Shi *et al. Journal of Neuroinflammation* (2025) 22:40
https://doi.org/10.1186/s12974-025-03372-z

Journal of Neuroinflammation

REVIEW Open Access

The interaction between central and peripheral immune systems in methamphetamine use disorder: current status and future directions

Sai Shi[1†], Yiwen Sun[1†], Guiying Zan[2] and Min Zhao[1,3,4,5*]

Abstract
Methamphetamine (METH) use disorder (MUD) is characterized by compulsive drug-seeking behavior and substantial neurotoxicity, posing a considerable burden on individuals and society. Traditionally perceived as a localized central nervous system disorder, recent preclinical and clinical studies have elucidated that MUD is a multifaceted disorder influenced by various biological systems, particularly the immune system. Emerging evidence suggests that both central and peripheral immune responses play a crucial role in the initiation and persistence of MUD. Conceptualizing it as a systemic immune process prompts significant inquiries regarding the mechanisms of communication between peripheral and central compartments. Also, whether this intercommunication could serve as diagnostic biomarkers or therapeutic targets. This review begins by offering an overview of mechanistic studies pertaining to the neuroimmune and peripheral immune systems. Finally, future directions are suggested through the integration of innovative technologies and multidimensional data to promote the translation of basic mechanistic research into clinical diagnostic and therapeutic interventions.

Keywords Methamphetamine, Immune system, Neuroinflammation, Substance use disorder

Introduction

MUD represents a critical public health concern, marked by compulsive drug-seeking behavior and significant neurotoxicity [1]. The neurobiological mechanisms underlying MUD are intricate and multifaceted, involving alterations in neural circuits and synaptic plasticity. While a substantial body of research has concentrated on the role of the central nervous system in MUD, emerging evidence indicates that the immune system also plays a pivotal role [2]. Chronic METH use induces systemic inflammation, characterized by elevated levels of inflammatory factors [3]. These interactions may contribute to the pathological motivation to seek drugs and the progression of substance use disorder (SUD). Consequently, immunomodulation of MUD represents a novel

†Sai Shi and Yiwen Sun contributed equally to this work.

*Correspondence:
Min Zhao
drminzhao@smhc.org.cn
[1]Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[2]CAS Key Laboratory of Receptor Research and State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, No. 555 Zuchongzhi Road, Shanghai 201203, China
[3]Shanghai Key Laboratory of Psychotic Disorders, Shanghai, China
[4]CAS Center for Excellence in Brain Science and Intelligence Technology (CEBSIT), Chinese Academy of Sciences, Shanghai, China
[5]Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 South Wan Ping Road, Shanghai 200030, China

and promising frontier with the potential to significantly enhance our understanding of the neurobiological mechanisms underlying SUD [4]. However, there is a notable gap concerning the contributions of both peripheral and central immune systems to MUD.

Recent studies have started to elucidate the substantial role that the central immune system plays in the development and maintenance of SUD [5, 6]. In the brain, resident immune cells, such as microglia and astrocytes, provide support and nutrients to neurons. These cells protect the central nervous system (CNS) from injury by upregulation of neuroimmune processes. However, glial overactivation can lead to severe neuronal damage which can further exacerbate neuroinflammation [7, 8]. For example, microglia often release pro-inflammatory cytokines (including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1beta (IL-1β)) or anti-inflammatory cytokines (including interleukin-4 (IL-4), interleukin-13 (IL-13), interleukin-10 (IL-10) and transforming growth factor-β (TGF-β)) [9]. METH induces the activation of microglia through the classical toll-like receptor 4(TLR4)– myeloid differentiation primary response 88 (MyD88) - nuclear factor kappa-B (NF-kB) signaling pathway [10]. The effects of METH on astrocytes may be direct and have been attributed to its binding to sigma-1 receptors [11]. This neuroinflammatory state induces neurotoxicity and alters neural functions involved in reward and motivation, thereby reinforcing addictive behaviors and increasing the risk of relapse. Notably, recent studies have found that METH promotes blood-brain barrier (BBB) damage by promoting the down-regulation of nuclear receptor related 1 protein (Nurr1) in astrocytes, a member of the nuclear receptor family, and by inducing inflammatory responses in both peripheral and central systems [12, 13]. This suggests a potential linkage between central and peripheral immunity.

Additionally, neuroimmune signals, such as cytokines and chemokines, are not confined exclusively to either the central or peripheral immune systems, as there is considerable overlap between the two [14]. The peripheral immune systems, encompassing the liver, spleen, gut, and lymph nodes, is comprised of the innate immune systems and adaptive immune systems. The innate immune system is composed of macrophages, dendritic cells, and natural killer (NK) cells, whereas the adaptive immune system comprises T cells and B cells, which also secrets cytokines and chemokines such as C-C motif chemokine ligand 2 (CCL2) [15]. The innate immune system performs several critical functions: it recruits immune cells to sites of inflammation via the production of cytokines and chemokines, activates the complement cascade to facilitate the clearance of dead cells, and initiates the adaptive immune response (including T cells and B cells) through a mechanism known as antigen presentation [16]. Previous studies have demonstrated that METH exposure modulates the function of immune cells, including processes such as phagocytosis, chemotaxis, and cytokine response, with notable increases in TNF-α, IL-6, and IL-1β [17, 18]. Chronic administration of METH results in a significant decrease in the activated T lymphocyte lineage, encompassing both CD4 + and CD8 + T cells [19]. Historically, research has predominantly focused on the isolated role of peripheral immunity in MUD. However, recent studies have demonstrated that drug-induced increases in leukocyte-endothelial adhesion are associated with elevated levels of inflammatory cytokines, which disrupt BBB homeostasis and permeability, thereby exacerbating neuroinflammation [20–22].

The exploration of the interactions between peripheral and central immunity in the context of MUD represents a novel area of research. This review aims to provide a concise overview of the alterations in these two systems in response to METH exposure. By clarifying the causal relationships between peripheral and central immune molecules in this process, we aim to facilitate the identification of biomarkers, the assessment of SUD severity, and the development of targeted immunotherapies.

Role of the central immune system in MUD

The impact of METH on the CNS is mediated through complex cellular and molecular pathways, which encompass the activation of resident immune cells and the subsequent release of inflammatory mediators [23]. An increasing body of evidence indicates that the activation of glia cells including microglia, astrocytes and oligodendrocytes is triggered in the CNS during the MUD (Fig. 1) [2, 11, 23]. Modulating the activity of glia cells influences animal behavior in response to METH, suggesting that central inflammatory responses play a pivotal role in the development and persistence of SUD [8].

Microglia

Microglia, as the primary immune cells within the CNS, constitute the first line of defense against pathogens and injury. These multifunctional cells engage in interactions with various other CNS cells, including neurons, astrocytes, and oligodendrocytes [24]. Microglia are regarded as the prototypical tissue-resident macrophage-like innate immune cells [25]. Upon activation, reactive microglia secrete pro-inflammatory cytokines, including IL-1β, TNF-α, IL-18, IL-6, and interleukin-23 (IL-23), and exert toxic effects on neural cells. Both in vivo and in vitro studies have demonstrated that acute METH exposure prompts microglia to transition from a homeostatic state to an activated state via the TLR4/myeloid differential protein 2 (MD-2) signaling pathway with

