, as assessed by the PET imaging with [11C]PBR28 [122]. On the other hand, immunohistochemistry of brain slices from cocaine users showed higher ricinus communis agglutinin-1 (RCA-1) - a lectin that specifically binds to microglia - and CD68 expression than matched controls [123].

Microglial cell activity can modify the molecular mechanisms and behavioral alterations induced by psychostimulants [36, 118, 124, 125]. Inhibition of microglial activation by minocycline, a tetracycline antibiotic widely used as a microglial inhibitor, reverses the behavioral sensitization, CPP, and the NAc dopamine release induced by cocaine [125, 126]. Besides, minocycline also alters cocaine reward after nicotine and morphine exposure [91, 124]. In addition, ibudilast, a PDE4 inhibitor and glial modulator, reduces cocaine-seeking and craving in mice and humans [127-129]. Moreover, microglia depletion with the CSF-1 inhibitor PLX3397 decreased behavioral alterations induced by cocaine [118, 124]. However, the role of microglia in cocaine addiction needs further investigation as some results are controversial. For example, reduced microglial number and activity induced by minocycline, PLX3397, GW2580, or Mac-1-saporin had no effect on the CPP induced by cocaine [29, 91].

Psychoactive substances are recognized as exogenous substances by microglial cells, leading to a neuroinflammatory response [36, 125]. Regarding the psychostimulants, most studies have focused on the direct activation of toll-like receptors (TLR) - a family of PPRs present in the microglia - that, when activated, can trigger the translocation of transcriptions factors such as NF-κB and, consequently, activation of these cells and the release of cytokines. Inhibition of

this transcription factor reduces both CPP and synaptic plasticity in the NAc induced by cocaine [18].

Northcutt *et al.* (2015) showed *in silico* docking and competitive binding assay that cocaine can directly bind in the classical myeloid differentiation factor 2 (MD-2) domain in TLR4 [125]. In microglia cell cultures and animal models, cocaine up-regulates the expression of TLR4 and other components of this receptor's pathway - MyD88, IRAK1, TRAF6, and NF-κB. Besides mediating microglial activation and cytokine release after cocaine treatment, activation of TLR4 by cocaine is also important for the increased dopamine levels in the NAc induced by this psychostimulant [115, 125, 130, 131]. Thus, modulation of TLR4 signaling appears to be important for addictive-like behaviors induced by cocaine.

The antagonism of TLR4 receptors by using (+)-naloxone and (+)-naltrexone inhibited the development of CPP and cocaine self-administration, respectively [125]. An intra-VTA injection of LPS from *Rhodobacter sphaeroides*, an antagonist of TLR4, also diminished cocaine seeking in a model of relapse-like behavior [115, 132] . Moreover, depending on the dose, $TLR4^{-/-}$ mice do not develop CPP and hyperlocomotion induced by cocaine [115, 132]. On the other hand, while activation of this receptor in the VTA by LPS reinstates cocaine-seeking behavior, stimulation with MPLA, a weak TLR4 activator, decreases the behavioral sensitization by this drug [36]. Finally, decreased TLR4-mediated neuroinflammation appears to be the mechanism of activation of other substances to protect against behavioral alterations induced by this psychostimulant. For example, exendin-4, an analog of glucagon-like peptide 1, decreased the TLR4, TNF-α, and IL-1β, as well as the CPP induced by cocaine [131]. In addition, engineered extracellular vesicles loaded with miR-124 inhibited cocaine-mediated TLR4 signaling and microglial activation [113].

Other receptors from the TLR family may be associated with cocaine-mediated microglia activation. Exposure of microglial cells to cocaine resulted in increased expression of TLR2 with concomitant induction of microglial activation [117]. It has been shown that cocaine induces the formation of reactive oxygen species, leading to endoplasmic reticulum stress and subsequent translocation of the transcription factor ATF4 to the nucleus, which induces TLR2 expression. Interestingly, the signaling activated by this receptor could be further stimulated by cocaine, which would induce microglial activation [117]. Pharmacological or genetic depletion of TLR3 reduces behavioral alterations induced by cocaine, such as CPP, self-administration, locomotor activity, and pathways necessary for NF-κB activation [133].

Finally, recent studies provide the involvement of another family of PPRs in microglial activation induced by cocaine, the nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), most specifically, the pyrin domain-containing 3 (NLRP3). Cocaine also induces NLRP3 expression and IL-1β formation in microglia. The reduction of NLRP3 activity reduced both effects induced by cocaine in the brain of mice [116]. In addition, KO mice for the CX3CR1, a receptor expressed solely by microglial cells, presented higher hyperlocomotion activity and CPP induced by cocaine and higher activity of NLRP3 [134]. Moreover, inhibition of cocaine-mediated increase in IL-1β in the VTA blocks the CPP and self-administration [125]. Thus, activation of this neuroinflammatory signaling in microglial cells appears to be involved in behavioral abnormalities induced by cocaine.

4.2. Microglia and Amphetamines

Amphetamine is one of the phenethylamine derivatives that includes d-amphetamine (d-AMPH), METH, and MDMA/ecstasy [135]. METH has been the most investigated for its properties to interfere with microglia activity. *In vitro* experiments using different lineages of microglial cells, such as N9, BV2, and highly aggressively proliferating immortalized cells (HAPI), have shown METH-induced microglial activation and up-regulation of IL-1β, IL-6, and TNF-α [136-140]. This also occurred in primary microglial cells [139, 141, 142] and mixed neuron/microglia culture [143]. Notably, the regulation of the cytokines may vary depending on the amphetamine class [144]. In BV2 cells, METH exposure also increases intracellular proteins related to inflammatory pathways such as the kinases p-p38 and MAPK [145], and the pro-apoptotic protein Bax, caspase-3, and caspase-9 [146]. This drug also increased the expression of iNOS and decreased arginase [147]. In the human microglial cell line (HTHU), METH also increased caspase-3/7 and -9 expressions and decreased mitochondrial (mt)DNA content [148]. Moreover, METH also upregulated CD11b in different hippocampal subregions of organotypic slices [149]. On the other hand, incubating microglia with METH did not alter the expression of genes involved in inflammatory processes, albeit it reduced IL-1β protein levels. In addition, only a high concentration of METH reduced cell viability [150].

METH can also alter microglial-like cell morphology. For example, N9 cells, which typically present ramifications indicative of surveillance, retract their filopodia and turn into a round shape, characteristic of activation, after being exposed to METH. This psychostimulant also reduced cell volume of NR-9460 microglia [151]. METH also altered microglia in neuron/glia cocultures, which authors describe as reactive cells [152]. However, it is worth noting that the evaluation of microglia morphology in cultures is often a topic of criticism due to the absence of other cells and environment necessary for a plain occurrence of this phenomenon.

In vivo, repeated administration of METH in mice or rats led to increased Iba-1 in the medial prefrontal cortex (mPFC), striatum (CPu), and hippocampus (Hip, including the CA1 and DG) [37, 136, 147, 153-160], parietal cortex [161] and other regions [162, 163]. Interestingly, METH increased Iba-1 expression that started 30 minutes after drug exposure and lasted seven days in the striatum [164]. On the other hand, other studies demonstrated that METH decreases Iba-1 expression in the hippocampus [165]. In addition, acute METH exposure can increase the other classical microglial marker CD11b in mice striatum [166] and hippocampus [167]. Besides, CD11b was upregulated in the VTA, striatum, and hippocampus following repeated METH administration [168-171]. Interestingly, repeated administration

of METH led to an accumulation of activated microglia, evaluated by CD11b immunoreactivity, in the striatum that peaked 3 days after the initial dose [172]. Moreover, METH increased the expression of CD68, a marker of phagocytic cells, in the striatum, hypothalamus, hippocampus, and cerebellum [37, 157, 160]. Furthermore, several works have used the isolectin B_4 (ILB_4) to evaluate microglial activation in the context of METH abuse. Repeated or acute METH injection increased the ILB_4 in the striatum [173-177]. Importantly, increased ILB_4 induced by METH was dose-dependent and coincided with the damage of dopamine nerve endings [178]. On the other hand, Thomas *et al.* (2009) found no difference in ILB_4 in the SNc or the VTA [179].

Microgliosis was also accessed by the saturation binding of the peripheral benzodiazepine receptor (PBR) ligand 1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide ([3H]PK 11195). Chronic METH exposure increased the [3H]PK 11195 binding in the striatum, NAc, hippocampus, frontal cortical areas, the rhinal cortices, and cerebellum [180-182]. Finally, METH also increased other microglial markers such as OX-42 and F4/80 in the striatum [183], and integrin-αM in the PFC and hippocampus [184], while decreased AF1 expression in the hippocampus [165]. Lloyd *et al.* (2017) also described an increased microglia activation in the striatum after 10 days of METH treatment, but decreased in the nucleus arcuate [185]. Moreover, Friend *et al.* (2013) also found a significant thickening of branches and more intense microglia cell-body staining in the striatum after acute toxicity induced by METH [166]. Finally, Canedo *et al.* (2021) found that METH induces a reduction in microglial total process length, territorial area and territorial volume, while increasing the number of branching points [37].

Other amphetamines also can alter microglial marker expression. Repeated amphetamine administration increased CD11b immunoreactivity in the hippocampus, in the prelimbic PFC but not infra-limbic PFC [186], as well as ILB_4 in the striatum and piriform cortex [187, 188]. Furthermore, para-methoxymethamphetamine (PMMA) - a para-ring-substituted amphetamine derivative - and methiopropamine - a METH analog - significantly increased Iba-1 in the striatum [189, 190]. Importantly, methiopropamine also increased the CD16, CD32, and CD86 mRNA expression [190]. In addition, reactive Iba-1 and ILB_4 expressing cells were also increased by MDMA in the hilus and striatum [187, 191]. At the same time, MDMA exposure increased OX-42 immunoreactivity in the hippocampus [192], frontal cortex, and hypothalamus [193, 194]. Regarding the CD11b, some studies have shown that this microglial marker was increased in the striatum [169, 195-199], motor cortex, NAc, VTA [198], CPu [200], frontal cortex, hypothalamus [201], SNc [199] and hippocampus [169]. However, some studies found no difference in CD11b in the striatum, SNc [202], hippocampus, and the mPFC [203] after MDMA exposure.

Amphetamines also alter the microglia number and morphology. It has been shown that these cells can exhibit increased soma size and thicker processes after METH exposure in the striatum [155, 204-207], hippocampus [147, 208], thalamus, dorsal raphe/central gray area, inferior colliculus [208], somatosensory and piriform cortices, periaqueductal gray [209] and substantia nigra pars compacta [210]. On the other hand, the total dendritic length and the cell soma area in the hilus were not different after the reinstatement of METH self-administration [211]. In addition, microglia with a morphology resembling activation were found in the parietal cortex after MDMA exposure [212].

In human studies, western blotting and immunohistochemistry assay from chronic METH users showed increased Iba-1 expression in the hippocampus [213]. Moreover, by using immunohistochemistry, Kitamura *et al.* (2010) found increased human glucose transporter 5 (hGLUT), a useful marker of microglia, in the striatum from METH abusers, but no difference in the CR3.43 - a major histocompatibility complex class II antigen specific for activated microglia [214]. In addition, positron emission tomography using the radiotracer ([3H]PK 11195) to evaluate activated microglia was higher in METH abusers in the striatum, midbrain, thalamus, and orbitofrontal and insular cortices. Importantly, the binding ([3H]PK 11195) was inversely associated with the duration of METH abstinence [215]. However, human studies appear to be contradictory. For example, a positron emission tomography study with the 18 kDa translocator protein radioligand [F-18]FEPPA to evaluate microgliosis found no difference between METH abusers and controls [216]. Further, human brain tissue from death cases of lethal intoxications by METH found no difference in TMEM119 [217]. Thus, more studies are necessary to understand how METH abuse can alter microglia activity since microglial markers themselves could be affected by METH exposure. For example, while METH exposure did not affect TMEM119 expression in mice striatum, other unique microglial markers, such as P2ry12 and Olfml3, were changed [218].

In silico modulations, molecular dynamics simulations and titrations showed that similar to cocaine, METH and AMPH are capable of binding in the TLR4/MD-2 complex [171, 219]. In the microglial cell line BV2, METH-induced microglial activation and cytokine release was mediated through the TLR4/NF-κB pathway [137, 138]. In this sense, METH exposure increases TLR4 expression and other signaling components such as NF-κB, MAPK, p-p65, p-p38 and Peli1 [137, 138, 145]. In addition, Wires *et al.* (2012) found that METH can increase NF-κB expression in the CHME-5 cell line [220]. Moreover, apart from altering NR-9460 cell morphology, METH can also alter the TLR4's distribution on the surfaces of these microglia-like cells [151].

Increased TLR4 signaling activation after METH exposure was also found *in vivo*. Yang *et al.* (2020) found that repeated METH administration leads to microglial activation and upregulation of TLR4, TRIF, Peli1, and IL-6 and TNF-α expression in the mouse brain [137]. Similarly, Xie *et al.* (2018) found increased TLR4, MyD88, TRAF6, NF-κB, PARP-1, IL-1β, IL-6 and TNF-α in the rat striatum [221]. Significantly, blocking TLR4 expression inhibited METH-induced neuroinflammation, which could be related to behavioral alterations induced by METH [222]. For example, the non-opioid TLR4 antagonist (+)-naloxone blocked METH-induced microglial activation and IL-6 expression and increased NAc dopamine and CPP induced by METH [171]. Injection of the classic TLR4 antagonist LPS-RS also blocked the increase in dopamine release in the NAc induced

by METH [171]. Furthermore, minocycline blocked the microglial activation and the increased TLR4, MyD88, and phosphorylation of NF-κB and TNF-α, improving recognition memory and spatial learning and memory impairments in the Novel object recognition and Morris water maze, respectively, induced by METH [223] [183]. In addition, ibudilast, its amino analog AV1013, and minocycline - which block microglial activity - reduced METH self-administration [224]. In fact, both ibudilast and AV1013 also blocked the development of behavioral sensitization induced by METH [225]. Interestingly, minocycline blocked the development of locomotor hypersensitivity to amphetamines in other neuroinflammatory models [226, 227]. Regarding the other amphetamine drug - the MDMA - minocycline prevented the MDMA-induced increase in microglial activation, NF-kB activation, and IL-1β release in the hippocampus, striatum, and frontal cortex [169, 201].

Postmortem analyses demonstrated an increased Iba-1 expression in the CA1 region of the hippocampus of chronic METH users. By performing a protein-protein interaction network analysis, the authors suggested an essential role of the TLR4 signaling in the effects of this psychoactive substance [213]. However, contradictory observations are reported. For example, in METH dependent volunteers, the anti-inflammatory ibudilast decreased some reward-related subjective effects [228] and peripheral inflammatory markers [229]. In addition, minocycline improved the psychotic symptoms of METH use disorder in a female patient [230], and there was no difference between ibudilast and the placebo group in METH abstinence in a randomized placebo-controlled trial, suggesting that ibudilast did not affect METH use frequency [231].

Apart from the TLR4 pathway, this class of psychostimulants can also induce microglia activation through other signaling mechanisms. For example, METH altered the expression of different cytokines in human macrophages by interfering with the MyD88-dependent TLR9 signaling pathway [232]. Furthermore, the drug also increased NLRP3 expression and caspase-1 cleavage in mice hippocampus and the microglia-like cell culture [233]. METH can also increase NLRP3, caspase-1, and IL-1β in the brain of METH users [213]. Importantly, blocking TLR4 expression also blocked the increase in caspase-1 induced by METH [222]. In addition, METH and MDMA increased $P2X_7$ expression in microglial cells *in vitro* and *in vivo* [192, 234]. Silencing the microglial $P2X_7$ decreases cytokine release induced by METH [234], while $P2X_7$ deficiency mice or $P2X_7$ pharmacological blockade protects against sensitization induced by amphetamine [235]. Moreover, microglial migration towards CX_3CL_1 is enhanced by METH, an effect that is reduced by $P2X_7$ blockage [234]. Despite microglial morphological alterations induced by METH occurring to the same extent among WT and CX_3CR_1 KO mice [176], the CX_3CR_1 KO mice showed minor locomotor alteration induced by amphetamine in comparison with the WT mice [236]. Further, by activating the CD200R, expressed specifically in microglia - there is a reduction in microglial activation after METH exposure [143]. Finally, microglia depletion induced by CD11b-$TK^{mt\text{-}30}$ transgene attenuates wake/sleeping abnormalities induced by METH [237]. Thus, different neuroinflammatory signaling appears to be involved in microglial activation induced by amphetamines.

Although psychostimulants activate microglia, it is not yet known whether this process occurs in a direct or indirect way. It has been shown that METH induces different inflammatory mediators *via* activation of the NF-κB and other pathways in N9 and BV2 microglial cell lines [136-138]. On the other hand, Canedo *et al.* (2016), Frank *et al.* (2021) and Bravo *et al.* (2022) have showed that METH can not directly activate microglial cells in primary cell culture models [37, 150, 238]. Instead, glutamate and TNF-α released by astrocytes mediated METH-induced microglial activation. Interestingly, neurons can modulate this astrocyte-microglia activation through the CD200/CD200r signaling [37, 238]. This would suggest that only microglia cell lines appear to directly respond to METH, but not primary cells. Thus, although different neuroinflammatory signaling appears to be involved in microglial activation induced by amphetamines, the mechanisms are unclear.

4.3. Effects of Psychostimulants on Inflammatory Mediators

Psychostimulants alter the activity of microglial cells, significant producers of cytokines, eicosanoids, and others, in the CNS. Besides, psychostimulants can also induce the release of inflammatory mediators by the peripheral immune system. Therefore, these drugs could influence microglia by acting in the CNS and in the periphery.

4.3.1. Cytokines

Although most of these studies were based on correlations between cytokine levels and behavioral outcomes, a few studies presented causal evidence for an involvement of neuroimmune responses in the central effects of psychostimulants (Tables **1** and **2**). For instance, in IL-6 knockout mice, several effects of METH were attenuated in the HPC, cortex, and the dorsal striatum, such as decreases in serotonin levels, dopamine transporter depletion, serotonin transporter depletion, and gliosis [239]. Repeated administration of IL-6 induces long-term increased sensitivity to locomotor effects of AMPH [240]. IL-6 is increased in METH users compared with the controls. In addition, the levels of this cytokine are positively associated with the corticostriatal pathway in the users [241]. On the other hand, it was suggested that IL-6 plays a role in the protective effect of memantine in the CPP induced by cocaine [242].

Similarly, the TNF-α knockout presented enhanced responses to reward, locomotor, and neurotoxic effects of METH. Also, exogenous TNF-α prevented these effects while potentiating dopamine reuptake [243]. Intriguingly, repeated cocaine administration activated microglia and enhanced TNF-α levels in the striatum. This was related to a decrease in synaptic strength in the glutamatergic neurons of the NAc core [36].

METH administration induces spatial memory deficits in the HPC, the main structure responsible for this task, and increases IL-1β levels [244]. More importantly, blocking IL-1β signaling prevented the deficits induced by METH [244].

However, neither IL-1β antagonists attenuated MDMA-induced hyperthermia [194], nor did their agonists impair locomotor sensitization induced by AMPH [245]. Notably, the increase in dopamine signaling in the NAc induced by cocaine is regulated by IL-1β/TLR4 in the VTA [125], suggesting an important role of this cytokine in modulating the reward properties of cocaine. In agreement with these reports, using the self-administration model, it was found that IL-1β mRNA levels increased in the VTA, and the antagonism of the IL-1β receptor in this structure reduced drug seeking [115]. More importantly, inflammatory responses to psychostimulants can also be part of a homeostatic response to the neurotoxic effect of these drugs. In this sense, exogenous IL-6 and TNF-α prevented METH-induced microglia death through the JAK-STAT3 pathway [246].

There may also be crosstalk between the cytokines in the context of drug use. For example, TGF-β is increased by cocaine in endothelial cells, which, in turn, down-regulates IL-8 [247]. In rats, cocaine withdrawal increased TGF-β expression in the NAc [248] and the dorsal HIP [249].

In addition to potential central mechanisms involved in the release of cytokines, it is important to notice that psychostimulants can decrease the integrity of the BBB. Cocaine affects the BBB integrity by increasing CXCL10 secretion by pericytes through c-Src kinase, activation of NF-kB pathway [250], the release of TNF-α, IL-1β, and IL-6 [251], and the induction of endoplasmic reticulum stress and autophagy mechanism [251]. Moreover, METH reduces tight junctions on the BBB [252, 253], induces the release of TNF-α, and increases vesicular transport across endothelial cells [254]. In addition, METH enhanced LPS-induced infiltration of macrophages, neutrophils, and leukocytes in the brain, and this was accompanied by higher levels of proinflammatory cytokines [255]. The hypothesis of peripheral immune infiltration is also supported by the correlation between circulating cytokines and the central effects of psychostimulants. For instance, IL-6 levels correlated with cognitive symptoms [256], IL-8 with the intensity of withdrawal symptoms [257], and IL-1β with the severity of the cocaine use disorders [258].

4.3.2. Chemokines

Psychostimulants modulate chemokine production. Human macrophages exposed to METH upregulate CXCL16, CXCL2, CCL20, CXCL1, CCL24, and CXCL13 and down-regulate CCL7 levels, which return to basal levels by 24h [232]. Certain chemokines correlate with substance use disorder symptoms. In cocaine users, CX_3CL_1 levels correlate with symptom severity [258]. In knock-out mice for the receptor of this cytokine, Cx3Cr1-KO, impairments were observed in the extinction but not in the acquisition or reinstatement of cocaine-induced CPP. In addition, after acute cocaine exposure, CX_3CL_1 is enhanced in the HPC [259] and in the PFC [260]. The release of this chemokine was accompanied by increased phosphorylation of ERK1/2 and p65 NF-kB, and after repeated treatment, cocaine increased the phosphorylation of p38, MAPK, NF-kB and CREB [259].

Similar to CX_3CR_1-KO, CCR2-KO also presented impairments in cocaine-induced locomotor sensitization and reductions in ERK phosphorylation and dopamine transporter regulation in the striatum [261]. Besides, the antagonism of CCR2 prevents METH-induced CPP [262, 263]. The ligand of this receptor, CCL2, was also altered after acute cocaine administration in the PFC, together with the chemokine CCL7 [260]. The increase in CCL2 was also observed in the PFC [263] and the striatum [262-264] after administration of METH. In addition, D1R receptor antagonism prevents the increase in the striatum [262]. CCL7, which can act as a microglia inhibitor, modulates the CPP induced by METH through the D_1 receptor signaling [265]. However, the role of chemokine mediating psychostimulants' effects seems to depend on the brain structure. In this sense, icv administration of CXCL12 potentiates ambulatory and stereotypic activity induced by cocaine. However, the administration of CXCL12 into the VTA potentiated cocaine-induced ambulatory activity, which is abolished when the same cytokine is administered into the NAc shell. No effect was found when administered into the core. Finally, when CXCL12 microinjections were into the caudate putamen, it increased stereotypic behaviors induced by cocaine [266].

4.3.3. Cyclo-Oxygenase and Eicosanoids

Microglia are an important source of cyclo-oxygenase (COX) and eicosanoids, which can be increased during various pathological conditions [267]. The role of these mediators in addiction has been suggested by evaluating the expression of the enzyme and its products and investigating the effects of its inhibitors in animal models. For instance, chronic consumption of METH decreases COX-2 [268]. After 24h of METH treatment, there is a reduction in striatal COX-2, but no changes were identified in COX-1 levels [269]. On the other hand, AMPH increases cortical COX-2 expression [270, 271] and a COX-2 inhibitor was able to attenuate this increase as well as the hyperlocomotion induced by AMPH [270]. Similarly, systemic or intra-VTA treatment with a COX inhibitor, but not a lipo-oxygenase inhibitor, impairs cocaine- and AMPH-induced locomotor sensitization [272]. Conversely, a dose of COX inhibitor reduced hyperlocomotion, but it did not affect AMPH self-administration [273], suggesting a COX-specific involvement in the psychomotor effects of AMPH. Some evidence indicates that COX is implicated in abstinence. Notably, 72h after METH consumption, COX-2 was upregulated, and their levels correlated with prostaglandin (PG) E_2 [269]. Consistently, diclofenac, a COX-2 inhibitor, attenuated the cue-dependent drug reinstatement [274]. Contrary to these preclinical data, a clinical trial with celecoxib, a COX-2 selective inhibitor, showed poor improvements in cocaine use and craving [275].

The described alterations in COX and PLA pathways due to psychostimulants are consequently linked to modification in eicosanoid levels. Thromboxanes [276] and prostaglandin [277] were altered in vessels due to psychostimulant exposure, albeit another study did not observe these alterations [278]. This may rely on differences in experimental models. It has also been suggested that eicosanoids alter hyperactivity, stereotypy and other behaviors induced by AMPH [279-282].

Table 1. Cytokines modulation by cocaine.

Name	Effect	Structure	Model	Refs.
IL-1β	No effect	PFC NAc	Chronic treatment in rodents	[120, 125, 283]
-	Increase	NAc Piriform cortex Somatosensory cortex HPC VTA	Plasma from patients Pericytes Acute or repeated treatment in rodents	[115, 120, 125, 251, 259, 284-286]
IL-2	Increase	-	Plasma from patients	[283]
IL-4	No effect	-	Plasma from patients	[287]
IL-6	No effect	NAc PFC Striatum	Plasma from patients after use Chronic treatment in rodents	[120, 286, 288]
-	Increase	-	Serum from patients Pericytes	[256, 285, 289]
-	Decrease	-	Chronic treatment in rodents	[283]
IL-8	No effect	-	Plasma from patients	[287]
IL-10	Increase	-	Plasma from patients Acute treatment in rodents	[285, 290, 291]
-	Decrease	Striatum	Plasma from patients Plasma from patients after use	[286, 289, 292, 293]
IL-17**α**	Decrease	-	Plasma from patients	[287]
IL-20	Decrease	-	Plasma from patients	[105]
IL-29	Decrease	-	Plasma from patients	[105]
INF-**γ**	No effect	-	Plasma from patients Acute treatment rodents	[287, 290]
-	Increase	-	Plasma from patients after use	[291]
-	Decrease	-	Plasma from patients	[291]
TNF-α	No effect	VTA NAc PFC Striatum	Repeated treatment in rodents	[115, 120, 286]
-	Increase	Striatum	Pericytes Repeated treatment in rodents	[36, 251]
-	Decreased	PFC NAc	Chronic and repeated treatment in rodents Plasma from patients	[242, 258, 283]

Table 2. Cytokines modulation by amphetamines.

Name	Effect	Structure	Model	Refs.
Amphetamine and D-Amphetamine				
IL-1β	Increase	-	Serum from patients	[294]
IL-2	Increase	-	Serum from patients	
-	Decrease	-	Lymphocytes	[295]
IL-4	No effect	-	Lymphocytes	

(Table 2) Contd….

Name	Effect	Structure	Model	Refs.
-	Increase	PFC Striatum	Chronic treatment in rodents Serum from patients	[294, 296-298]
IL-5	Increase	-	Serum from patients	[294]
IL-6	Increase	PFC Striatum	Chronic treatment in rodents Serum from patients	[294, 297, 298]
IL-8	Decreased	-	Serum from abstinent patients	[294]
IL-10	Increase	PFC Striatum	Chronic treatment in rodents Serum from patients	[294, 296-298]
-	Decreased	-	Serum from abstinent patients	[294]
TNF-α	Increase	PFC Striatum	Chronic treatment in rodents Macrophages Human endothelial cells	[296-298] [299, 300]
Methamphetamine				
IL-1β	No effect	HPC Striatum PFC VTA Nac	Acute treatment in rodents Serum from abstinent patients Hippocampal neurons	[171, 238, 301, 302]
-	Decrease	-	Serum from abstinent patients	[302]
-	Increase	HPC PFC Nac Striatum VTA HPT	Repeated and acute treatment in rodents Highly aggressively proliferating immortalized (HAPI)	[140, 150, 184, 223, 244, 252, 264, 303-305]
IL-2	No effect	-	Serum from abstinent patients	[302]
-	Increase	-	Serum from abstinent patients	
IL-4	No effect	-	Serum from abstinent patients	
-	Decrease	-	Serum from abstinent patients	
-	Increase	-	Serum from abstinent patients	
IL-5	No effect	-	Serum from abstinent patients	
-	Increase	-	Serum from abstinent patients	
IL-6	No effect	Nac PFC	BV-2 cells Hippocampal neurons Serum from abstinent patients Acute treatment in rodents	[139, 171, 238, 302]
-	Increase	HPC PFC VTA Nac Striatum	Repeated and acute treatment in rodents Neuroblastoma (SY5Y) Astrocytes Highly aggressively proliferating immortalized (HAPI) Serum from abstinent patients Serum from rodents after acute or chronic treatment N9 cells	[136, 140, 150, 171, 183, 184, 223, 252, 264, 301, 302, 306-310]
IL-7	Increase	-	Macrophages Serum from abstinent patients	[232, 302]
IL-8	Increase	-	Macrophages Astrocytes	[232, 308]

(Table 2) Contd….

Name	Effect	Structure	Model	Refs.
IL-9	Decrease	-	Serum from abstinent patients	[302]
-	Increase	-	Serum from abstinent patients	[238, 302]
IL-10	No effect	-	Hippocampal neurons	-
-	Decrease	-	Serum from abstinent patients	[302]
-	Increase	-	Macrophages Serum from rodents after acute treatment	[232, 310]
IL-12p70	Increase	-	Serum from abstinent patients	[302]
IL-13	No effect	-	Serum from abstinent patients	
-	Increase	-	Serum from abstinent patients	
IL-15	No effect	-	Serum from abstinent patients	
-	Decrease	-	Serum from abstinent patients	
IL-17a	No effect	-	Serum from abstinent patients	
IL-18	Increase	-	Serum from abstinent patients	
IFN-**γ**	No effect	-	Serum from abstinent patients	
	Increase	-	Serum from abstinent patients	
TNF-α	No effect	Striatum VTA NAc PFC	BV-2 cells Hippocampal neurons Acute treatment in rodents	[139, 171, 238, 301]
-	Increase	HPC PFC VTA NAc Striatum Serum	Repeated and acute treatment in rodents Neuroblastoma (SY5Y) Macrophages Highly aggressively proliferating immortalized (HAPI) Human microvascular endothelial cells Serum from abstinent patients Serum from rodents after chronic treatment N9 cells	[136, 140, 150, 167, 171, 183, 184, 223, 243, 252, 264, 299, 301, 302, 306, 307, 309, 311-313]
3, 4-Methylenedioxymethamphetamine (MDMA)				
IL-1β	Increase	HPC Frontal cortex HPT	Sub chronic or acute treatment in rodents	[194, 201, 314, 315]
IL2	Increase	-	Acute treatment in rodents Macrophages	[316, 317]
IL-4	No effect	-	Macrophages	[317]
IL-10	Increase	-	Serum from patients after use	[318]
TNF-α	Increase	Striatum	Acute treatment in rodents	[319]
-	Decrease	-	Macrophages	[317]

CONCLUSION

The mechanisms by which psychoactive substances induce addiction are complex and depend on various factors like the type of the drug, environment, genetics, and others. In the case of psychostimulants, these substances may first increase dopamine, norepinephrine, and serotonin levels as they alter the reuptake of these neurotransmitters. In addition to monoamines, glutamatergic neurotransmission is also increased, affecting various cells. In neurons, a series of intracellular modifications could happen after activating dopamine receptors, including the recruitment of the cAMP/PKA/ERK pathways that activate different transcription factors, such as CREB, ΔFosB, MEF2, and NF-κB. Thus, genes involved in cell morphology, plasticity, and excitability could be expressed. As a result, alterations in the cell activity pattern, as well as its morphological aspects, could occur and be associated with the addiction process. Although acute exposure to psychoactive substances could lead to cell modifications, sustained exposure could alter neuronal networks that could be important for the onset and maintenance of drug dependence.

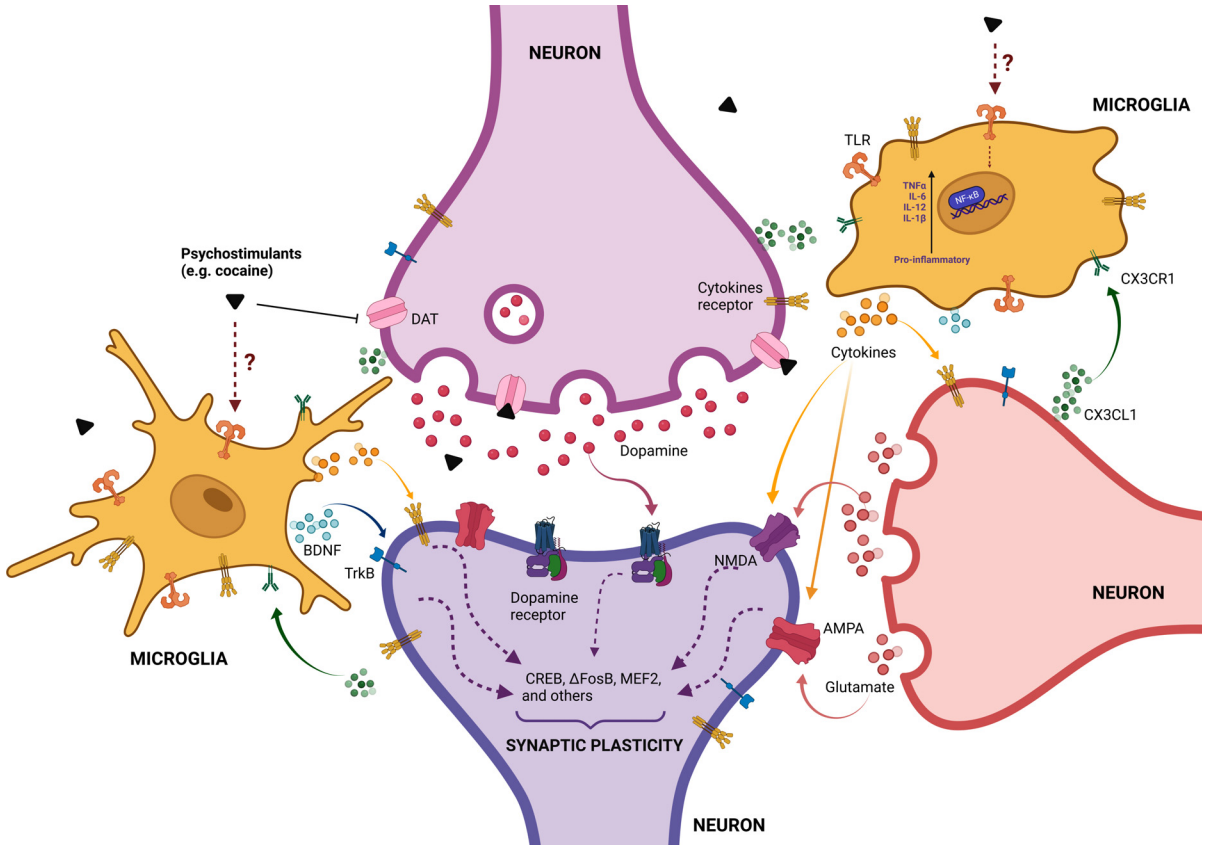

Fig. (1). Role of microglia in synaptic plasticity induced by psychostimulant abuse. Psychostimulants increase dopaminergic and glutamatergic neurotransmission, leading to neural plasticity. In addition, psychostimulants induce the neuronal release of ligands that mediate microglial cell activation, such as CX3CL1. In parallel, psychostimulants may directly bind to microglial TLR4 leading to cytokine and neurotrophic factors release, which, in turn, modulate neurotransmission and intracellular pathways that mediate synaptic plasticity. Created with BioRender.com. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Various studies have shown that microglia may be important in this phenomenon as inhibiting these cells reduces some addiction-related behavior. Acutely, psychostimulants may activate microglia to produce inflammatory mediators that regulate neurotransmission and the activity of other cell types. It is still not clear the outcome of these initial events. However, chronic reexposure to the drug may contribute to the long-term alterations observed in the context of addiction.

Psychostimulants can, directly or indirectly, activate microglia. A direct activation could occur *via* the binding of psychostimulants to a microglial receptor, such as the TLR family, producing an inflammatory milieu in the CNS and neurotrophin release. In this sense, TLR4 activation by psychostimulants could induce the NF-κB translocation to the nucleus and promote the release of different cytokines, which, in turn, can modulate both synaptic plasticity and neuronal activity. For example, TNF-α release by microglia modulates induced behavioral sensitization by cocaine through AMPA/NMDA ratio alterations [36].

On the other hand, microglia possess neurotransmitter receptors, including D_1 and D_2, as well as glutamate receptors, which could be stimulated during the use of psychoactive substances. Activation of these receptors in microglia may be important not only for controlling the production of inflammatory and neurotrophic factors but also for synaptic changes. For example, the pattern of D_1 expression in the NAc can be mediated by the microglia [26]. In addition, psychostimulants can also modulate neuron expression and release of molecules related to synaptic pruning or synaptic formation by microglia. Collectively, these mechanisms could reorganize brain networks, cellular responses, neuronal communications, and neuro-immune communications, leading to addiction (Fig. **1**).

In conclusion, increasing evidence indicates that microglia are involved in the pathogenesis of addiction, albeit the mechanisms are unclear. It is also essential to determine the role of these cells in either acute or chronic exposure to psychostimulants. This knowledge would contribute to the development of pharmacological therapies for the treatment of substance use disorder.

LIMITATIONS

Although some studies point to a potential role of microglia in drug addiction, which would suggest these cells as pharmacological targets in this psychiatric condition, the literature in this field is still scarce. Fewer studies have evaluated the psychostimulants effects in microglial cells number and morphology. In addition, very few studies have tried to

understand the molecular mechanism that psychoactive substances can modulate microglia's activity and how these cells can contribute or protect against drug-induced alterations. Although we described the alterations in microglia morphology induced by psychostimulants in *in vitro* studies, evaluation of these cell morphology in cell culture may be considered unreliable nowadays. Moreover, some papers have shown that alterations in microglia number or morphology *in vivo* can occur in acute or chronic exposure, but it is still unclear the timeline for these events. The molecular effects associated with inflammation induced by the drugs may not be dependent only on microglia, since there is an important communication between them and other glial or immune cells that release inflammatory factors. Finally, some data found in the current literature are also contradictory, which raises questions about how the psychostimulants activate these immune cells. In this sense, further studies are necessary for a better understanding of the role of microglia in drug addiction.

LIST OF ABBREVIATIONS

CD	=	Clusters of Differentiation
CNS	=	Central Nervous System
COX	=	Cyclo-Oxygenase
DAMPs	=	Damage-Associated Molecular Patterns
DAT	=	Dopamine Transporter
ERK	=	Extracellular Signal-Regulated Kinase
hGLUT	=	Human Glucose Transporter 5
LTP	=	Long-Term Potentiation
MEF2	=	Myocyte Enhancing Factor 2
MHC	=	Major Histocompatibility Complex
mPFC	=	Medial Prefrontal Cortex
MSN	=	Medium Spiny Neurons
NAc	=	Nucleus Accumbens
NO	=	Nitric Oxide
PAMPs	=	Pathogen-Associated Molecular Patterns
PG	=	Prostaglandin
PKA	=	Protein Kinase A
PRRs	=	Pattern Recognition Receptors
TH	=	Tyrosine Hydroxylase
TNF	=	Tumor Necrosis Factor
VMAT2	=	Vesicular Monoamine Transporters

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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

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REFERENCES

[1] Olive, M.F.; Taylor, ; Lewis, The neurocircuitry of illicit psychostimulant addiction: acute and chronic effects in humans. *Subst. Abuse Rehabil.,* **2013**, *4*, 29-43. http://dx.doi.org/10.2147/SAR.S39684 PMID: 24648786

[2] McFarland, K.; Kalivas, P.W. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J. Neurosci.,* **2001**, *21*(21), 8655-8663. http://dx.doi.org/10.1523/JNEUROSCI.21-21-08655.2001 PMID: 11606653

[3] Volkow, N.D.; Michaelides, M.; Baler, R. The neuroscience of drug reward and addiction. *Physiol. Rev.,* **2019**, *99*(4), 2115-2140. http://dx.doi.org/10.1152/physrev.00014.2018 PMID: 31507244

[4] World Drug Report 2021 (United Nations publication, Sales No. E.21.XI.8).

[5] Hasin, D.S.; O'Brien, C.P.; Auriacombe, M.; Borges, G.; Bucholz, K.; Budney, A.; Compton, W.M.; Crowley, T.; Ling, W.; Petry, N.M.; Schuckit, M.; Grant, B.F. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am. J. Psychiatry,* **2013**, *170*(8), 834-851. http://dx.doi.org/10.1176/appi.ajp.2013.12060782 PMID: 23903334

[6] Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl. Acad. Sci. USA,* **1988**, *85*(14), 5274-5278. http://dx.doi.org/10.1073/pnas.85.14.5274 PMID: 2899326

[7] Miller, D.R.; Guenther, D.T.; Maurer, A.P.; Hansen, C.A.; Zalesky, A.; Khoshbouei, H. Dopamine transporter is a master regulator of dopaminergic neural network connectivity. *J. Neurosci.,* **2021**, *41*(25), 5453-5470. http://dx.doi.org/10.1523/JNEUROSCI.0223-21.2021 PMID: 33980544

[8] Partilla, J.S.; Dempsey, A.G.; Nagpal, A.S.; Blough, B.E.; Baumann, M.H.; Rothman, R.B. Interaction of amphetamines and related compounds at the vesicular monoamine transporter. *J. Pharmacol. Exp. Ther.,* **2006**, *319*(1), 237-246. http://dx.doi.org/10.1124/jpet.106.103622 PMID: 16835371

[9] Goodwin, J.S.; Larson, G.A.; Swant, J.; Sen, N.; Javitch, J.A.; Zahniser, N.R.; De Felice, L.J.; Khoshbouei, H. Amphetamine and methamphetamine differentially affect dopamine transporters *in vitro* and *in vivo*. *J. Biol. Chem.,* **2009**, *284*(5), 2978-2989. http://dx.doi.org/10.1074/jbc.M805298200 PMID: 19047053

[10] Lin, M.; Sambo, D.; Khoshbouei, H. Methamphetamine regulation of firing activity of dopamine neurons. *J. Neurosci.,* **2016**, *36*(40), 10376-10391. http://dx.doi.org/10.1523/JNEUROSCI.1392-16.2016 PMID: 27707972

[11] Sambo, D.O.; Lebowitz, J.J.; Khoshbouei, H. The sigma-1 receptor as a regulator of dopamine neurotransmission: A potential thera-

peutic target for methamphetamine addiction. *Pharmacol. Ther.,* **2018**, *186*, 152-167.
http://dx.doi.org/10.1016/j.pharmthera.2018.01.009 PMID: 29360540

[12] Khoshbouei, H.; Wang, H.; Lechleiter, J.D.; Javitch, J.A.; Galli, A. Amphetamine-induced dopamine efflux. A voltage-sensitive and intracellular Na+-dependent mechanism. *J. Biol. Chem.,* **2003**, *278*(14), 12070-12077.
http://dx.doi.org/10.1074/jbc.M212815200 PMID: 12556446

[13] Saha, K.; Sambo, D.; Richardson, B.D.; Lin, L.M.; Butler, B.; Villarroel, L.; Khoshbouei, H. Intracellular methamphetamine prevents the dopamine-induced enhancement of neuronal firing. *J. Biol. Chem.,* **2014**, *289*(32), 22246-22257.
http://dx.doi.org/10.1074/jbc.M114.563056 PMID: 24962577

[14] Richardson, B.D.; Saha, K.; Krout, D.; Cabrera, E.; Felts, B.; Henry, L.K.; Swant, J.; Zou, M.F.; Newman, A.H.; Khoshbouei, H. Membrane potential shapes regulation of dopamine transporter trafficking at the plasma membrane. *Nat. Commun.,* **2016**, *7*(1), 10423.
http://dx.doi.org/10.1038/ncomms10423 PMID: 26804245

[15] Andrianarivelo, A.; Saint-Jour, E.; Walle, R.; Trifilieff, P.; Vanhoutte, P. Modulation and functions of dopamine receptor heteromers in drugs of abuse-induced adaptations. *Neuropharmacology,* **2019**, *152*, 42-50.
http://dx.doi.org/10.1016/j.neuropharm.2018.12.003 PMID: 30529032

[16] Nestler, E.J. Transcriptional mechanisms of drug addiction. *Clin. Psychopharmacol. Neurosci.,* **2012**, *10*(3), 136-143.
http://dx.doi.org/10.9758/cpn.2012.10.3.136 PMID: 23430970

[17] Teague, CD; Nestler, EJ Key transcription factors mediating cocaine-induced plasticity in the nucleus accumbens. *Mol Psychiatry,* **2021**, *27*, 687-709.
http://dx.doi.org/10.1038/s41380-021-01163-5

[18] Russo, S.J.; Wilkinson, M.B.; Mazei-Robison, M.S.; Dietz, D.M.; Maze, I.; Krishnan, V.; Renthal, W.; Graham, A.; Birnbaum, S.G.; Green, T.A.; Robison, B.; Lesselyong, A.; Perrotti, L.I.; Bolaños, C.A.; Kumar, A.; Clark, M.S.; Neumaier, J.F.; Neve, R.L.; Bhakar, A.L.; Barker, P.A.; Nestler, E.J. Nuclear factor kappa B signaling regulates neuronal morphology and cocaine reward. *J. Neurosci.,* **2009**, *29*(11), 3529-3537.
http://dx.doi.org/10.1523/JNEUROSCI.6173-08.2009 PMID: 19295158

[19] Pulipparacharuvil, S.; Renthal, W.; Hale, C.F.; Taniguchi, M.; Xiao, G.; Kumar, A.; Russo, S.J.; Sikder, D.; Dewey, C.M.; Davis, M.M.; Greengard, P.; Nairn, A.C.; Nestler, E.J.; Cowan, C.W. Cocaine regulates MEF2 to control synaptic and behavioral plasticity. *Neuron,* **2008**, *59*(4), 621-633.
http://dx.doi.org/10.1016/j.neuron.2008.06.020 PMID: 18760698

[20] Krasnova, I.N.; Chiflikyan, M.; Justinova, Z.; McCoy, M.T.; Ladenheim, B.; Jayanthi, S.; Quintero, C.; Brannock, C.; Barnes, C.; Adair, J.E.; Lehrmann, E.; Kobeissy, F.H.; Gold, M.S.; Becker, K.G.; Goldberg, S.R.; Cadet, J.L. CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. *Neurobiol. Dis.,* **2013**, *58*, 132-143.
http://dx.doi.org/10.1016/j.nbd.2013.05.009 PMID: 23726845

[21] Dong, Y.; Taylor, J.R.; Wolf, M.E.; Shaham, Y. Circuit and synaptic plasticity mechanisms of drug relapse. *J. Neurosci.,* **2017**, *37*(45), 10867-10876.
http://dx.doi.org/10.1523/JNEUROSCI.1821-17.2017 PMID: 29118216

[22] Wolf, M.E. Synaptic mechanisms underlying persistent cocaine craving. *Nat. Rev. Neurosci.,* **2016**, *17*(6), 351-365.
http://dx.doi.org/10.1038/nrn.2016.39 PMID: 27150400

[23] Argilli, E.; Sibley, D.R.; Malenka, R.C.; England, P.M.; Bonci, A. Mechanism and time course of cocaine-induced long-term potentiation in the ventral tegmental area. *J. Neurosci.,* **2008**, *28*(37), 9092-9100.
http://dx.doi.org/10.1523/JNEUROSCI.1001-08.2008 PMID: 18784289

[24] Dong, Y.; Saal, D.; Thomas, M.; Faust, R.; Bonci, A.; Robinson, T.; Malenka, R.C. Cocaine-induced potentiation of synaptic strength in dopamine neurons: Behavioral correlates in GluRA(-/-) mice. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(39), 14282-14287.
http://dx.doi.org/10.1073/pnas.0401553101 PMID: 15375209

[25] Zinsmaier, A.K.; Dong, Y.; Huang, Y.H. Cocaine-induced projection-specific and cell type-specific adaptations in the nucleus accumbens. *Mol. Psychiatry,* **2022**, *27*(1), 669-686.
http://dx.doi.org/10.1038/s41380-021-01112-2 PMID: 33963288

[26] Kopec, AM; Smith, CJ; Ayre, NR; Sweat, SC; Bilbo, SD Microglial dopamine receptor elimination defines sex-specific nucleus accumbens development and social behavior in adolescent rats. *Nat Commun,* **2018**, *9*, 1-16.
http://dx.doi.org/10.1038/s41467-018-06118-z

[27] Smith, B.L.; Laaker, C.J.; Lloyd, K.R.; Hiltz, A.R.; Reyes, T.M. Adolescent microglia play a role in executive function in male mice exposed to perinatal high fat diet. *Brain Behav. Immun.,* **2020**, *84*, 80-89.
http://dx.doi.org/10.1016/j.bbi.2019.11.010 PMID: 31765789

[28] Catale, C; Lo Iacono, L; Martini, A; Heil, C; Guatteo, E; Mercuri, NB Early life social stress causes sex- and region-dependent dopaminergic changes that are prevented by minocycline. *Mol Neurobiol,* **2022**, *59*, 3913-3932.
http://dx.doi.org/10.1007/s12035-022-02830-6

[29] Lo Iacono, L.; Catale, C.; Martini, A.; Valzania, A.; Viscomi, M.T.; Chiurchiù, V.; Guatteo, E.; Bussone, S.; Perrone, F.; Di Sabato, P.; Aricò, E.; D'Argenio, A.; Troisi, A.; Mercuri, N.B.; Maccarrone, M.; Puglisi-Allegra, S.; Casella, P.; Carola, V. From traumatic childhood to cocaine abuse: The critical function of the immune system. *Biol. Psychiatry,* **2018**, *84*(12), 905-916.
http://dx.doi.org/10.1016/j.biopsych.2018.05.022 PMID: 30029767

[30] Liu, Y.; Zhou, L.J.; Wang, J.; Li, D.; Ren, W.J.; Peng, J.; Wei, X.; Xu, T.; Xin, W.J.; Pang, R.P.; Li, Y.Y.; Qin, Z.H.; Murugan, M.; Mattson, M.P.; Wu, L.J.; Liu, X.G. TNF-α differentially regulates synaptic plasticity in the hippocampus and spinal cord by microglia-dependent mechanisms after peripheral nerve injury. *J. Neurosci.,* **2017**, *37*(4), 871-881.
http://dx.doi.org/10.1523/JNEUROSCI.2235-16.2016 PMID: 28123022

[31] Ji, K.; Akgul, G.; Wollmuth, L.P.; Tsirka, S.E. Microglia actively regulate the number of functional synapses. *PLoS One,* **2013**, *8*(2), e56293.
http://dx.doi.org/10.1371/journal.pone.0056293 PMID: 23393609

[32] Riazi, K.; Galic, M.A.; Kentner, A.C.; Reid, A.Y.; Sharkey, K.A.; Pittman, Q.J. Microglia-dependent alteration of glutamatergic synaptic transmission and plasticity in the hippocampus during peripheral inflammation. *J. Neurosci.,* **2015**, *35*(12), 4942-4952.
http://dx.doi.org/10.1523/JNEUROSCI.4485-14.2015 PMID: 25810524

[33] Basilico, B.; Ferrucci, L.; Ratano, P.; Golia, M.T.; Grimaldi, A.; Rosito, M.; Ferretti, V.; Reverte, I.; Sanchini, C.; Marrone, M.C.; Giubettini, M.; De Turris, V.; Salerno, D.; Garofalo, S.; St-Pierre, M.K.; Carrier, M.; Renzi, M.; Pagani, F.; Modi, B.; Raspa, M.; Scavizzi, F.; Gross, C.T.; Marinelli, S.; Tremblay, M.È.; Caprioli, D.; Maggi, L.; Limatola, C.; Di Angelantonio, S.; Ragozzino, D. Microglia control glutamatergic synapses in the adult mouse hippocampus. *Glia,* **2022**, *70*(1), 173-195.
http://dx.doi.org/10.1002/glia.24101 PMID: 34661306

[34] Domercq, M.; Vázquez-Villoldo, N.; Matute, C. Neurotransmitter signaling in the pathophysiology of microglia. *Front. Cell. Neurosci.,* **2013**, *7*, 49.
http://dx.doi.org/10.3389/fncel.2013.00049 PMID: 23626522

[35] Yan, Y.; Jiang, W.; Liu, L.; Wang, X.; Ding, C.; Tian, Z.; Zhou, R. Dopamine controls systemic inflammation through inhibition of NLRP3 inflammasome. *Cell,* **2015**, *160*(1-2), 62-73.
http://dx.doi.org/10.1016/j.cell.2014.11.047 PMID: 25594175

[36] Lewitus, G.M.; Konefal, S.C.; Greenhalgh, A.D.; Pribiag, H.; Augereau, K.; Stellwagen, D. Microglial TNF-α suppresses cocaine-induced plasticity and behavioral sensitization. *Neuron,* **2016**, *90*(3), 483-491.
http://dx.doi.org/10.1016/j.neuron.2016.03.030 PMID: 27112496

[37] Canedo, T; Portugal, CC; Socodato, R; Almeida, TO; Terceiro, AF; Bravo, J Astrocyte-derived TNF and glutamate critically modulate microglia activation by methamphetamine. *Neuropsychopharmacol,* **2021**, *46*(13), 2358-2370.
http://dx.doi.org/10.1038/s41386-021-01139-7

[38] Kettenmann, H.; Hanisch, U.K.; Noda, M.; Verkhratsky, A. Physiology of Microglia. *Physiol. Rev.,* **2011**, *91*(2), 461-553.
http://dx.doi.org/10.1152/physrev.00011.2010 PMID: 21527731

[39] Prinz, M.; Jung, S.; Priller, J. Microglia biology: One century of evolving concepts. *Cell,* **2019**, *179*(2), 292-311. http://dx.doi.org/10.1016/j.cell.2019.08.053 PMID: 31585077

[40] Frank, M.G.; Fonken, L.K.; Watkins, L.R.; Maier, S.F. Microglia: Neuroimmune-sensors of stress. *Semin. Cell Dev. Biol.,* **2019**, *94*, 176-185. http://dx.doi.org/10.1016/j.semcdb.2019.01.001 PMID: 30638704

[41] Grabert, K; Michoel, T; Karavolos, MH; Clohisey, S; Kenneth Baillie, J; Stevens, MP Microglial brain region−dependent diversity and selective regional sensitivities to aging. *Nat Neurosci,* **2016**, *19*(3), 504-516. http://dx.doi.org/10.1038/nn.4222

[42] Nimmerjahn, A.; Kirchhoff, F.; Helmchen, F. Resting microglial cells are highly dynamic surveillants of brain parenchyma *in vivo*. *Science,* **2005**, *308*(5726), 1314-1318. http://dx.doi.org/10.1126/science.1110647 PMID: 15831717

[43] Rodríguez-Gómez, J.A.; Kavanagh, E.; Engskog-Vlachos, P.; Engskog, M.K.R.; Herrera, A.J.; Espinosa-Oliva, A.M.; Joseph, B.; Hajji, N.; Venero, J.L.; Burguillos, M.A. Microglia: Agents of the CNS Pro-Inflammatory Response. *Cells,* **2020**, *9*(7), 1717. http://dx.doi.org/10.3390/cells9071717 PMID: 32709045

[44] de Oliveira, A.C.P.; Yousif, N.M.; Bhatia, H.S.; Hermanek, J.; Huell, M.; Fiebich, B.L. Poly(I:C) increases the expression of mPGES-1 and COX-2 in rat primary microglia. *J. Neuroinflammation,* **2016**, *13*(1), 11. http://dx.doi.org/10.1186/s12974-015-0473-7 PMID: 26780827

[45] Shaerzadeh, F.; Phan, L.; Miller, D.; Dacquel, M.; Hachmeister, W.; Hansen, C.; Bechtle, A.; Tu, D.; Martcheva, M.; Foster, T.C.; Kumar, A.; Streit, W.J.; Khoshbouei, H. Microglia senescence occurs in both substantia nigra and ventral tegmental area. *Glia,* **2020**, *68*(11), 2228-2245. http://dx.doi.org/10.1002/glia.23834 PMID: 32275335

[46] Fernández-Arjona, M.M.; Grondona, J.M.; Granados-Durán, P.; Fernández-Llebrez, P.; López-Ávalos, M.D. Microglia morphological categorization in a rat model of neuroinflammation by hierarchical cluster and principal components analysis. *Front. Cell. Neurosci.,* **2017**, *11*, 235. http://dx.doi.org/10.3389/fncel.2017.00235 PMID: 28848398

[47] Rao, Y.; Du, S.; Yang, B.; Wang, Y.; Li, Y.; Li, R.; Zhou, T.; Du, X.; He, Y.; Wang, Y.; Zhou, X.; Yuan, T.F.; Mao, Y.; Peng, B. NeuroD1 induces microglial apoptosis and cannot induce microglia-to-neuron cross-lineage reprogramming. *Neuron,* **2021**, *109*(24), 4094-4108.e5. http://dx.doi.org/10.1016/j.neuron.2021.11.008 PMID: 34875233

[48] Takayama, F; Hayashi, Y; Wu, Z; Liu, Y; Nakanishi, H Diurnal dynamic behavior of microglia in response to infected bacteria through the UDP-P2Y6 receptor system. *Sci Reports,* **2016**, *6*(1), 1-10. http://dx.doi.org/10.1038/srep30006

[49] Murray, P.J.; Allen, J.E.; Biswas, S.K.; Fisher, E.A.; Gilroy, D.W.; Goerdt, S.; Gordon, S.; Hamilton, J.A.; Ivashkiv, L.B.; Lawrence, T.; Locati, M.; Mantovani, A.; Martinez, F.O.; Mege, J.L.; Mosser, D.M.; Natoli, G.; Saeij, J.P.; Schultze, J.L.; Shirey, K.A.; Sica, A.; Suttles, J.; Udalova, I.; van Ginderachter, J.A.; Vogel, S.N.; Wynn, T.A. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity,* **2014**, *41*(1), 14-20. http://dx.doi.org/10.1016/j.immuni.2014.06.008 PMID: 25035950

[50] Martinez, F.O.; Gordon, S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep.,* **2014**, *6*, 13. http://dx.doi.org/10.12703/P6-13 PMID: 24669294

[51] Ransohoff, R.M. A polarizing question: do M1 and M2 microglia exist? *Nat. Neurosci.,* **2016**, *19*(8), 987-991. http://dx.doi.org/10.1038/nn.4338 PMID: 27459405

[52] Ginhoux, F; Schultze, JL; Murray, PJ; Ochando, J; Biswas, SK New insights into the multidimensional concept of macrophage ontogeny, activation and function. *Nat Immunol,* **2015**, *17*(1), 34-40. http://dx.doi.org/10.1038/ni.3324

[53] Stratoulias, V.; Venero, J.L.; Tremblay, M.È.; Joseph, B. Microglial subtypes: diversity within the microglial community. *EMBO J.,* **2019**, *38*(17), e101997. http://dx.doi.org/10.15252/embj.2019101997 PMID: 31373067

[54] Zhou, M.; Cornell, J.; Salinas, S.; Huang, H-Y. Microglia regulation of synaptic plasticity and learning and memory. *Neural. Regen. Res.,* **2022**, *17*(4), 705-716. http://dx.doi.org/10.4103/1673-5374.322423 PMID: 34472455

[55] Nguyen, P.T.; Dorman, L.C.; Pan, S.; Vainchtein, I.D.; Han, R.T.; Nakao-Inoue, H.; Taloma, S.E.; Barron, J.J.; Molofsky, A.B.; Kheirbek, M.A.; Molofsky, A.V. Microglial remodeling of the extracellular matrix promotes synapse plasticity. *Cell,* **2020**, *182*(2), 388-403.e15. http://dx.doi.org/10.1016/j.cell.2020.05.050 PMID: 32615087

[56] Wallace, J.; Lord, J.; Dissing-Olesen, L.; Stevens, B.; Murthy, V.N. Microglial depletion disrupts normal functional development of adult-born neurons in the olfactory bulb. *eLife,* **2020**, *9*, e50531. http://dx.doi.org/10.7554/eLife.50531 PMID: 32150529

[57] Cheadle, L.; Rivera, S.A.; Phelps, J.S.; Ennis, K.A.; Stevens, B.; Burkly, L.C.; Lee, W.C.A.; Greenberg, M.E. Sensory experience engages microglia to shape neural connectivity through a non-phagocytic mechanism. *Neuron,* **2020**, *108*(3), 451-468.e9. http://dx.doi.org/10.1016/j.neuron.2020.08.002 PMID: 32931754

[58] Salter, MW; Stevens, B Microglia emerge as central players in brain disease. *Nat Med,* **2017**, *23*(9), 1018-1027. http://dx.doi.org/10.1038/nm.4397

[59] Coomey, R.; Stowell, R.; Majewska, A.; Tropea, D. The role of microglia in neurodevelopmental disorders and their therapeutics. *Curr. Top. Med. Chem.,* **2020**, *20*(4), 272-276. http://dx.doi.org/10.2174/1568026620666200221172619 PMID: 32091337

[60] Reshef, R.; Kudryavitskaya, E.; Shani-Narkiss, H.; Isaacson, B.; Rimmerman, N.; Mizrahi, A.; Yirmiya, R. The role of microglia and their CX3CR1 signaling in adult neurogenesis in the olfactory bulb. *eLife,* **2017**, *6*, e30809. http://dx.doi.org/10.7554/eLife.30809 PMID: 29251592

[61] Bertot, C.; Groc, L.; Avignone, E. Role of CX3CR1 signaling on the maturation of GABAergic transmission and neuronal network activity in the neonate hippocampus. *Neuroscience,* **2019**, *406*, 186-201. http://dx.doi.org/10.1016/j.neuroscience.2019.03.006 PMID: 30872165

[62] Stellwagen, D; Malenka, RC Synaptic scaling mediated by glial TNF-α. *Nat,* **2006**, *440*(7087), 1054-1059. http://dx.doi.org/10.1038/nature04671

[63] Clark, A.K.; Gruber-Schoffnegger, D.; Drdla-Schutting, R.; Gerhold, K.J.; Malcangio, M.; Sandkühler, J. Selective activation of microglia facilitates synaptic strength. *J. Neurosci.,* **2015**, *35*(11), 4552-4570. http://dx.doi.org/10.1523/JNEUROSCI.2061-14.2015 PMID: 25788673

[64] Chen, Z; Jalabi, W; Hu, W; Park, HJ; Gale, JT; Kidd, GJ Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. *Nat Commun,* **2014**, *5*(1), 1-12. http://dx.doi.org/10.1038/ncomms5486

[65] Tremblay, M.È.; Lowery, R.L.; Majewska, A.K. Microglial interactions with synapses are modulated by visual experience. *PLoS Biol.,* **2010**, *8*(11), e1000527. http://dx.doi.org/10.1371/journal.pbio.1000527 PMID: 21072242

[66] Schafer, D.P.; Lehrman, E.K.; Kautzman, A.G.; Koyama, R.; Mardinly, A.R.; Yamasaki, R.; Ransohoff, R.M.; Greenberg, M.E.; Barres, B.A.; Stevens, B. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron,* **2012**, *74*(4), 691-705. http://dx.doi.org/10.1016/j.neuron.2012.03.026 PMID: 22632727

[67] Wang, C; Yue, H; Hu, Z; Shen, Y; Ma, J; Li, J Microglia mediate forgetting *via* complement-dependent synaptic elimination. *Science (80-),* **2020**, *367*, 688-694. http://dx.doi.org/10.1126/science.aaz2288

[68] Lehrman, E.K.; Wilton, D.K.; Litvina, E.Y.; Welsh, C.A.; Chang, S.T.; Frouin, A.; Walker, A.J.; Heller, M.D.; Umemori, H.; Chen, C.; Stevens, B. CD47 Protects synapses from excess microglia-mediated pruning during development. *Neuron,* **2018**, *100*(1), 120-134.e6. http://dx.doi.org/10.1016/j.neuron.2018.09.017 PMID: 30308165

[69] Chamera, K.; Trojan, E.; Szuster-Głuszczak, M.; Basta-Kaim, A. The Potential role of dysfunctions in neuron-microglia communica-

tion in the pathogenesis of brain disorders. *Curr. Neuropharmacol.,* **2020**, *18*(5), 408-430. http://dx.doi.org/10.2174/1570159X17666191113101629 PMID: 31729301

[70] Liu, C.; Shen, Y.; Tang, Y.; Gu, Y. The role of N-glycosylation of CD200-CD200R1 interaction in classical microglial activation. *J. Inflamm. (Lond.),* **2018**, *15*(1), 28. http://dx.doi.org/10.1186/s12950-018-0205-8 PMID: 30574022

[71] Feng, D.; Huang, A.; Yan, W.; Chen, D. CD200 dysfunction in neuron contributes to synaptic deficits and cognitive impairment. *Biochem. Biophys. Res. Commun.,* **2019**, *516*(4), 1053-1059. http://dx.doi.org/10.1016/j.bbrc.2019.06.134 PMID: 31277944

[72] Pluvinage, J V.; Haney, MS; Smith, BAH; Sun, J; Iram, T; Bonanno, L CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. *Nat,* **2019**, *568*(7751), 187-192. http://dx.doi.org/10.1038/s41586-019-1088-4

[73] Mott, R.T.; Ait-Ghezala, G.; Town, T.; Mori, T.; Vendrame, M.; Zeng, J.; Ehrhart, J.; Mullan, M.; Tan, J. Neuronal expression of CD22: Novel mechanism for inhibiting microglial proinflammatory cytokine production. *Glia,* **2004**, *46*(4), 369-379. http://dx.doi.org/10.1002/glia.20009 PMID: 15095367

[74] Aires, V.; Coulon-Bainier, C.; Pavlovic, A.; Ebeling, M.; Schmucki, R.; Schweitzer, C.; Kueng, E.; Gutbier, S.; Harde, E. CD22 Blockage restores age-related impairments of microglia surveillance capacity. *Front. Immunol.,* **2021**, *12*, 684430. http://dx.doi.org/10.3389/fimmu.2021.684430 PMID: 34140954

[75] Meng, H.L.; Li, X.X.; Chen, Y.T.; Yu, L.J.; Zhang, H.; Lao, J.M.; Zhang, X.; Xu, Y. Neuronal soluble fas ligand drives M1-microglia polarization after cerebral ischemia. *CNS Neurosci. Ther.,* **2016**, *22*(9), 771-781. http://dx.doi.org/10.1111/cns.12575 PMID: 27283206

[76] Zuliani, C.; Kleber, S.; Klussmann, S.; Wenger, T.; Kenzelmann, M.; Schreglmann, N.; Martinez, A.; del Rio, J.A.; Soriano, E.; Vodrazka, P.; Kuner, R.; Groene, H-J.; Herr, I.; Krammer, P.H.; Martin-Villalba, A. Control of neuronal branching by the death receptor CD95 (Fas/Apo-1). *Cell Death Differ.,* **2006**, *13*(1), 31-40. http://dx.doi.org/10.1038/sj.cdd.4401720 PMID: 16003386

[77] Reich, A.; Spering, C.; Schulz, J.B. Death receptor Fas (CD95) signaling in the central nervous system: tuning neuroplasticity? *Trends Neurosci.,* **2008**, *31*(9), 478-486. http://dx.doi.org/10.1016/j.tins.2008.06.007 PMID: 18676032

[78] Parkhurst, C.N.; Yang, G.; Ninan, I.; Savas, J.N.; Yates, J.R., III; Lafaille, J.J.; Hempstead, B.L.; Littman, D.R.; Gan, W.B. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell,* **2013**, *155*(7), 1596-1609. http://dx.doi.org/10.1016/j.cell.2013.11.030 PMID: 24360280

[79] Lim, S.H.; Park, E.; You, B.; Jung, Y.; Park, A.R.; Park, S.G.; Lee, J.R. Neuronal synapse formation induced by microglia and interleukin 10. *PLoS One,* **2013**, *8*(11), e81218. http://dx.doi.org/10.1371/journal.pone.0081218 PMID: 24278397

[80] Fontaine, RH; Cases, O; Lelièvre, V; Mesplès, B; Renauld, JC; Loron, G IL-9/IL-9 receptor signaling selectively protects cortical neurons against developmental apoptosis. *Cell Death Differ,* **2008**, *15*(10), 1542-1552. http://dx.doi.org/10.1038/cdd.2008.79

[81] Aw, E.; Zhang, Y.; Carroll, M. Microglial responses to peripheral type 1 interferon. *J. Neuroinflammation,* **2020**, *17*(1), 340. http://dx.doi.org/10.1186/s12974-020-02003-z PMID: 33183319

[82] Yli-Karjanmaa, M.; Larsen, K.S.; Fenger, C.D.; Kristensen, L.K.; Martin, N.A.; Jensen, P.T.; Breton, A.; Nathanson, L.; Nielsen, P.V.; Lund, M.C.; Carlsen, S.L.; Gramsbergen, J.B.; Finsen, B.; Stubbe, J.; Frich, L.H.; Stolp, H.; Brambilla, R.; Anthony, D.C.; Meyer, M.; Lambertsen, K.L. TNF deficiency causes alterations in the spatial organization of neurogenic zones and alters the number of microglia and neurons in the cerebral cortex. *Brain Behav. Immun.,* **2019**, *82*, 279-297. http://dx.doi.org/10.1016/j.bbi.2019.08.195 PMID: 31505254

[83] Sipe, GO; Lowery, RL; Tremblay, M; Kelly, EA; Lamantia, CE; Majewska, AK Microglial P2Y12 is necessary for synaptic plasticity in mouse visual cortex. *Nat Commun,* **2016**, *7*(1), 1-15. http://dx.doi.org/10.1038/ncomms10905

[84] Stowell, RD; Sipe, GO; Dawes, RP; Batchelor, HN; Lordy, KA; Whitelaw, BS Noradrenergic signaling in the wakeful state inhibits microglial surveillance and synaptic plasticity in the mouse visual cortex. *Nat Neurosci,* **2019**, *22*(11), 1782-1792. http://dx.doi.org/10.1038/s41593-019-0514-0

[85] Pascual, O.; Ben Achour, S.; Rostaing, P.; Triller, A.; Bessis, A. Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. *Proc. Natl. Acad. Sci. USA,* **2012**, *109*(4), E197-E205. http://dx.doi.org/10.1073/pnas.1111098109 PMID: 22167804

[86] Geraghty, A.C.; Gibson, E.M.; Ghanem, R.A.; Greene, J.J.; Ocampo, A.; Goldstein, A.K.; Ni, L.; Yang, T.; Marton, R.M.; Paşca, S.P.; Greenberg, M.E.; Longo, F.M.; Monje, M. Loss of adaptive myelination contributes to methotrexate chemotherapy-related cognitive impairment. *Neuron,* **2019**, *103*(2), 250-265.e8. http://dx.doi.org/10.1016/j.neuron.2019.04.032 PMID: 31122677

[87] Miranda, M.; Morici, J.F.; Zanoni, M.B.; Bekinschtein, P. Brain-derived neurotrophic factor: A key molecule for memory in the healthy and the pathological brain. *Front. Cell. Neurosci.,* **2019**, *13*, 363. http://dx.doi.org/10.3389/fncel.2019.00363 PMID: 31440144

[88] Harley, S.B.R.; Willis, E.F.; Shaikh, S.N.; Blackmore, D.G.; Sah, P.; Ruitenberg, M.J.; Bartlett, P.F.; Vukovic, J. Selective ablation of BDNF from microglia reveals novel roles in self-renewal and hippocampal neurogenesis. *J. Neurosci.,* **2021**, *41*(19), 4172-4186. http://dx.doi.org/10.1523/JNEUROSCI.2539-20.2021 PMID: 33785644

[89] Coull, J.A.M.; Beggs, S.; Boudreau, D.; Boivin, D.; Tsuda, M.; Inoue, K.; Gravel, C.; Salter, M.W.; De Koninck, Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature,* **2005**, *438*(7070), 1017-1021. http://dx.doi.org/10.1038/nature04223 PMID: 16355225

[90] Ferrini, F.; Trang, T.; Mattioli, T.A.M.; Laffray, S.; Del'Guidice, T.; Lorenzo, L.E.; Castonguay, A.; Doyon, N.; Zhang, W.; Godin, A.G.; Mohr, D.; Beggs, S.; Vandal, K.; Beaulieu, J.M.; Cahill, C.M.; Salter, M.W.; De Koninck, Y. Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl− homeostasis. *Nat. Neurosci.,* **2013**, *16*(2), 183-192. http://dx.doi.org/10.1038/nn.3295 PMID: 23292683

[91] Taylor, A.M.W.; Castonguay, A.; Ghogha, A.; Vayssiere, P.; Pradhan, A.A.A.; Xue, L.; Mehrabani, S.; Wu, J.; Levitt, P.; Olmstead, M.C.; De Koninck, Y.; Evans, C.J.; Cahill, C.M. Neuroimmune regulation of GABAergic neurons within the ventral tegmental area during withdrawal from chronic morphine. *Neuropsychopharmacology,* **2016**, *41*(4), 949-959. http://dx.doi.org/10.1038/npp.2015.221 PMID: 26202104

[92] Cotto, B.; Li, H.; Tuma, R.F.; Ward, S.J.; Langford, D. Cocaine-mediated activation of microglia and microglial MeCP2 and BDNF production. *Neurobiol. Dis.,* **2018**, *117*, 28-41. http://dx.doi.org/10.1016/j.nbd.2018.05.017 PMID: 29859319

[93] Wu, S.Y.; Pan, B.S.; Tsai, S.F.; Chiang, Y.T.; Huang, B.M.; Mo, F.E.; Kuo, Y.M. BDNF reverses aging-related microglial activation. *J. Neuroinflammation,* **2020**, *17*(1), 210. http://dx.doi.org/10.1186/s12974-020-01887-1 PMID: 32664974

[94] Ferrini, F.; De Koninck, Y. Microglia control neuronal network excitability *via* BDNF signalling. *Neural Plast.,* **2013**, *2013*, 1-11. http://dx.doi.org/10.1155/2013/429815 PMID: 24089642

[95] Gupta, N.; Jadhav, S.; Tan, K.L.; Saw, G.; Mallilankaraman, K.B.; Dheen, S.T. miR-142-3p regulates BDNF expression in activated rodent microglia through its target CAMK2A. *Front. Cell. Neurosci.,* **2020**, *14*, 132. http://dx.doi.org/10.3389/fncel.2020.00132 PMID: 32508597

[96] Saw, G.; Krishna, K.; Gupta, N.; Soong, T.W.; Mallilankaraman, K.; Sajikumar, S.; Dheen, S.T. Epigenetic regulation of microglial phosphatidylinositol 3-kinase pathway involved in long-term potentiation and synaptic plasticity in rats. *Glia,* **2020**, *68*(3), 656-669. http://dx.doi.org/10.1002/glia.23748 PMID: 31702864

[97] Zhou, L.J.; Peng, J.; Xu, Y.N.; Zeng, W.J.; Zhang, J.; Wei, X.; Mai, C.L.; Lin, Z.J.; Liu, Y.; Murugan, M.; Eyo, U.B.; Umpierre, A.D.; Xin, W.J.; Chen, T.; Li, M.; Wang, H.; Richardson, J.R.; Tan, Z.; Liu, X.G.; Wu, L.J. Microglia are indispensable for synaptic plasticity in the spinal dorsal horn and chronic pain. *Cell Rep.,* **2019**, *27*(13), 3844-3859.e6. http://dx.doi.org/10.1016/j.celrep.2019.05.087 PMID: 31242418

[98] Long, T.; He, W.; Pan, Q.; Zhang, S.; Zhang, D.; Qin, G.; Chen, L.; Zhou, J. Microglia P2X4R-BDNF signalling contributes to central

sensitization in a recurrent nitroglycerin-induced chronic migraine model. *J. Headache Pain,* **2020**, *21*(1), 4. http://dx.doi.org/10.1186/s10194-019-1070-4 PMID: 31937253

[99] Zhang, X.; Xu, P.; Li, C.; Zhu, W.; Wu, S.; Yu, A.; Ding, Y.; Wang, Q.; Zhang, Z. Spinal microglial P2X4 receptor-brain-derived neurotrophic factor signaling regulates nicotine withdrawal-induced hyperalgesia. *Neuroreport,* **2017**, *28*(6), 339-347. http://dx.doi.org/10.1097/WNR.0000000000000769 PMID: 28306606

[100] Guo, L.; Zhang, Y.; Lv, Q.; Zhang, Z. Nicotine induces P2X4 receptor, interleukin-1 beta, and brain-derived neurotrophic factor expression in BV2 microglia cells. *Neuroreport,* **2020**, *31*(18), 1249-1255. http://dx.doi.org/10.1097/WNR.0000000000001546 PMID: 33165201

[101] Zhao, Y.N.; Wang, F.; Fan, Y.X.; Ping, G.F.; Yang, J.Y.; Wu, C.F. Activated microglia are implicated in cognitive deficits, neuronal death, and successful recovery following intermittent ethanol exposure. *Behav. Brain Res.,* **2013**, *236*(1), 270-282. http://dx.doi.org/10.1016/j.bbr.2012.08.052 PMID: 22985845

[102] Gofman, L.; Fernandes, N.C.; Potula, R. Relative role of AKT, ERK and CREB in alcohol-induced microglia P2X4R receptor expression. *Alcohol Alcohol.,* **2016**, *51*(6), 647-654. http://dx.doi.org/10.1093/alcalc/agw009 PMID: 26946194

[103] Warden, A.S.; Wolfe, S.A.; Khom, S.; Varodayan, F.P.; Patel, R.R.; Steinman, M.Q.; Bajo, M.; Montgomery, S.E.; Vlkolinsky, R.; Nadav, T.; Polis, I.; Roberts, A.J.; Mayfield, R.D.; Harris, R.A.; Roberto, M. Microglia control escalation of drinking in alcohol-dependent mice: genomic and synaptic drivers. *Biol. Psychiatry,* **2020**, *88*(12), 910-921. http://dx.doi.org/10.1016/j.biopsych.2020.05.011 PMID: 32680583

[104] Doggui, R.; Elsawy, W.; Conti, A.A.; Baldacchino, A. Association between chronic psychoactive substances use and systemic inflammation: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.,* **2021**, *125*, 208-220. http://dx.doi.org/10.1016/j.neubiorev.2021.02.031 PMID: 33639179

[105] Stamatovich, S.N.; Lopez-Gamundi, P.; Suchting, R.; Colpo, G.D.; Walss-Bass, C.; Lane, S.D.; Schmitz, J.M.; Wardle, M.C. Plasma pro- and anti-inflammatory cytokines may relate to cocaine use, cognitive functioning, and depressive symptoms in cocaine use disorder. *Am. J. Drug Alcohol Abuse,* **2021**, *47*(1), 52-64. http://dx.doi.org/10.1080/00952990.2020.1828439 PMID: 33119414

[106] Stolyarova, A; Thompson, AB; Barrientos, RM; Izquierdo, A reductions in frontocortical cytokine levels are associated with long-lasting alterations in reward valuation after methamphetamine. *Neuropsychopharmacol,* **2014**, *40*(5), 1234-1242. http://dx.doi.org/10.1038/npp.2014.309

[107] Taylor, A.M.W.; Castonguay, A.; Taylor, A.J.; Murphy, N.P.; Ghogha, A.; Cook, C.; Xue, L.; Olmstead, M.C.; De Koninck, Y.; Evans, C.J.; Cahill, C.M. Microglia disrupt mesolimbic reward circuitry in chronic pain. *J. Neurosci.,* **2015**, *35*(22), 8442-8450. http://dx.doi.org/10.1523/JNEUROSCI.4036-14.2015 PMID: 26041913

[108] Douma, E.H.; de Kloet, E.R. Stress-induced plasticity and functioning of ventral tegmental dopamine neurons. *Neurosci. Biobehav. Rev.,* **2020**, *108*, 48-77. http://dx.doi.org/10.1016/j.neubiorev.2019.10.015 PMID: 31666179

[109] Wang, J.; Lai, S.; Li, G.; Zhou, T.; Wang, B.; Cao, F.; Chen, T.; Zhang, X.; Chen, Y. Microglial activation contributes to depressive-like behavior in dopamine D3 receptor knockout mice. *Brain Behav. Immun.,* **2020**, *83*, 226-238. http://dx.doi.org/10.1016/j.bbi.2019.10.016 PMID: 31626970

[110] Wang, J.; Jia, Y.; Li, G.; Wang, B.; Zhou, T.; Zhu, L.; Chen, T.; Chen, Y. The dopamine receptor D3 regulates lipopolysaccharide-induced depressive-like behavior in mice. *Int. J. Neuropsychopharmacol.,* **2018**, *21*(5), 448-460. http://dx.doi.org/10.1093/ijnp/pyy005 PMID: 29390063

[111] Jarvis, R.; Tamashiro-Orrego, A.; Promes, V.; Tu, L.; Shi, J.; Yang, Y. Cocaine self-administration and extinction inversely alter neuron to glia exosomal dynamics in the nucleus accumbens. *Front. Cell. Neurosci.,* **2020**, *13*, 581. http://dx.doi.org/10.3389/fncel.2019.00581 PMID: 31998080

[112] Costa, B.M.; Yao, H.; Yang, L.; Buch, S. Role of endoplasmic reticulum (ER) stress in cocaine-induced microglial cell death. *J. Neuroimmune Pharmacol.,* **2013**, *8*(3), 705-714. http://dx.doi.org/10.1007/s11481-013-9438-8 PMID: 23404095

[113] Chivero, E.T.; Liao, K.; Niu, F.; Tripathi, A.; Tian, C.; Buch, S.; Hu, G. Engineered extracellular vesicles loaded with miR-124 Attenuate cocaine-mediated activation of microglia. *Front. Cell Dev. Biol.,* **2020**, *8*, 573. http://dx.doi.org/10.3389/fcell.2020.00573 PMID: 32850781

[114] Chivero, E.T.; Sil, S.; Singh, S.; Thangaraj, A.; Gordon, L.; Evah-Nzoughe, G.B.; Ferguson, N.; Callen, S.; Buch, S. Protective role of *Lactobacillus rhamnosus* probiotic in reversing cocaine-induced oxidative stress, glial activation and locomotion in mice. *J. Neuroimmune Pharmacol.,* **2021**, *17*(1-2): 6275. http://dx.doi.org/10.1007/s11481-021-10020-9 PMID: 34628571

[115] Brown, K.T.; Levis, S.C.; O'Neill, C.E.; Northcutt, A.L.; Fabisiak, T.J.; Watkins, L.R.; Bachtell, R.K. Innate immune signaling in the ventral tegmental area contributes to drug-primed reinstatement of cocaine seeking. *Brain Behav. Immun.,* **2018**, *67*, 130-138. http://dx.doi.org/10.1016/j.bbi.2017.08.012 PMID: 28813640

[116] Chivero, E.T.; Thangaraj, A.; Tripathi, A.; Periyasamy, P.; Guo, M.L.; Buch, S. NLRP3 inflammasome blockade reduces cocaine-induced microglial activation and neuroinflammation. *Mol. Neurobiol.,* **2021**, *58*(5), 2215-2230. http://dx.doi.org/10.1007/s12035-020-02184-x PMID: 33417223

[117] Liao, K.; Guo, M.; Niu, F.; Yang, L.; Callen, S.E.; Buch, S. Cocaine-mediated induction of microglial activation involves the ER stress-TLR2 axis. *J. Neuroinflammation,* **2016**, *13*(1), 33. http://dx.doi.org/10.1186/s12974-016-0501-2 PMID: 26860188

[118] da Silva, MCM; Gomes, GF; de Barros Fernandes, H; da Silva, AM; Teixeira, AL; Moreira, FA Inhibition of CSF1R, a receptor involved in microglia viability, alters behavioral and molecular changes induced by cocaine. *Sci. Reports,* **2021**, *11*(1), 1-15. http://dx.doi.org/10.1038/s41598-021-95059-7

[119] Thangaraj, A.; Periyasamy, P.; Guo, M.L.; Chivero, E.T.; Callen, S.; Buch, S. Mitigation of cocaine-mediated mitochondrial damage, defective mitophagy and microglial activation by superoxide dismutase mimetics. *Autophagy,* **2020**, *16*(2), 289-312. http://dx.doi.org/10.1080/15548627.2019.1607686 PMID: 30990365

[120] Burkovetskaya, M.E.; Small, R.; Guo, L.; Buch, S.; Guo, M.L. Cocaine self-administration differentially activates microglia in the mouse brain. *Neurosci. Lett.,* **2020**, *728*, 134951. http://dx.doi.org/10.1016/j.neulet.2020.134951 PMID: 32278944

[121] Smith, H.R.; Beveridge, T.J.R.; Nader, S.H.; Nader, M.A.; Porrino, L.J. Regional elevations in microglial activation and cerebral glucose utilization in frontal white matter tracts of rhesus monkeys following prolonged cocaine self-administration. *Brain Struct. Funct.,* **2019**, *224*(4), 1417-1428. http://dx.doi.org/10.1007/s00429-019-01846-4 PMID: 30747315

[122] Narendran, R.; Lopresti, B.J.; Mason, N.S.; Deuitch, L.; Paris, J.; Himes, M.L.; Kodavali, C.V.; Nimgaonkar, V.L. Cocaine abuse in humans is not associated with increased microglial activation: an 18-kDa translocator protein positron emission tomography imaging study with [11C]PBR28. *J. Neurosci.,* **2014**, *34*(30), 9945-9950. http://dx.doi.org/10.1523/JNEUROSCI.0928-14.2014 PMID: 25057196

[123] Little, K.Y.; Ramssen, E.; Welchko, R.; Volberg, V.; Roland, C.J.; Cassin, B. Decreased brain dopamine cell numbers in human cocaine users. *Psychiatry Res.,* **2009**, *168*(3), 173-180. http://dx.doi.org/10.1016/j.psychres.2008.10.034 PMID: 19233481

[124] Linker, K.E.; Gad, M.; Tawadrous, P.; Cano, M.; Green, K.N.; Wood, M.A.; Leslie, F.M. Microglial activation increases cocaine self-administration following adolescent nicotine exposure. *Nat. Commun.,* **2020**, *11*(1), 306. http://dx.doi.org/10.1038/s41467-019-14173-3 PMID: 31949158

[125] Northcutt, A.L.; Hutchinson, M.R.; Wang, X.; Baratta, M.V.; Hiranita, T.; Cochran, T.A.; Pomrenze, M.B.; Galer, E.L.; Kopajtic, T.A.; Li, C.M.; Amat, J.; Larson, G.; Cooper, D.C.; Huang, Y.; O'Neill, C.E.; Yin, H.; Zahniser, N.R.; Katz, J.L.; Rice, K.C.; Maier, S.F.; Bachtell, R.K.; Watkins, L.R. DAT isn't all that: cocaine reward and reinforcement require Toll-like receptor 4 signaling. *Mol. Psychiatry,* **2015**, *20*(12), 1525-1537.

http://dx.doi.org/10.1038/mp.2014.177 PMID: 25644383
[126] Chen, H.; Uz, T.; Manev, H. Minocycline affects cocaine sensitization in mice. *Neurosci. Lett.,* **2009**, *452*(3), 258-261. http://dx.doi.org/10.1016/j.neulet.2009.01.078 PMID: 19348734
[127] Poland, R.S.; Hahn, Y.K.; Knapp, P.E.; Beardsley, P.M.; Bowers, M.S. Ibudilast attenuates expression of behavioral sensitization to cocaine in male and female rats. *Neuropharmacology,* **2016**, *109*, 281-292. http://dx.doi.org/10.1016/j.neuropharm.2016.06.024 PMID: 27343385
[128] Metz, V.E.; Jones, J.D.; Manubay, J.; Sullivan, M.A.; Mogali, S.; Segoshi, A.; Madera, G.; Johnson, K.W.; Comer, S.D. Effects of ibudilast on the subjective, reinforcing, and analgesic effects of oxycodone in recently detoxified adults with opioid dependence. *Neuropsychopharmacology,* **2017**, *42*(9), 1825-1832. http://dx.doi.org/10.1038/npp.2017.70 PMID: 28393896
[129] Mu, L.; Liu, X.; Yu, H.; Hu, M.; Friedman, V.; Kelly, T.J.; Zhao, L.; Liu, Q. Ibudilast attenuates cocaine self-administration and prime- and cue-induced reinstatement of cocaine seeking in rats. *Neuropharmacology,* **2021**, *201*, 108830. http://dx.doi.org/10.1016/j.neuropharm.2021.108830 PMID: 34626665
[130] Periyasamy, P.; Liao, K.; Kook, Y.H.; Niu, F.; Callen, S.E.; Guo, M.L.; Buch, S. Cocaine-mediated downregulation of miR-124 activates microglia by targeting KLF4 and TLR4 signaling. *Mol. Neurobiol.,* **2018**, *55*(4), 3196-3210. http://dx.doi.org/10.1007/s12035-017-0584-5 PMID: 28478506
[131] Zhu, C.; Tao, H.; Rong, S.; Xiao, L.; Li, X.; Jiang, S.; Guo, B.; Wang, L.; Ding, J.; Gao, C.; Chang, H.; Sun, T.; Wang, F. Glucagon-like peptide-1 analog exendin-4 ameliorates cocaine-mediated behavior by inhibiting toll-like receptor 4 signaling in mice. *Front. Pharmacol.,* **2021**, *12*, 694476. http://dx.doi.org/10.3389/fphar.2021.694476 PMID: 34349653
[132] Kashima, D.T.; Grueter, B.A. Toll-like receptor 4 deficiency alters nucleus accumbens synaptic physiology and drug reward behavior. *Proc. Natl. Acad. Sci. USA,* **2017**, *114*(33), 8865-8870. http://dx.doi.org/10.1073/pnas.1705974114 PMID: 28760987
[133] Zhu, R.; Bu, Q.; Fu, D.; Shao, X.; Jiang, L.; Guo, W.; Chen, B.; Liu, B.; Hu, Z.; Tian, J.; Zhao, Y.; Cen, X. Toll-like receptor 3 modulates the behavioral effects of cocaine in mice. *J. Neuroinflammation,* **2018**, *15*(1), 93. http://dx.doi.org/10.1186/s12974-018-1130-8 PMID: 29571298
[134] Guo, M.L.; Chivero, E.T.; Callen, S.E.; Buch, S. NLRP3 inflammasome is involved in cocaine-mediated potentiation on behavioral changes in CX3CR1-deficient mice. *J. Pers. Med.,* **2021**, *11*(10), 963. http://dx.doi.org/10.3390/jpm11100963 PMID: 34683104
[135] Steinkellner, T.; Freissmuth, M.; Sitte, H.H.; Montgomery, T. The ugly side of amphetamines: short- and long-term toxicity of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'), methamphetamine and d-amphetamine. *Biol. Chem.,* **2011**, *392*(1-2), 103-115. http://dx.doi.org/10.1515/bc.2011.016 PMID: 21194370
[136] Gou, H.; sun, D.; Hao, L.; An, M.; Xie, B.; Cong, B.; Ma, C.; Wen, D. Cholecystokinin-8 attenuates methamphetamine-induced inflammatory activation of microglial cells through CCK2 receptor. *Neurotoxicology,* **2020**, *81*, 70-79. http://dx.doi.org/10.1016/j.neuro.2020.09.001 PMID: 32916201
[137] Yang, T.; Zang, S.; Wang, Y.; Zhu, Y.; Jiang, L.; Chen, X.; Zhang, X.; Cheng, J.; Gao, R.; Xiao, H.; Wang, J. Methamphetamine induced neuroinflammation in mouse brain and microglial cell line BV2: Roles of the TLR4/TRIF/Peli1 signaling axis. *Toxicol. Lett.,* **2020**, *333*, 150-158. http://dx.doi.org/10.1016/j.toxlet.2020.07.028 PMID: 32768653
[138] Wan, F.; Zang, S.; Yu, G.; Xiao, H.; Wang, J.; Tang, J.; Ginkgolide, B. Ginkgolide B suppresses methamphetamine-induced microglial activation through TLR4-NF-κB signaling pathway in BV2 cells. *Neurochem. Res.,* **2017**, *42*(10), 2881-2891. http://dx.doi.org/10.1007/s11064-017-2309-6 PMID: 28712049
[139] Wang, B.; Chen, T.; Wang, J.; Jia, Y.; Ren, H.; Wu, F.; Hu, M.; Chen, Y. Methamphetamine modulates the production of interleukin-6 and tumor necrosis factor-alpha *via* the cAMP/PKA/CREB signaling pathway in lipopolysaccharide-activated microglia. *Int. Immunopharmacol.,* **2018**, *56*, 168-178. http://dx.doi.org/10.1016/j.intimp.2018.01.024 PMID: 29414647
[140] Tocharus, J.; Khonthun, C.; Chongthammakun, S.; Govitrapong, P. Melatonin attenuates methamphetamine-induced overexpression of pro-inflammatory cytokines in microglial cell lines. *J. Pineal Res.,* **2010**, *48*(4), 347-352. http://dx.doi.org/10.1111/j.1600-079X.2010.00761.x PMID: 20374443
[141] Xu, E.; Liu, J.; Liu, H.; Wang, X.; Xiong, H. Inflammasome activation by methamphetamine potentiates lipopolysaccharide stimulation of IL-1β production in microglia. *J. Neuroimmune Pharmacol.,* **2018**, *13*(2), 237-253. http://dx.doi.org/10.1007/s11481-018-9780-y PMID: 29492824
[142] Wang, J.; Qian, W.; Liu, J.; Zhao, J.; Yu, P.; Jiang, L.; Zhou, J.; Gao, R.; Xiao, H. Effect of methamphetamine on the microglial damage: role of potassium channel Kv1.3. *PLoS One,* **2014**, *9*(2), e88642. http://dx.doi.org/10.1371/journal.pone.0088642 PMID: 24533129
[143] Yue, X.; Qiao, D.; Wang, A.; Tan, X.; Li, Y.; Liu, C.; Wang, H. CD200 attenuates methamphetamine-induced microglial activation and dopamine depletion. *J. Huazhong Univ. Sci. Technolog. Med. Sci.,* **2012**, *32*(3), 415-421. http://dx.doi.org/10.1007/s11596-012-0072-0 PMID: 22684568
[144] Shanks, R.A.; Anderson, J.R.; Taylor, J.R.; Lloyd, S.A. Amphetamine and methamphetamine have a direct and differential effect on BV2 microglia cells. *Bull. Exp. Biol. Med.,* **2012**, *154*(2), 228-232. http://dx.doi.org/10.1007/s10517-012-1919-x PMID: 23330132
[145] Yu, G.; Song, Y.; Xie, C.; Tao, L.; Wan, F.; Jiang, L.; Wang, J.; Tang, J. MiR-142a-3p and miR-155-5p reduce methamphetamine-induced inflammation: Role of the target protein Peli1. *Toxicol. Appl. Pharmacol.,* **2019**, *370*, 145-153. http://dx.doi.org/10.1016/j.taap.2019.03.019 PMID: 30914375
[146] Shen, K.; Zhang, Y.; Lv, X.; Chen, X.; Zhou, R.; Nguyen, L.K.; Wu, X.; Yao, H. Molecular mechanisms involving sigma-1 receptor in cell apoptosis of BV-2 microglial cells induced by methamphetamine. *CNS Neurol. Disord. Drug Targets,* **2016**, *15*(7), 857-865. http://dx.doi.org/10.2174/1871527315666160518122816 PMID: 27189473
[147] Chao, J; Zhang, Y; Du, L; Zhou, R; Wu, X; Shen, K Molecular mechanisms underlying the involvement of the sigma-1 receptor in methamphetamine-mediated microglial polarization. *Sci Reports,* **2017**, *7*(1), 1-13. http://dx.doi.org/10.1038/s41598-017-11065-8
[148] Sharikova, A.V.; Quaye, E.; Park, J.Y.; Maloney, M.C.; Desta, H.; Thiyagarajan, R.; Seldeen, K.L.; Parikh, N.U.; Sandhu, P.; Khmaladze, A.; Troen, B.R.; Schwartz, S.A.; Mahajan, S.D. Methamphetamine induces apoptosis of microglia *via* the intrinsic mitochondrial-dependent pathway. *J. Neuroimmune Pharmacol.,* **2018**, *13*(3), 396-411. http://dx.doi.org/10.1007/s11481-018-9787-4 PMID: 29644532
[149] Gonçalves, J.; Ribeiro, C.F.; Malva, J.O.; Silva, A.P. Protective role of neuropeptide YY_2 receptors in cell death and microglial response following methamphetamine injury. *Eur. J. Neurosci.,* **2012**, *36*(9), 3173-3183. http://dx.doi.org/10.1111/j.1460-9568.2012.08232.x PMID: 22805317
[150] Frank, M.G.; Adhikary, S.; Sobesky, J.L.; Weber, M.D.; Watkins, L.R.; Maier, S.F. The danger-associated molecular pattern HMGB1 mediates the neuroinflammatory effects of methamphetamine. *Brain Behav. Immun.,* **2016**, *51*, 99-108. http://dx.doi.org/10.1016/j.bbi.2015.08.001 PMID: 26254235
[151] Vargas, A.M.; Rivera-Rodriguez, D.E.; Martinez, L.R. Methamphetamine alters the TLR4 signaling pathway, NF-κB activation, and pro-inflammatory cytokine production in LPS-challenged NR-9460 microglia-like cells. *Mol. Immunol.,* **2020**, *121*, 159-166. http://dx.doi.org/10.1016/j.molimm.2020.03.013 PMID: 32222586
[152] Huang, Y.N.; Wu, C.H.; Lin, T.C.; Wang, J.Y. Methamphetamine induces heme oxygenase-1 expression in cortical neurons and glia to prevent its toxicity. *Toxicol. Appl. Pharmacol.,* **2009**, *240*(3), 315-326. http://dx.doi.org/10.1016/j.taap.2009.06.021 PMID: 19576919
[153] Kawasaki, T.; Ishihara, K.; Ago, Y.; Nakamura, S.; Itoh, S.; Baba, A.; Matsuda, T. Protective effect of the radical scavenger edara-

vone against methamphetamine-induced dopaminergic neurotoxicity in mouse striatum. *Eur. J. Pharmacol.,* **2006**, *542*(1-3), 92-99. http://dx.doi.org/10.1016/j.ejphar.2006.05.012 PMID: 16784740

[154] Mendieta, L.; Granado, N.; Aguilera, J.; Tizabi, Y.; Moratalla, R.; Fragment, C. Fragment C domain of tetanus toxin mitigates methamphetamine neurotoxicity and its motor consequences in mice. *Int. J. Neuropsychopharmacol.,* **2016**, *19*(8), pyw021. http://dx.doi.org/10.1093/ijnp/pyw021 PMID: 26945022

[155] Dang, D.K.; Shin, E.J.; Nam, Y.; Ryoo, S.; Jeong, J.H.; Jang, C.G.; Nabeshima, T.; Hong, J.S.; Kim, H.C. Apocynin prevents mitochondrial burdens, microglial activation, and pro-apoptosis induced by a toxic dose of methamphetamine in the striatum of mice *via* inhibition of p47phox activation by ERK. *J. Neuroinflammation,* **2016**, *13*(1), 12. http://dx.doi.org/10.1186/s12974-016-0478-x PMID: 26780950

[156] Shin, E.J.; Shin, S.W.; Nguyen, T.T.L.; Park, D.H.; Wie, M.B.; Jang, C.G.; Nah, S.Y.; Yang, B.W.; Ko, S.K.; Nabeshima, T.; Kim, H.C. Ginsenoside Re rescues methamphetamine-induced oxidative damage, mitochondrial dysfunction, microglial activation, and dopaminergic degeneration by inhibiting the protein kinase Cδ gene. *Mol. Neurobiol.,* **2014**, *49*(3), 1400-1421. http://dx.doi.org/10.1007/s12035-013-8617-1 PMID: 24430743

[157] Robson, M.J.; Turner, R.C.; Naser, Z.J.; McCurdy, C.R.; Huber, J.D.; Matsumoto, R.R. SN79, a sigma receptor ligand, blocks methamphetamine-induced microglial activation and cytokine upregulation. *Exp. Neurol.,* **2013**, *247*, 134-142. http://dx.doi.org/10.1016/j.expneurol.2013.04.009 PMID: 23631864

[158] Kikuchi-Utsumi, K.; Ishizaka, M.; Matsumura, N.; Watabe, M.; Aoyama, K.; Sasakawa, N.; Nakaki, T. Involvement of the α(1D)-adrenergic receptor in methamphetamine-induced hyperthermia and neurotoxicity in rats. *Neurotox. Res.,* **2013**, *24*(2), 130-138. http://dx.doi.org/10.1007/s12640-012-9369-9 PMID: 23283760

[159] Granado, N.; Lastres-Becker, I.; Ares-Santos, S.; Oliva, I.; Martin, E.; Cuadrado, A.; Moratalla, R. Nrf2 deficiency potentiates methamphetamine-induced dopaminergic axonal damage and gliosis in the striatum. *Glia,* **2011**, *59*(12), 1850-1863. http://dx.doi.org/10.1002/glia.21229 PMID: 21882243

[160] Buchanan, J.B.; Sparkman, N.L.; Johnson, R.W. A neurotoxic regimen of methamphetamine exacerbates the febrile and neuroinflammatory response to a subsequent peripheral immune stimulus. *J. Neuroinflammation,* **2010**, *7*(1), 82. http://dx.doi.org/10.1186/1742-2094-7-82 PMID: 21092194

[161] Bowyer, J.F.; Tranter, K.M.; Sarkar, S.; George, N.I.; Hanig, J.P.; Kelly, K.A.; Michalovicz, L.T.; Miller, D.B.; O'Callaghan, J.P. Corticosterone and exogenous glucose alter blood glucose levels, neurotoxicity, and vascular toxicity produced by methamphetamine. *J. Neurochem.,* **2017**, *143*(2), 198-213. http://dx.doi.org/10.1111/jnc.14143 PMID: 28792619

[162] Carmena, A.; Granado, N.; Ares-Santos, S.; Alberquilla, S.; Tizabi, Y.; Moratalla, R. Methamphetamine-induced toxicity in indusium griseum of mice is associated with astro- and microgliosis. *Neurotox. Res.,* **2015**, *27*(3), 209-216. http://dx.doi.org/10.1007/s12640-014-9505-9 PMID: 25492248

[163] Bowyer, J.F.; Sarkar, S.; Tranter, K.M.; Hanig, J.P.; Miller, D.B.; O'Callaghan, J.P. Vascular-directed responses of microglia produced by methamphetamine exposure: indirect evidence that microglia are involved in vascular repair? *J. Neuroinflammation,* **2016**, *13*(1), 64. http://dx.doi.org/10.1186/s12974-016-0526-6 PMID: 26970737

[164] Dang, D.K.; Shin, E.J.; Kim, D.J.; Tran, H.Q.; Jeong, J.H.; Jang, C.G.; Ottersen, O.P.; Nah, S.Y.; Hong, J.S.; Nabeshima, T.; Kim, H.C. PKCδ-dependent p47phox activation mediates methamphetamine-induced dopaminergic neurotoxicity. *Free Radic. Biol. Med.,* **2018**, *115*, 318-337. http://dx.doi.org/10.1016/j.freeradbiomed.2017.12.018 PMID: 29269308

[165] Zhang, Y.; Shen, K.; Bai, Y.; Lv, X.; Huang, R.; Zhang, W.; Chao, J.; Nguyen, L.K.; Hua, J.; Gan, G.; Hu, G.; Yao, H. *Mir143* -BBC3 cascade reduces microglial survival *via* interplay between apoptosis and autophagy: Implications for methamphetamine-mediated neurotoxicity. *Autophagy,* **2016**, *12*(9), 1538-1559. http://dx.doi.org/10.1080/15548627.2016.1191723 PMID: 27464000

[166] Friend, D.M.; Keefe, K.A. Glial reactivity in resistance to methamphetamine-induced neurotoxicity. *J. Neurochem.,* **2013**, *125*(4), 566-574. http://dx.doi.org/10.1111/jnc.12201 PMID: 23414433

[167] Gonçalves, J.; Baptista, S.; Martins, T.; Milhazes, N.; Borges, F.; Ribeiro, C.F.; Malva, J.O.; Silva, A.P. Methamphetamine-induced neuroinflammation and neuronal dysfunction in the mice hippocampus: preventive effect of indomethacin. *Eur. J. Neurosci.,* **2010**, *31*(2), 315-326. http://dx.doi.org/10.1111/j.1460-9568.2009.07059.x PMID: 20074221

[168] Asanuma, M.; Miyazaki, I.; Higashi, Y.; Tsuji, T.; Ogawa, N. Specific gene expression and possible involvement of inflammation in methamphetamine-induced neurotoxicity. *Ann. N. Y. Acad. Sci.,* **2004**, *1025*(1), 69-75. http://dx.doi.org/10.1196/annals.1316.009 PMID: 15542702

[169] Zhang, L.; Shirayama, Y.; Shimizu, E.; Iyo, M.; Hashimoto, K. Protective effects of minocycline on 3,4-methylenedioxymethamphetamine-induced neurotoxicity in serotonergic and dopaminergic neurons of mouse brain. *Eur. J. Pharmacol.,* **2006**, *544*(1-3), 1-9. http://dx.doi.org/10.1016/j.ejphar.2006.05.047 PMID: 16859675

[170] Hozumi, H.; Asanuma, M.; Miyazaki, I.; Fukuoka, S.; Kikkawa, Y.; Kimoto, N.; Kitamura, Y.; Sendo, T.; Kita, T.; Gomita, Y. Protective effects of interferon-γ against methamphetamine-induced neurotoxicity. *Toxicol. Lett.,* **2008**, *177*(2), 123-129. http://dx.doi.org/10.1016/j.toxlet.2008.01.005 PMID: 18282668

[171] Wang, X.; Northcutt, A.L.; Cochran, T.A.; Zhang, X.; Fabisiak, T.J.; Haas, M.E.; Amat, J.; Li, H.; Rice, K.C.; Maier, S.F.; Bachtell, R.K.; Hutchinson, M.R.; Watkins, L.R. Methamphetamine activates toll-like receptor 4 to induce central immune signaling within the ventral tegmental area and contributes to extracellular dopamine increase in the nucleus accumbens shell. *ACS Chem. Neurosci.,* **2019**, *10*(8), 3622-3634. http://dx.doi.org/10.1021/acschemneuro.9b00225 PMID: 31282647

[172] Asanuma, M.; Tsuji, T.; Miyazaki, I.; Miyoshi, K.; Ogawa, N. Methamphetamine-induced neurotoxicity in mouse brain is attenuated by ketoprofen, a non-steroidal anti-inflammatory drug. *Neurosci. Lett.,* **2003**, *352*(1), 13-16. http://dx.doi.org/10.1016/j.neulet.2003.08.015 PMID: 14615038

[173] Thomas, D.M.; Kuhn, D.M. MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. *Brain Res.,* **2005**, *1050*(1-2), 190-198. http://dx.doi.org/10.1016/j.brainres.2005.05.049 PMID: 15987631

[174] Thomas, D.M.; Kuhn, D.M. Attenuated microglial activation mediates tolerance to the neurotoxic effects of methamphetamine. *J. Neurochem.,* **2005**, *92*(4), 790-797. http://dx.doi.org/10.1111/j.1471-4159.2004.02906.x PMID: 15686480

[175] Thomas, D.M.; Francescutti-Verbeem, D.M.; Kuhn, D.M. The newly synthesized pool of dopamine determines the severity of methamphetamine-induced neurotoxicity. *J. Neurochem.,* **2008**, *105*(3), 605-616. http://dx.doi.org/10.1111/j.1471-4159.2007.05155.x PMID: 18088364

[176] Thomas, D.M.; Francescutti-Verbeem, D.M.; Kuhn, D.M. Methamphetamine-induced neurotoxicity and microglial activation are not mediated by fractalkine receptor signaling. *J. Neurochem.,* **2008**, *106*(2), 696-705. http://dx.doi.org/10.1111/j.1471-4159.2008.05421.x PMID: 18410508

[177] Kuhn, D.M.; Francescutti-Verbeem, D.M.; Thomas, D.M. Dopamine disposition in the presynaptic process regulates the severity of methamphetamine-induced neurotoxicity. *Ann. N. Y. Acad. Sci.,* **2008**, *1139*(1), 118-126. http://dx.doi.org/10.1196/annals.1432.026 PMID: 18991856

[178] Thomas, D.M.; Walker, P.D.; Benjamins, J.A.; Geddes, T.J.; Kuhn, D.M. Methamphetamine neurotoxicity in dopamine nerve endings of the striatum is associated with microglial activation. *J. Pharmacol. Exp. Ther.,* **2004**, *311*(1), 1-7. http://dx.doi.org/10.1124/jpet.104.070961 PMID: 15163680

[179] Thomas, D.M.; Francescutti-Verbeem, D.M.; Kuhn, D.M. Increases in cytoplasmic dopamine compromise the normal resistance of

the nucleus accumbens to methamphetamine neurotoxicity. *J. Neurochem.,* **2009**, *109*(6), 1745-1755. http://dx.doi.org/10.1111/j.1471-4159.2009.06094.x PMID: 19457119

[180] Thanos, P.K.; Kim, R.; Delis, F.; Ananth, M.; Chachati, G.; Rocco, M.J.; Masad, I.; Muniz, J.A.; Grant, S.C.; Gold, M.S.; Cadet, J.L.; Volkow, N.D. Chronic methamphetamine effects on brain structure and function in rats. *PLoS One,* **2016**, *11*(6), e0155457. http://dx.doi.org/10.1371/journal.pone.0155457 PMID: 27275601

[181] Fantegrossi, W.E.; Ciullo, J.R.; Wakabayashi, K.T.; De La Garza, R., II; Traynor, J.R.; Woods, J.H. A comparison of the physiological, behavioral, neurochemical and microglial effects of methamphetamine and 3,4-methylenedioxymethamphetamine in the mouse. *Neuroscience,* **2008**, *151*(2), 533-543. http://dx.doi.org/10.1016/j.neuroscience.2007.11.007 PMID: 18082974

[182] Escubedo, E.; Guitart, L.; Sureda, F.X.; Jiménez, A.; Pubill, D.; Pallàs, M.; Camins, A.; Camarasa, J. Microgliosis and down-regulation of adenosine transporter induced by methamphetamine in rats. *Brain Res.,* **1998**, *814*(1-2), 120-126. http://dx.doi.org/10.1016/S0006-8993(98)01065-8 PMID: 9838075

[183] Sriram, K.; Miller, D.B.; O'Callaghan, J.P. Minocycline attenuates microglial activation but fails to mitigate striatal dopaminergic neurotoxicity: role of tumor necrosis factor-alpha. *J. Neurochem.,* **2006**, *96*(3), 706-718. http://dx.doi.org/10.1111/j.1471-4159.2005.03566.x PMID: 16405514

[184] Namyen, J.; Permpoonputtana, K.; Nopparat, C.; Tocharus, J.; Tocharus, C.; Govitrapong, P. Protective effects of melatonin on methamphetamine-induced blood-brain barrier dysfunction in rat model. *Neurotox. Res.,* **2020**, *37*(3), 640-660. http://dx.doi.org/10.1007/s12640-019-00156-1 PMID: 31900895

[185] Lloyd, S.A.; Corkill, B.; Bruster, M.C.; Roberts, R.L.; Shanks, R.A. Chronic methamphetamine exposure significantly decreases microglia activation in the arcuate nucleus. *J. Chem. Neuroanat.,* **2017**, *82*, 5-11. http://dx.doi.org/10.1016/j.jchemneu.2017.03.001 PMID: 28323108

[186] Marchese, N.A.; Occhieppo, V.B.; Basmadjian, O.M.; Casarsa, B.S.; Baiardi, G.; Bregonzio, C. Angiotensin II modulates amphetamine-induced glial and brain vascular responses, and attention deficit *via* angiotensin type 1 receptor: Evidence from brain regional sensitivity to amphetamine. *Eur. J. Neurosci.,* **2020**, *51*(4), 1026-1041. http://dx.doi.org/10.1111/ejn.14605 PMID: 31646669

[187] Thomas, D.M.; Dowgiert, J.; Geddes, T.J.; Francescutti-Verbeem, D.; Liu, X.; Kuhn, D.M. Microglial activation is a pharmacologically specific marker for the neurotoxic amphetamines. *Neurosci. Lett.,* **2004**, *367*(3), 349-354. http://dx.doi.org/10.1016/j.neulet.2004.06.065 PMID: 15337264

[188] Bowyer, J.F.; Peterson, S.L.; Rountree, R.L.; Tor-Agbidye, J.; Wang, G.J. Neuronal degeneration in rat forebrain resulting from d-amphetamine-induced convulsions is dependent on seizure severity and age. *Brain Res.,* **1998**, *809*(1), 77-90. http://dx.doi.org/10.1016/S0006-8993(98)00846-4 PMID: 9795148

[189] Shin, E.J.; Dang, D.K.; Tran, H.Q.; Nam, Y.; Jeong, J.H.; Lee, Y.H.; Park, K.T.; Lee, Y.S.; Jang, C.G.; Hong, J.S.; Nabeshima, T.; Kim, H.C. PKCδ knockout mice are protected from para-methoxymethamphetamine-induced mitochondrial stress and associated neurotoxicity in the striatum of mice. *Neurochem. Int.,* **2016**, *100*, 146-158. http://dx.doi.org/10.1016/j.neuint.2016.09.008 PMID: 27623093

[190] Nguyen, P.T.; Dang, D.K.; Tran, H.Q.; Shin, E.J.; Jeong, J.H.; Nah, S.Y.; Cho, M.C.; Lee, Y.S.; Jang, C.G.; Kim, H.C. Methiopropamine, a methamphetamine analogue, produces neurotoxicity *via* dopamine receptors. *Chem. Biol. Interact.,* **2019**, *305*, 134-147. http://dx.doi.org/10.1016/j.cbi.2019.03.017 PMID: 30922767

[191] Lopez-Rodriguez, A.B.; Llorente-Berzal, A.; Garcia-Segura, L.M.; Viveros, M.P. Sex-dependent long-term effects of adolescent exposure to THC and/or MDMA on neuroinflammation and serotoninergic and cannabinoid systems in rats. *Br. J. Pharmacol.,* **2014**, *171*(6), 1435-1447. http://dx.doi.org/10.1111/bph.12519 PMID: 24236988

[192] Rubio-Araiz, A.; Perez-Hernandez, M.; Urrutia, A.; Porcu, F.; Borcel, E.; Gutierrez-Lopez, M.D.; O'Shea, E.; Colado, M.I. 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) disrupts blood-brain barrier integrity through a mechanism involving P2X7 receptors. *Int. J. Neuropsychopharmacol.,* **2014**, *17*(8), 1243-1255. http://dx.doi.org/10.1017/S1461145714000145 PMID: 24626059

[193] Torres, E.; Gutierrez-Lopez, M.D.; Borcel, E.; Peraile, I.; Mayado, A.; O'Shea, E.; Colado, M.I. Evidence that MDMA ('ecstasy') increases cannabinoid CB_2 receptor expression in microglial cells: role in the neuroinflammatory response in rat brain. *J. Neurochem.,* **2010**, *113*(1), 67-78. http://dx.doi.org/10.1111/j.1471-4159.2010.06578.x PMID: 20067581

[194] Orio, L.; O'Shea, E.; Sanchez, V.; Pradillo, J.M.; Escobedo, I.; Camarero, J.; Moro, M.A.; Green, A.R.; Colado, M.I. 3,4-Methylenedioxymethamphetamine increases interleukin-1β levels and activates microglia in rat brain: studies on the relationship with acute hyperthermia and 5-HT depletion. *J. Neurochem.,* **2004**, *89*(6), 1445-1453. http://dx.doi.org/10.1111/j.1471-4159.2004.02443.x PMID: 15189347

[195] Ruiz-Medina, J.; Pinto-Xavier, A.; Rodríguez-Arias, M.; Miñarro, J.; Valverde, O. Influence of chronic caffeine on MDMA-induced behavioral and neuroinflammatory response in mice. *Psychopharmacology (Berl.),* **2013**, *226*(2), 433-444. http://dx.doi.org/10.1007/s00213-012-2918-3 PMID: 23187789

[196] Frau, L.; Simola, N.; Plumitallo, A.; Morelli, M. Microglial and astroglial activation by 3,4-methylenedioxymethamphetamine (MDMA) in mice depends on S(+) enantiomer and is associated with an increase in body temperature and motility. *J. Neurochem.,* **2013**, *124*(1), 69-78. http://dx.doi.org/10.1111/jnc.12060 PMID: 23083295

[197] Ruiz-Medina, J.; Ledent, C.; Carretón, O.; Valverde, O. The A2a adenosine receptor modulates the reinforcement efficacy and neurotoxicity of MDMA. *J. Psychopharmacol.,* **2011**, *25*(4), 550-564. http://dx.doi.org/10.1177/0269881110389210 PMID: 21262860

[198] Costa, G.; Porceddu, P.; Serra, M.; Casu, M.; Schiano, V.; Napolitano, F.; Pinna, A.; Usiello, A.; Morelli, M. Lack of rhes increases mdma-induced neuroinflammation and dopamine neuron degeneration: Role of gender and age. *Int. J. Mol. Sci.,* **2019**, *20*(7), 1556. http://dx.doi.org/10.3390/ijms20071556 PMID: 30925704

[199] Khairnar, A.; Plumitallo, A.; Frau, L.; Schintu, N.; Morelli, M. Caffeine enhances astroglia and microglia reactivity induced by 3,4-methylenedioxymethamphetamine ('ecstasy') in mouse brain. *Neurotox. Res.,* **2010**, *17*(4), 435-439. http://dx.doi.org/10.1007/s12640-009-9125-y PMID: 19882200

[200] Frau, L.; Simola, N.; Porceddu, P.F.; Morelli, M. Effect of crowding, temperature and age on glia activation and dopaminergic neurotoxicity induced by MDMA in the mouse brain. *Neurotoxicology,* **2016**, *56*, 127-138. http://dx.doi.org/10.1016/j.neuro.2016.07.008 PMID: 27451954

[201] Orio, L.; Llopis, N.; Torres, E.; Izco, M.; O'Shea, E.; Colado, M.I. A study on the mechanisms by which minocycline protects against MDMA ('ecstasy')-induced neurotoxicity of 5-HT cortical neurons. *Neurotox. Res.,* **2010**, *18*(2), 187-199. http://dx.doi.org/10.1007/s12640-009-9120-3 PMID: 19777321

[202] Costa, G.; Frau, L.; Wardas, J.; Pinna, A.; Plumitallo, A.; Morelli, M. MPTP-induced dopamine neuron degeneration and glia activation is potentiated in MDMA-pretreated mice. *Mov. Disord.,* **2013**, *28*(14), 1957-1965. http://dx.doi.org/10.1002/mds.25646 PMID: 24108425

[203] Costa, G.; Simola, N.; Morelli, M. MDMA administration during adolescence exacerbates MPTP-induced cognitive impairment and neuroinflammation in the hippocampus and prefrontal cortex. *Psychopharmacology (Berl.),* **2014**, *231*(20), 4007-4018. http://dx.doi.org/10.1007/s00213-014-3536-z PMID: 24687411

[204] Masai, K.; Kuroda, K.; Isooka, N.; Kikuoka, R.; Murakami, S.; Kamimai, S.; Wang, D.; Liu, K.; Miyazaki, I.; Nishibori, M.; Asanuma, M. Neuroprotective effects of anti-high mobility group box-1 monoclonal antibody against methamphetamine-induced dopaminergic neurotoxicity. *Neurotox. Res.,* **2021**, *39*(5), 1511-1523. http://dx.doi.org/10.1007/s12640-021-00402-5 PMID: 34417986

[205] Campeão, M.; Fernandes, L.; Pita, I.R.; Lemos, C.; Ali, S.F.; Carvalho, F.; Rodrigues-Santos, P.; Fontes-Ribeiro, C.A.; Soares, E.;

Viana, S.D.; Pereira, F.C. Acute MDPV binge paradigm on mice emotional behavior and glial signature. *Pharmaceuticals (Basel),* **2021**, *14*(3), 271. http://dx.doi.org/10.3390/ph14030271 PMID: 33809599

[206] Raineri, M.; Gonzalez, B.; Goitia, B.; Garcia-Rill, E.; Krasnova, I.N.; Cadet, J.L.; Urbano, F.J.; Bisagno, V. Modafinil abrogates methamphetamine-induced neuroinflammation and apoptotic effects in the mouse striatum. *PLoS One,* **2012**, *7*(10), e46599. http://dx.doi.org/10.1371/journal.pone.0046599 PMID: 23056363

[207] McConnell, S.E.A.; O'Banion, M.K.; Cory-Slechta, D.A.; Olschowka, J.A.; Opanashuk, L.A. Characterization of binge-dosed methamphetamine-induced neurotoxicity and neuroinflammation. *Neurotoxicology,* **2015**, *50*, 131-141. http://dx.doi.org/10.1016/j.neuro.2015.08.006 PMID: 26283213

[208] Guilarte, T.R.; Nihei, M.K.; McGlothan, J.L.; Howard, A.S. Methamphetamine-induced deficits of brain monoaminergic neuronal markers: distal axotomy or neuronal plasticity. *Neuroscience,* **2003**, *122*(2), 499-513. http://dx.doi.org/10.1016/S0306-4522(03)00476-7 PMID: 14614914

[209] LaVoie, M.J.; Card, J.P.; Hastings, T.G. Microglial activation precedes dopamine terminal pathology in methamphetamine-induced neurotoxicity. *Exp. Neurol.,* **2004**, *187*(1), 47-57. http://dx.doi.org/10.1016/j.expneurol.2004.01.010 PMID: 15081587

[210] Blaker, A.L.; Rodriguez, E.A.; Yamamoto, B.K. Neurotoxicity to dopamine neurons after the serial exposure to alcohol and methamphetamine: Protection by COX-2 antagonism. *Brain Behav. Immun.,* **2019**, *81*, 317-328. http://dx.doi.org/10.1016/j.bbi.2019.06.028 PMID: 31228610

[211] Takashima, Y.; Fannon, M.J.; Galinato, M.H.; Steiner, N.L.; An, M.; Zemljic-Harpf, A.E.; Somkuwar, S.S.; Head, B.P.; Mandyam, C.D. Neuroadaptations in the dentate gyrus following contextual cued reinstatement of methamphetamine seeking. *Brain Struct. Funct.,* **2018**, *223*(5), 2197-2211. http://dx.doi.org/10.1007/s00429-018-1615-3 PMID: 29441405

[212] Herndon, J.M.; Cholanians, A.B.; Lau, S.S.; Monks, T.J. Glial cell response to 3,4-(+/-)-methylenedioxymethamphetamine and its metabolites. *Toxicol. Sci.,* **2014**, *138*(1), 130-138. http://dx.doi.org/10.1093/toxsci/kft275 PMID: 24299738

[213] Mahmoudiasl, G.R.; Abbaszadeh, H.A.; Rezaei-Tavirani, M.; Abdollahifar, M.A.; Sadeghi, Y.; Khoramgah, M.S.; Niknazar, S.; Darabi, S. Postmortem Study of Molecular and Histological Changes in the CA1 Hippocampal Region of Chronic Methamphetamine User. *Iran. J. Pharm. Res.,* **2019**, *18*(4), 2067-2082. http://dx.doi.org/10.22037/IJPR.2019.15483.13123 PMID: 32184870

[214] Kitamura, O.; Takeichi, T.; Wang, E.L.; Tokunaga, I.; Ishigami, A.; Kubo, S. Microglial and astrocytic changes in the striatum of methamphetamine abusers. *Leg. Med. (Tokyo),* **2010**, *12*(2), 57-62. http://dx.doi.org/10.1016/j.legalmed.2009.11.001 PMID: 20110187

[215] Sekine, Y.; Ouchi, Y.; Sugihara, G.; Takei, N.; Yoshikawa, E.; Nakamura, K.; Iwata, Y.; Tsuchiya, K.J.; Suda, S.; Suzuki, K.; Kawai, M.; Takebayashi, K.; Yamamoto, S.; Matsuzaki, H.; Ueki, T.; Mori, N.; Gold, M.S.; Cadet, J.L. Methamphetamine causes microglial activation in the brains of human abusers. *J. Neurosci.,* **2008**, *28*(22), 5756-5761. http://dx.doi.org/10.1523/JNEUROSCI.1179-08.2008 PMID: 18509037

[216] Rathitharan, G.; Truong, J.; Tong, J.; McCluskey, T.; Meyer, J.H.; Mizrahi, R.; Warsh, J.; Rusjan, P.; Kennedy, J.L.; Houle, S.; Kish, S.J.; Boileau, I. Microglia imaging in methamphetamine use disorder: a positron emission tomography study with the 18 kDa translocator protein radioligand [F-18]FEPPA. *Addict. Biol.,* **2021**, *26*(1), e12876. http://dx.doi.org/10.1111/adb.12876 PMID: 32017280

[217] Bohnert, S.; Georgiades, K.; Monoranu, C.M.; Bohnert, M.; Büttner, A.; Ondruschka, B. Quantitative evidence of suppressed TMEM119 microglial immunohistochemistry in fatal morphine intoxications. *Int. J. Legal Med.,* **2021**, *135*(6), 2315-2322. http://dx.doi.org/10.1007/s00414-021-02699-5 PMID: 34553260

[218] Kays, J.S.; Yamamoto, B.K. Evaluation of microglia/macrophage cells from rat striatum and prefrontal cortex reveals differential expression of inflammatory-related mRNA after methamphetamine. *Brain Sci.,* **2019**, *9*(12), 340. http://dx.doi.org/10.3390/brainsci9120340 PMID: 31775383

[219] Zhang, X.; Wang, Y.; Wang, H.; Li, H.; Zhang, T.; Peng, Y.; Wang, X. Exploring methamphetamine nonenantioselectively targeting toll-like receptor 4/myeloid differentiation protein 2 by *in silico* simulations and wet-lab techniques. *J. Chem. Inf. Model.,* **2020**, *60*(3), 1607-1613. http://dx.doi.org/10.1021/acs.jcim.9b01040 PMID: 31935095

[220] Wires, E.S.; Alvarez, D.; Dobrowolski, C.; Wang, Y.; Morales, M.; Karn, J.; Harvey, B.K. Methamphetamine activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and induces human immunodeficiency virus (HIV) transcription in human microglial cells. *J. Neurovirol.,* **2012**, *18*(5), 400-410. http://dx.doi.org/10.1007/s13365-012-0103-4 PMID: 22618514

[221] Xie, X.L.; Zhou, W.T.; Zhang, K.K.; Chen, L.J.; Wang, Q. METH-Induced Neurotoxicity Is Alleviated by Lactulose Pretreatment Through Suppressing Oxidative Stress and Neuroinflammation in Rat Striatum. *Front. Neurosci.,* **2018**, *12*, 802. http://dx.doi.org/10.3389/fnins.2018.00802 PMID: 30450033

[222] Du, S.H.; Qiao, D.F.; Chen, C.X.; Chen, S.; Liu, C.; Lin, Z.; Wang, H.; Xie, W.B. Toll-like receptor 4 mediates methamphetamine-induced neuroinflammation through caspase-11 signaling pathway in astrocytes. *Front. Mol. Neurosci.,* **2017**, *10*, 409. http://dx.doi.org/10.3389/fnmol.2017.00409 PMID: 29311802

[223] Lwin, T.; Yang, J.L.; Ngampramuan, S.; Viwatpinyo, K.; Chancharoen, P.; Veschsanit, N.; Pinyomahakul, J.; Govitrapong, P.; Mukda, S. Melatonin ameliorates methamphetamine-induced cognitive impairments by inhibiting neuroinflammation *via* suppression of the TLR4/MyD88/NFκB signaling pathway in the mouse hippocampus. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2021**, *111*, 110109. http://dx.doi.org/10.1016/j.pnpbp.2020.110109 PMID: 32941923

[224] Snider, S.E.; Hendrick, E.S.; Beardsley, P.M. Glial cell modulators attenuate methamphetamine self-administration in therat. *Eur. J. Pharmacol.,* **2013**, *701*(1-3), 124-130. http://dx.doi.org/10.1016/j.ejphar.2013.01.016 PMID: 23375937

[225] Snider, S.E.; Vunck, S.A.; van den Oord, E.J.C.G.; Adkins, D.E.; McClay, J.L.; Beardsley, P.M. The glial cell modulators, ibudilast and its amino analog, AV1013, attenuate methamphetamine locomotor activity and its sensitization in mice. *Eur. J. Pharmacol.,* **2012**, *679*(1-3), 75-80. http://dx.doi.org/10.1016/j.ejphar.2012.01.013 PMID: 22306241

[226] Drouin-Ouellet, J.; Brownell, A.L.; Saint-Pierre, M.; Fasano, C.; Emond, V.; Trudeau, L.E.; Lévesque, D.; Cicchetti, F. Neuroinflammation is associated with changes in glial mGluR5 expression and the development of neonatal excitotoxic lesions. *Glia,* **2011**, *59*(2), 188-199. http://dx.doi.org/10.1002/glia.21086 PMID: 21125661

[227] Giovanoli, S.; Engler, H.; Engler, A.; Richetto, J.; Feldon, J.; Riva, M.A.; Schedlowski, M.; Meyer, U. Preventive effects of minocycline in a neurodevelopmental two-hit model with relevance to schizophrenia. *Transl. Psychiatry,* **2016**, *6*(4), e772. http://dx.doi.org/10.1038/tp.2016.38 PMID: 27045842

[228] Worley, M.J.; Heinzerling, K.G.; Roche, D.J.O.; Shoptaw, S.; Shoptaw, S. Ibudilast attenuates subjective effects of methamphetamine in a placebo-controlled inpatient study. *Drug Alcohol Depend.,* **2016**, *162*, 245-250. http://dx.doi.org/10.1016/j.drugalcdep.2016.02.036 PMID: 26993372

[229] Li, M.J.; Briones, M.S.; Heinzerling, K.G.; Kalmin, M.M.; Shoptaw, S.J. Ibudilast attenuates peripheral inflammatory effects of methamphetamine in patients with methamphetamine use disorder. *Drug Alcohol Depend.,* **2020**, *206*, 107776. http://dx.doi.org/10.1016/j.drugalcdep.2019.107776 PMID: 31812878

[230] Tanibuchi, Y.; Shimagami, M.; Fukami, G.; Sekine, Y.; Iyo, M.; Hashimoto, K. A case of methamphetamine use disorder treated with the antibiotic drug minocycline. *Gen. Hosp. Psychiatry,* **2010**, *32*(5), 559.e1-559.e3. http://dx.doi.org/10.1016/j.genhosppsych.2009.12.005 PMID: 20851278

[231] Heinzerling, K.G.; Briones, M.; Thames, A.D.; Hinkin, C.H.; Zhu, T.; Wu, Y.N.; Shoptaw, S.J. Randomized, placebo-controlled trial

of targeting neuroinflammation with ibudilast to treat methamphetamine use disorder. *J. Neuroimmune Pharmacol.,* **2020**, *15*(2), 238-248.
http://dx.doi.org/10.1007/s11481-019-09883-w PMID: 31820289

[232] Burns, A.; Ciborowski, P. Acute exposure to methamphetamine alters TLR9-mediated cytokine expression in human macrophage. *Immunobiology,* **2016**, *221*(2), 199-207.
http://dx.doi.org/10.1016/j.imbio.2015.09.006 PMID: 26387832

[233] Du, L.; Shen, K.; Bai, Y.; Chao, J.; Hu, G.; Zhang, Y.; Yao, H. Involvement of NLRP3 inflammasome in methamphetamine-induced microglial activation through miR-143/PUMA axis. *Toxicol. Lett.,* **2019**, *301*, 53-63.
http://dx.doi.org/10.1016/j.toxlet.2018.10.020 PMID: 30394308

[234] Fernandes, N.C.; Sriram, U.; Gofman, L.; Cenna, J.M.; Ramirez, S.H.; Potula, R. Methamphetamine alters microglial immune function through P2X7R signaling. *J. Neuroinflammation,* **2016**, *13*(1), 91.
http://dx.doi.org/10.1186/s12974-016-0553-3 PMID: 27117066

[235] Bhattacharya, A.; Wang, Q.; Ao, H.; Shoblock, J.R.; Lord, B.; Aluisio, L.; Fraser, I.; Nepomuceno, D.; Neff, R.A.; Welty, N.; Lovenberg, T.W.; Bonaventure, P.; Wickenden, A.D.; Letavic, M.A. Pharmacological characterization of a novel centrally permeable P2X7 receptor antagonist: JNJ-47965567. *Br. J. Pharmacol.,* **2013**, *170*(3), 624-640.
http://dx.doi.org/10.1111/bph.12314 PMID: 23889535

[236] Tristão, F.S.M.; Lazzarini, M.; Martin, S.; Amar, M.; Stühmer, W.; Kirchhoff, F.; Gomes, L.A.C.; Lanfumey, L.; Prediger, R.D.; Sepulveda, J.E.; Del-Bel, E.A.; Raisman-Vozari, R. CX3CR1 disruption differentially influences dopaminergic neuron degeneration in parkinsonian mice depending on the neurotoxin and route of administration. *Neurotox. Res.,* **2016**, *29*(3), 364-380.
http://dx.doi.org/10.1007/s12640-015-9557-5 PMID: 26403659

[237] Wisor, J.P.; Schmidt, M.A.; Clegern, W.C. Cerebral microglia mediate sleep/wake and neuroinflammatory effects of methamphetamine. *Brain Behav. Immun.,* **2011**, *25*(4), 767-776.
http://dx.doi.org/10.1016/j.bbi.2011.02.002 PMID: 21333736

[238] Bravo, J.; Ribeiro, I.; Terceiro, A.F.; Andrade, E.B.; Portugal, C.C.; Lopes, I.M.; Azevedo, M.M.; Sousa, M.; Lopes, C.D.F.; Lobo, A.C.; Canedo, T.; Relvas, J.B.; Summavielle, T. Neuron-microglia contact-dependent mechanisms attenuate methamphetamine-induced microglia reactivity and enhance neuronal plasticity. *Cells,* **2022**, *11*(3), 355.
http://dx.doi.org/10.3390/cells11030355 PMID: 35159165

[239] Ladenheim, B.; Krasnova, I.N.; Deng, X.; Oyler, J.M.; Polettini, A.; Moran, T.H.; Huestis, M.A.; Cadet, J.L. Methamphetamine-induced neurotoxicity is attenuated in transgenic mice with a null mutation for interleukin-6. *Mol. Pharmacol.,* **2000**, *58*(6), 1247-1256.
http://dx.doi.org/10.1124/mol.58.6.1247 PMID: 11093760

[240] Zalcman, S.; Savina, I.; Wise, R.A. Interleukin-6 increases sensitivity to the locomotor-stimulating effects of amphetamine in rats. *Brain Res.,* **1999**, *847*(2), 276-283.
http://dx.doi.org/10.1016/S0006-8993(99)02063-6 PMID: 10575098

[241] Kohno, M.; Loftis, J.M.; Huckans, M.; Dennis, L.E.; McCready, H.; Hoffman, W.F. The relationship between interleukin-6 and functional connectivity in methamphetamine users. *Neurosci. Lett.,* **2018**, *677*, 49-54.
http://dx.doi.org/10.1016/j.neulet.2018.04.037 PMID: 29689344

[242] Lin, K.Y.; Cherng, C.G.; Yang, F.R.; Lin, L.C.; Lu, R.B.; Yu, L. Memantine abolishes the formation of cocaine-induced conditioned place preference possibly *via* its IL-6-modulating effect in medial prefrontal cortex. *Behav. Brain Res.,* **2011**, *220*(1), 126-131.
http://dx.doi.org/10.1016/j.bbr.2011.01.031 PMID: 21277908

[243] Nakajima, A.; Yamada, K.; Nagai, T.; Uchiyama, T.; Miyamoto, Y.; Mamiya, T.; He, J.; Nitta, A.; Mizuno, M.; Tran, M.H.; Seto, A.; Yoshimura, M.; Kitaichi, K.; Hasegawa, T.; Saito, K.; Yamada, Y.; Seishima, M.; Sekikawa, K.; Kim, H.C.; Nabeshima, T. Role of tumor necrosis factor-alpha in methamphetamine-induced drug dependence and neurotoxicity. *J. Neurosci.,* **2004**, *24*(9), 2212-2225.
http://dx.doi.org/10.1523/JNEUROSCI.4847-03.2004 PMID: 14999072

[244] Liśkiewicz, A.; Przybyła, M.; Park, M.; Liśkiewicz, D.; Nowacka-Chmielewska, M.; Małecki, A.; Barski, J.; Lewin-Kowalik, J.; Toborek, M. Methamphetamine-associated cognitive decline is attenuated by neutralizing IL-1 signaling. *Brain Behav. Immun.,* **2019**, *80*, 247-254.
http://dx.doi.org/10.1016/j.bbi.2019.03.016 PMID: 30885840

[245] Schmidt, E.D.; Tilders, F.J.H.; Binnekade, R.; Schoffelmeer, A.N.M.; De Vries, T.J. Stressor- or drug-induced sensitization of the corticosterone response is not critically involved in the long-term expression of behavioural sensitization to amphetamine. *Neuroscience,* **1999**, *92*(1), 343-352.
http://dx.doi.org/10.1016/S0306-4522(98)00725-8 PMID: 10392855

[246] Coelho-Santos, V.; Gonçalves, J.; Fontes-Ribeiro, C.; Silva, A.P. Prevention of methamphetamine-induced microglial cell death by TNF-α and IL-6 through activation of the JAK-STAT pathway. *J. Neuroinflammation,* **2012**, *9*(1), 565.
http://dx.doi.org/10.1186/1742-2094-9-103 PMID: 22642790

[247] Mao, J.T.; Zhu, L.X.; Sharma, S.; Chen, K.; Huang, M.; Santiago, S.J.; Gulsurd, J.; Tashkin, D.P.; Dubinett, S.M. Cocaine inhibits human endothelial cell IL-8 production: The role of transforming growth factor-β. *Cell. Immunol.,* **1997**, *181*(1), 38-43.
http://dx.doi.org/10.1006/cimm.1997.1185 PMID: 9344494

[248] Gancarz-Kausch, A.M.; Schroeder, G.L.; Panganiban, C.; Adank, D.; Humby, M.S.; Kausch, M.A.; Clark, S.D.; Dietz, D.M. Transforming growth factor beta receptor 1 is increased following abstinence from cocaine self-administration, but not cocaine sensitization. *PLoS One,* **2013**, *8*(12), e83834.
http://dx.doi.org/10.1371/journal.pone.0083834 PMID: 24386286

[249] Werner, C.T.; Mitra, S.; Auerbach, B.D.; Wang, Z.J.; Martin, J.A.; Stewart, A.F.; Gobira, P.H.; Iida, M.; An, C.; Cobb, M.M.; Caccamise, A.; Salvi, R.J.; Neve, R.L.; Gancarz, A.M.; Dietz, D.M. Neuroadaptations in the dorsal hippocampus underlie cocaine seeking during prolonged abstinence. *Proc. Natl. Acad. Sci. USA,* **2020**, *117*(42), 26460-26469.
http://dx.doi.org/10.1073/pnas.2006133117 PMID: 33020308

[250] Niu, F.; Liao, K.; Hu, G.; Sil, S.; Callen, S.; Guo, M.; Yang, L.; Buch, S. Cocaine-induced release of CXCL10 from pericytes regulates monocyte transmigration into the CNS. *J. Cell Biol.,* **2019**, *218*(2), 700-721.
http://dx.doi.org/10.1083/jcb.201712011 PMID: 30626719

[251] Sil, S.; Niu, F.; Tom, E.; Liao, K.; Periyasamy, P.; Buch, S. Cocaine mediated neuroinflammation: Role of dysregulated autophagy inpericytes. *Mol. Neurobiol.,* **2019**, *56*(5), 3576-3590.
http://dx.doi.org/10.1007/s12035-018-1325-0 PMID: 30151726

[252] Shen, S.; Zhao, J.; Dai, Y.; Chen, F.; Zhang, Z.; Yu, J.; Wang, K. Methamphetamine-induced alterations in intestinal mucosal barrier function occur *via* the microRNA-181c/ TNF-α/tight junction axis. *Toxicol. Lett.,* **2020**, *321*, 73-82.
http://dx.doi.org/10.1016/j.toxlet.2019.12.020 PMID: 31862507

[253] Parikh, N.U.; Aalinkeel, R.; Reynolds, J.L.; Nair, B.B.; Sykes, D.E.; Mammen, M.J.; Schwartz, S.A.; Mahajan, S.D. Galectin-1 suppresses methamphetamine induced neuroinflammation in human brain microvascular endothelial cells: Neuroprotective role in maintaining blood brain barrier integrity. *Brain Res.,* **2015**, *1624*, 175-187.
http://dx.doi.org/10.1016/j.brainres.2015.07.033 PMID: 26236024

[254] Coelho-Santos, V.; Leitão, R.A.; Cardoso, F.L.; Palmela, I.; Rito, M.; Barbosa, M.; Brito, M.A.; Fontes-Ribeiro, C.A.; Silva, A.P. The TNF-α/NF-κB signaling pathway has a key role in methamphetamine-induced blood-brain barrier dysfunction. *J. Cereb. Blood Flow Metab.,* **2015**, *35*(8), 1260-1271.
http://dx.doi.org/10.1038/jcbfm.2015.59 PMID: 25899299

[255] DiCaro, D.; Lee, H.H.; Belisario, C.; Ramos, R.L.; Martinez, L.R. Combination of acute intravenous methamphetamine injection and LPS challenge facilitate leukocyte infiltration into the central nervous system of C57BL/6 mice. *Int. Immunopharmacol.,* **2019**, *75*, 105751.
http://dx.doi.org/10.1016/j.intimp.2019.105751 PMID: 31319359

[256] Levandowski, M.L.; Hess, A.R.B.; Grassi-Oliveira, R.; de Almeida, R.M.M. Plasma interleukin-6 and executive function in crack cocaine-dependent women. *Neurosci. Lett.,* **2016**, *628*, 85-90.
http://dx.doi.org/10.1016/j.neulet.2016.06.023 PMID: 27297769

[257] Feng, L.; He, W.; Lin, S.; Ruan, Y.; Yuan, C.; Qiu, H.; Ren, W.; He, J. The association between interleukin-8 levels and the devel-

opment of withdrawal symptoms during methamphetamine abstinence. *Hum. Psychopharmacol.,* **2020**, *35*(4), e2736. http://dx.doi.org/10.1002/hup.2736 PMID: 32352600

[258] Araos, P.; Pedraz, M.; Serrano, A.; Lucena, M.; Barrios, V.; García-Marchena, N.; Campos-Cloute, R.; Ruiz, J.J.; Romero, P.; Suárez, J.; Baixeras, E.; de la Torre, R.; Montesinos, J.; Guerri, C.; Rodríguez-Arias, M.; Miñarro, J.; Martínez-Riera, R.; Torrens, M.; Chowen, J.A.; Argente, J.; Mason, B.J.; Pavón, F.J.; Rodríguez de Fonseca, F. Plasma profile of pro-inflammatory cytokines and chemokines in cocaine users under outpatient treatment: influence of cocaine symptom severity and psychiatric co-morbidity. *Addict. Biol.,* **2015**, *20*(4), 756-772. http://dx.doi.org/10.1111/adb.12156 PMID: 24854157

[259] Montesinos, J.; Castilla-Ortega, E.; Sánchez-Marín, L.; Montagud-Romero, S.; Araos, P.; Pedraz, M.; Porras-Perales, Ó.; García-Marchena, N.; Serrano, A.; Suárez, J.; Baixeras, E.; Rodríguez-Arias, M.; Santín, L.J.; Miñarro, J.; Guerri, C.; Rodríguez de Fonseca, F.; Pavón, F.J. Cocaine-induced changes in CX_3CL1 and inflammatory signaling pathways in the hippocampus: Association with IL1β. *Neuropharmacology,* **2020**, *162*, 107840. http://dx.doi.org/10.1016/j.neuropharm.2019.107840 PMID: 31704270

[260] Saika, F.; Matsuzaki, S.; Kobayashi, D.; Kiguchi, N.; Kishioka, S. Chemokine CXCL1 is responsible for cocaine-induced reward in mice. *Neuropsychopharmacol. Rep.,* **2018**, *38*(3), 145-148. http://dx.doi.org/10.1002/npr2.12018 PMID: 30175527

[261] Trocello, J.M.; Rostene, W.; Melik-Parsadaniantz, S.; Godefroy, D.; Roze, E.; Kitabgi, P.; Kuziel, W.A.; Chalon, S.; Caboche, J.; Apartis, E. Implication of CCR_2 chemokine receptor in cocaine-induced sensitization. *J. Mol. Neurosci.,* **2011**, *44*(3), 147-151. http://dx.doi.org/10.1007/s12031-011-9508-4 PMID: 21424761

[262] Saika, F.; Kiguchi, N.; Wakida, N.; Kobayashi, D.; Fukazawa, Y.; Matsuzaki, S.; Kishioka, S. Upregulation of CCL7 and CCL2 in reward system mediated through dopamine D1 receptor signaling underlies methamphetamine-induced place preference in mice. *Neurosci. Lett.,* **2018**, *665*, 33-37. http://dx.doi.org/10.1016/j.neulet.2017.11.042 PMID: 29174638

[263] Wakida, N.; Kiguchi, N.; Saika, F.; Nishiue, H.; Kobayashi, Y.; Kishioka, S. CC-chemokine ligand 2 facilitates conditioned place preference to methamphetamine through the activation of dopamine systems. *J. Pharmacol. Sci.,* **2014**, *125*(1), 68-73. http://dx.doi.org/10.1254/jphs.14032FP PMID: 24748435

[264] Kelly, K.A.; Miller, D.B.; Bowyer, J.F.; O'Callaghan, J.P. Chronic exposure to corticosterone enhances the neuroinflammatory and neurotoxic responses to methamphetamine. *J. Neurochem.,* **2012**, *122*(5), 995-1009. http://dx.doi.org/10.1111/j.1471-4159.2012.07864.x PMID: 22776046

[265] Li, J; Deng, G; Wang, H; Yang, M; Yang, R; Li, X Interleukin-1β pre-treated bone marrow stromal cells alleviate neuropathic pain through CCL7-mediated inhibition of microglial activation in the spinal cord. *Sci Reports,* **2017**, *7*(1), 1-15. http://dx.doi.org/10.1038/srep42260

[266] Trecki, J.; Unterwald, E.M. Modulation of cocaine-induced activity by intracerebral administration of CXCL12. *Neuroscience,* **2009**, *161*(1), 13-22. http://dx.doi.org/10.1016/j.neuroscience.2009.03.027 PMID: 19303923

[267] Westwell-Roper, C.; Stewart, S.E. Commentary: Neurobiology and therapeutic potential of cyclooxygenase-2 (COX-2) inhibitors for inflammation in neuropsychiatric disorders. *Front. Psychiatry,* **2020**, *11*, 264. http://dx.doi.org/10.3389/fpsyt.2020.00264 PMID: 32425818

[268] Avila, J.A.; Zanca, R.M.; Shor, D.; Paleologos, N.; Alliger, A.A.; Figueiredo-Pereira, M.E.; Serrano, P.A. Chronic voluntary oral methamphetamine induces deficits in spatial learning and hippocampal protein kinase Mzeta with enhanced astrogliosis and cyclooxygenase-2 levels. *Heliyon,* **2018**, *4*(2), e00509. http://dx.doi.org/10.1016/j.heliyon.2018.e00509 PMID: 29560440

[269] Zhang, X.; Dong, F.; Mayer, G.E.; Bruch, D.C.; Ren, J.; Culver, B. Selective inhibition of cyclooxygenase-2 exacerbates methamphetamine-induced dopamine depletion in the striatum in rats. *Neuroscience,* **2007**, *150*(4), 950-958. http://dx.doi.org/10.1016/j.neuroscience.2007.09.059 PMID: 17988800

[270] Phan, D.H.; Shin, E.J.; Jeong, J.H.; Tran, H.Q.; Sharma, N.; Nguyen, B.T.; Jung, T.W.; Nah, S.Y.; Saito, K.; Nabeshima, T.; Kim, H.C. Lithium attenuates d-amphetamine-induced hyperlocomotor activity in mice *via* inhibition of interaction between cyclooxygenase-2 and indoleamine-2,3-dioxygenase. *Clin. Exp. Pharmacol. Physiol.,* **2020**, *47*(5), 790-797. http://dx.doi.org/10.1111/1440-1681.13243 PMID: 31883280

[271] Toledano, A.; Álvarez, M.I.; Caballero, I.; Carmona, P.; De Miguel, E. Immunohistochemical increase in cyclooxygenase-2 without apoptosis in different brain areas of subchronic nicotine- and d-amphetamine-treated rats. *J. Neural Transm. (Vienna),* **2008**, *115*(8), 1093-1108. http://dx.doi.org/10.1007/s00702-008-0040-9 PMID: 18351285

[272] Reid, M.S.; Ho, L.B.; Hsu, K.; Fox, L.; Tolliver, B.K.; Adams, J.U.; Franco, A.; Berger, S.P. Evidence for the involvement of cyclooxygenase activity in the development of cocaine sensitization. *Pharmacol. Biochem. Behav.,* **2002**, *71*(1-2), 37-54. http://dx.doi.org/10.1016/S0091-3057(01)00614-1 PMID: 11812506

[273] Ross, B.M.; Brooks, R.J.; Lee, M.; Kalasinsky, K.S.; Vorce, S.P.; Seeman, M.; Fletcher, P.J.; Turenne, S.D. Cyclooxygenase inhibitor modulation of dopamine-related behaviours. *Eur. J. Pharmacol.,* **2002**, *450*(2), 141-151. http://dx.doi.org/10.1016/S0014-2999(02)02104-0 PMID: 12206852

[274] Anggadiredja, K.; Nakamichi, M.; Hiranita, T.; Tanaka, H.; Shoyama, Y.; Watanabe, S.; Yamamoto, T. Endocannabinoid system modulates relapse to methamphetamine seeking: possible mediation by the arachidonic acid cascade. *Neuropsychopharmacology,* **2004**, *29*(8), 1470-1478. http://dx.doi.org/10.1038/sj.npp.1300454 PMID: 15085091

[275] Reid, M.S.; Angrist, B.; Baker, S.; Woo, C.; Schwartz, M.; Montgomery, A.; Majewska, D.; Robinson, J.; Rotrosen, J. A placebo-controlled screening trial of celecoxib for the treatment of cocaine dependence. *Addiction,* **2005**, *100*(Suppl. 1), 32-42. http://dx.doi.org/10.1111/j.1360-0443.2005.00989.x PMID: 15730348

[276] Eichhorn, E.J.; Demian, S.E.; Alvarez, L.G.; Willard, J.E.; Molina, S.; Bartula, L.L.; Dale Prince, M.; Inman, L.R.; Grayburn, P.A.; Myers, S.I. Cocaine-induced alterations in prostaglandin production in rabbit aorta. *J. Am. Coll. Cardiol.,* **1992**, *19*(3), 696-703. http://dx.doi.org/10.1016/S0735-1097(10)80295-5 PMID: 1538030

[277] Cejtin, H.E.; Parsons, M.T.; Wilson, L., Jr Cocaine use and its effect on umbilical artery prostacyclin production. *Prostaglandins,* **1990**, *40*(3), 249-257. http://dx.doi.org/10.1016/0090-6980(90)90013-L PMID: 2247615

[278] Cook, J.L.; Randalla, C.L. Cocaine does not affect prostacyclin, thromboxane or prostaglandin E production in human umbilical veins. *Drug Alcohol Depend.,* **1996**, *41*(2), 113-118. http://dx.doi.org/10.1016/0376-8716(96)01229-X PMID: 8809499

[279] Schwarz, R.D.; Uretsky, N.J.; Bianchine, J.R. Prostaglandin inhibition of amphetamine-induced circling in mice. *Psychopharmacology (Berl.),* **1982**, *78*(4), 317-321. http://dx.doi.org/10.1007/BF00433733 PMID: 6818591

[280] Poddubiuk, ZM; Kleinrok, Z A comparison of the central actions of prostaglandins A1, E1, E2, F1α, and F2α in the rat. *Psychopharmacol,* **1976**, *50*(1), 95-102. http://dx.doi.org/10.1007/BF00634162

[281] Bloss, J.L.; Singer, G.H. Neuropharmacological and behavioral evaluation of prostaglandin E2 and 11-thiol-11-desoxy prostaglandin E2 in the mouse and rat. *Psychopharmacology (Berl.),* **1978**, *57*(3), 295-302. http://dx.doi.org/10.1007/BF00426754 PMID: 97712

[282] Kitaoka, S.; Furuyashiki, T.; Nishi, A.; Shuto, T.; Koyasu, S.; Matsuoka, T.; Miyasaka, M.; Greengard, P.; Narumiya, S. Prostaglandin E2 acts on EP1 receptor and amplifies both dopamine D1 and D2 receptor signaling in the striatum. *J. Neurosci.,* **2007**, *27*(47), 12900-12907. http://dx.doi.org/10.1523/JNEUROSCI.3257-07.2007 PMID: 18032663

[283] Chang, S.L.; Bersig, J.; Felix, B.; Fiala, M.; House, S.D. Chronic cocaine alters hemodynamics and leukocyte-endothelial interactions in rat mesenteric venules. *Life Sci.,* **2000**, *66*(24), 2357-2369. http://dx.doi.org/10.1016/S0024-3205(00)00566-X PMID: 10864098

[284] Cearley, C.N.; Blindheim, K.; Sorg, B.A.; Krueger, J.M.; Churchill, L. Acute cocaine increases interleukin-1β mRNA and immunoreactive cells in the cortex and nucleus accumbens. *Neurochem. Res.,* **2011**, *36*(4), 686-692. http://dx.doi.org/10.1007/s11064-011-0410-9 PMID: 21399909

[285] Narvaez, J.C.M.; Magalhães, P.V.; Fries, G.R.; Colpo, G.D.; Czepielewski, L.S.; Vianna, P.; Chies, J.A.B.; Rosa, A.R.; Von Diemen, L.; Vieta, E.; Pechansky, F.; Kapczinski, F. Peripheral toxicity in crack cocaine use disorders. *Neurosci. Lett.,* **2013**, *544*, 80-84. http://dx.doi.org/10.1016/j.neulet.2013.03.045 PMID: 23597759

[286] Roodsari, SK; Cheng, Y; Reed, KM; Wellman, LL; Sanford, LD; Kim, W-K Sleep disturbance alters cocaine-induced locomotor activity: Involvement of striatal neuroimmune and dopamine signaling. *Biomed,* **2022**, *10*, 1161. http://dx.doi.org/10.3390/biomedicines10051161

[287] Maza-Quiroga, R.; García-Marchena, N.; Romero-Sanchiz, P.; Barrios, V.; Pedraz, M.; Serrano, A.; Nogueira-Arjona, R.; Ruiz, J.J.; Soria, M.; Campos, R.; Chowen, J.A.; Argente, J.; Torrens, M.; López-Gallardo, M.; Marco, E.M.; Rodríguez de Fonseca, F.; Pavón, F.J.; Araos, P. Evaluation of plasma cytokines in patients with cocaine use disorders in abstinence identifies transforming growth factor alpha (TGFα) as a potential biomarker of consumption and dual diagnosis. *PeerJ,* **2017**, *5*, e3926. http://dx.doi.org/10.7717/peerj.3926 PMID: 29038767

[288] Gupta, K.; Sharma, R.; Singh, V.; Masoomi, R.; Dileepan, K.N.; He, J.; Smith, D.D.; Dawn, B.; Grasing, K. Intravenous cocaine results in an acute decrease in levels of biomarkers of vascular Inflammation in humans. *Cardiovasc. Toxicol.,* **2018**, *18*(4), 295-303. http://dx.doi.org/10.1007/s12012-017-9440-0 PMID: 29372505

[289] Moreira, F.P.; Medeiros, J.R.C.; Lhullier, A.C.; Souza, L.D.M.; Jansen, K.; Portela, L.V.; Lara, D.R.; Silva, R.A.; Wiener, C.D.; Oses, J.P. Cocaine abuse and effects in the serum levels of cytokines IL-6 and IL-10. *Drug Alcohol Depend.,* **2016**, *158*, 181-185. http://dx.doi.org/10.1016/j.drugalcdep.2015.11.024 PMID: 26679059

[290] Rofael, H.Z.; Turkall, R.M.; Abdel-Rahman, M.S. Effect of ketamine on cocaine-induced immunotoxicity in rats. *Int. J. Toxicol.,* **2003**, *22*(5), 343-358. http://dx.doi.org/10.1177/109158180302200503 PMID: 14555406

[291] Gan, X.; Zhang, L.; Newton, T.; Chang, S.L.; Ling, W.; Kermani, V.; Berger, O.; Graves, M.C.; Fiala, M. Cocaine infusion increases interferon-gamma and decreases interleukin-10 in cocaine-dependent subjects. *Clin. Immunol. Immunopathol.,* **1998**, *89*(2), 181-190. http://dx.doi.org/10.1006/clin.1998.4607 PMID: 9787120

[292] Fox, H.C.; D'Sa, C.; Kimmerling, A.; Siedlarz, K.M.; Tuit, K.L.; Stowe, R.; Sinha, R. Immune system inflammation in cocaine dependent individuals: implications for medications development. *Hum. Psychopharmacol.,* **2012**, *27*(2), 156-166. http://dx.doi.org/10.1002/hup.1251 PMID: 22389080

[293] Gan, X.; Zhang, L.; Berger, O.; Stins, M.F.; Way, D.; Taub, D.D.; Chang, S.L.; Kim, K.S.; House, S.D.; Weinand, M.; Witte, M.; Graves, M.C.; Fiala, M. Cocaine enhances brain endothelial adhesion molecules and leukocyte migration. *Clin. Immunol.,* **1999**, *91*(1), 68-76. http://dx.doi.org/10.1006/clim.1998.4683 PMID: 10219256

[294] Kuo, S.C.; Yeh, Y.W.; Chen, C.Y.; Huang, C.C.; Ho, P.S.; Liang, C.S.; Lin, C.L.; Yeh, T.C.; Tsou, C.C.; Yang, B.Z.; Lu, R.B.; Huang, S.Y. Differential effect of the DRD3 genotype on inflammatory cytokine responses during abstinence in amphetamine-dependent women. *Psychoneuroendocrinology,* **2018**, *97*, 37-46. http://dx.doi.org/10.1016/j.psyneuen.2018.06.023 PMID: 30005280

[295] House, R.V.; Thomas, P.T.; Bhargava, H.N. Comparison of immune functional parameters following *in vitro* exposure to natural and synthetic amphetamines. *Immunopharmacol. Immunotoxicol.,* **1994**, *16*(1), 1-21. http://dx.doi.org/10.3109/08923979409029897 PMID: 8169319

[296] Valvassori, S.S.; Dal-Pont, G.C.; Tonin, P.T.; Varela, R.B.; Ferreira, C.L.; Gava, F.F.; Andersen, M.L.; Soares, J.C.; Quevedo, J. Coadministration of lithium and celecoxib attenuates the behavioral alterations and inflammatory processes induced by amphetamine in an animal model of mania. *Pharmacol. Biochem. Behav.,* **2019**, *183*, 56-63. http://dx.doi.org/10.1016/j.pbb.2019.05.009 PMID: 31158395

[297] Valvassori, S.S.; Resende, W.R.; Varela, R.B.; Arent, C.O.; Gava, F.F.; Peterle, B.R.; Dal-Pont, G.C.; Carvalho, A.F.; Andersen, M.L.; Quevedo, J. The effects of histone deacetylase inhibition on the levels of cerebral cytokines in an animal model of mania induced by dextroamphetamine. *Mol. Neurobiol.,* **2018**, *55*(2), 1430-1439. http://dx.doi.org/10.1007/s12035-017-0384-y PMID: 28168425

[298] Valvassori, S.S.; Tonin, P.T.; Varela, R.B.; Carvalho, A.F.; Mariot, E.; Amboni, R.T.; Bianchini, G.; Andersen, M.L.; Quevedo, J. Lithium modulates the production of peripheral and cerebral cytokines in an animal model of mania induced by dextroamphetamine. *Bipolar Disord.,* **2015**, *17*(5), 507-517. http://dx.doi.org/10.1111/bdi.12299 PMID: 25929806

[299] Liu, X.; Silverstein, P.S.; Singh, V.; Shah, A.; Qureshi, N.; Kumar, A. Methamphetamine increases LPS-mediated expression of IL-8, TNF-α and IL-1β in human macrophages through common signaling pathways. *PLoS One,* **2012**, *7*(3), e33822. http://dx.doi.org/10.1371/journal.pone.0033822 PMID: 22479453

[300] Gebhard, C.; Breitenstein, A.; Akhmedov, A.; Gebhard, C.E.; Camici, G.G.; Lüscher, T.F.; Tanner, F.C. Amphetamines induce tissue factor and impair tissue factor pathway inhibitor: role of dopamine receptor type 4. *Eur. Heart J.,* **2010**, *31*(14), 1780-1791. http://dx.doi.org/10.1093/eurheartj/ehp598 PMID: 20118172

[301] Gonçalves, J.; Martins, T.; Ferreira, R.; Milhazes, N.; Borges, F.; Ribeiro, C.F.; Malva, J.O.; Macedo, T.R.; Silva, A.P. Methamphetamine-induced early increase of IL-6 and TNF-alpha mRNA expression in the mouse brain. *Ann. N. Y. Acad. Sci.,* **2008**, *1139*(1), 103-111. http://dx.doi.org/10.1196/annals.1432.043 PMID: 18991854

[302] Re, G.F.; Jia, J.; Xu, Y.; Zhang, Z.; Xie, Z.R.; Kong, D.; Lu, D.; Li, Y.; Peng, Q.Y.; Yu, J.; Kuang, Y.Q.; Wang, K.H. Dynamics and correlations in multiplex immune profiling reveal persistent immune inflammation in male drug users after withdrawal. *Int. Immunopharmacol.,* **2022**, *107*, 108696. http://dx.doi.org/10.1016/j.intimp.2022.108696 PMID: 35303506

[303] Seminerio, M.J.; Robson, M.J.; McCurdy, C.R.; Matsumoto, R.R. Sigma receptor antagonists attenuate acute methamphetamine-induced hyperthermia by a mechanism independent of IL-1β mRNA expression in the hypothalamus. *Eur. J. Pharmacol.,* **2012**, *691*(1-3), 103-109. http://dx.doi.org/10.1016/j.ejphar.2012.07.029 PMID: 22820108

[304] Yamaguchi, T.; Kuraishi, Y.; Minami, M.; Yabuuchi, K.; Satoh, M. Involvement of central β-adrenoceptors in the induction of hypothalamic interleukin-1β mRNA by methamphetamine. *Neurosci. Res.,* **1991**, *12*(3), 432-439. http://dx.doi.org/10.1016/0168-0102(91)90074-9 PMID: 1686311

[305] Yamaguchi, T.; Kuraishi, Y.; Minami, M.; Nakai, S.; Hirai, Y.; Satoh, M. Methamphetamine-induced expression of interleukin-1β mRNA in the rat hypothalamus. *Neurosci. Lett.,* **1991**, *128*(1), 90-92. http://dx.doi.org/10.1016/0304-3940(91)90766-M PMID: 1922954

[306] Park, J.H.; Seo, Y.H.; Jang, J.H.; Jeong, C.H.; Lee, S.; Park, B. Asiatic acid attenuates methamphetamine-induced neuroinflammation and neurotoxicity through blocking of NF-kB/STAT3/ERK and mitochondria-mediated apoptosis pathway. *J. Neuroinflammation,* **2017**, *14*(1), 240. http://dx.doi.org/10.1186/s12974-017-1009-0 PMID: 29228978

[307] Beirami, E.; Oryan, S.; Seyedhosseini Tamijani, S.M.; Ahmadiani, A.; Dargahi, L. Intranasal insulin treatment alleviates methamphetamine induced anxiety-like behavior and neuroinflammation. *Neurosci. Lett.,* **2017**, *660*, 122-129. http://dx.doi.org/10.1016/j.neulet.2017.09.026 PMID: 28917981

[308] Shah, A.; Silverstein, P.S.; Singh, D.P.; Kumar, A. Involvement of metabotropic glutamate receptor 5, AKT/PI3K Signaling and NF-κB pathway in methamphetamine-mediated increase in IL-6 and IL-8 expression in astrocytes. *J. Neuroinflammation,* **2012**, *9*(1), 52.

http://dx.doi.org/10.1186/1742-2094-9-52 PMID: 22420994

[309] Luo, Y.; He, H.; Ou, Y.; Zhou, Y.; Fan, N. Elevated serum levels of TNF-α, IL-6, and IL-18 in chronic methamphetamine users. *Hum. Psychopharmacol.,* **2022**, *37*(1), e2810. http://dx.doi.org/10.1002/hup.2810 PMID: 34432333

[310] Kobeissy, F.H.; Shakkour, Z.; Hayek, S.E.; Mohamed, W.; Gold, M.S.; Wang, K.K.W. Elevation of pro-inflammatory and anti-inflammatory cytokines in rat serum after acute methamphetamine treatment and traumatic brain injury. *J. Mol. Neurosci.,* **2022**, *72*(1), 158-168. http://dx.doi.org/10.1007/s12031-021-01886-8 PMID: 34542809

[311] Wongprayoon, P.; Govitrapong, P. Melatonin attenuates methamphetamine-induced neuroinflammation through the melatonin receptor in the SH-SY5Y cell line. *Neurotoxicology,* **2015**, *50*, 122-130. http://dx.doi.org/10.1016/j.neuro.2015.08.008 PMID: 26283214

[312] Lai, Y.T.; Tsai, Y.P.N.; Cherng, C.G.; Ke, J.J.; Ho, M.C.; Tsai, C.W.; Yu, L. Lipopolysaccharide mitagates methamphetamine-induced striatal dopamine depletion *via* modulating local TNF-α and dopamine transporter expression. *J. Neural Transm. (Vienna),* **2009**, *116*(4), 405-415. http://dx.doi.org/10.1007/s00702-009-0204-2 PMID: 19271121

[313] Lee, Y.W.; Hennig, B.; Yao, J.; Toborek, M. Methamphetamine induces AP-1 and NF-?B binding and transactivation in human brain endothelial cells. *J. Neurosci. Res.,* **2001**, *66*(4), 583-591. http://dx.doi.org/10.1002/jnr.1248 PMID: 11746378

[314] Johansson, E.M.; García-Gutiérrez, M.S.; Moscoso-Castro, M.; Manzanares, J.; Valverde, O. Reduced Contextual Discrimination following Alcohol Consumption or MDMA Administration in Mice. *PLoS One,* **2015**, *10*(11), e0142978. http://dx.doi.org/10.1371/journal.pone.0142978 PMID: 26566284

[315] Mayado, A.; Torres, E.; Gutierrez-Lopez, M.D.; Colado, M.I.; O'Shea, E. Increased interleukin-1β levels following low dose MDMA induces tolerance against the 5-HT neurotoxicity produced by challenge MDMA. *J. Neuroinflammation,* **2011**, *8*(1), 165. http://dx.doi.org/10.1186/1742-2094-8-165 PMID: 22114930

[316] Connor, T.J.; Kelly, J.P.; Leonard, B.E. An assessment of the acute effects of the serotonin releasers methylenedioxymethamphetamine, methylenedioxyamphetamine and fenfluramine on immunity in rats. *Immunopharmacology,* **2000**, *46*(3), 223-235. http://dx.doi.org/10.1016/S0162-3109(99)00180-0 PMID: 10741902

[317] House, R.V.; Thomas, P.T.; Bhargava, H.N. Selective modulation of immune function resulting from *in vitro* exposure to methylenedioxymethamphetamine (Ecstasy). *Toxicology,* **1995**, *96*(1), 59-69. http://dx.doi.org/10.1016/0300-483X(94)02955-T PMID: 7863512

[318] Pacifici, R.; Pichini, S.; Zuccaro, P.; Farré, M.; Segura, M.; Ortuño, J.; Di Carlo, S.; Bacosi, A.; Roset, P.N.; Segura, J.; de la Torre, R. Paroxetine inhibits acute effects of 3,4-methylenedioxymethamphetamine on the immune system in humans. *J. Pharmacol. Exp. Ther.,* **2004**, *309*(1), 285-292. http://dx.doi.org/10.1124/jpet.103.061374 PMID: 14722327

[319] Frau, L.; Costa, G.; Porceddu, P.F.; Khairnar, A.; Castelli, M.P.; Ennas, M.G.; Madeddu, C.; Wardas, J.; Morelli, M. Influence of caffeine on 3,4-methylenedioxymethamphetamine-induced dopaminergic neuron degeneration and neuroinflammation is age-dependent. *J. Neurochem.,* **2016**, *136*(1), 148-162. http://dx.doi.org/10.1111/jnc.13377 PMID: 26442661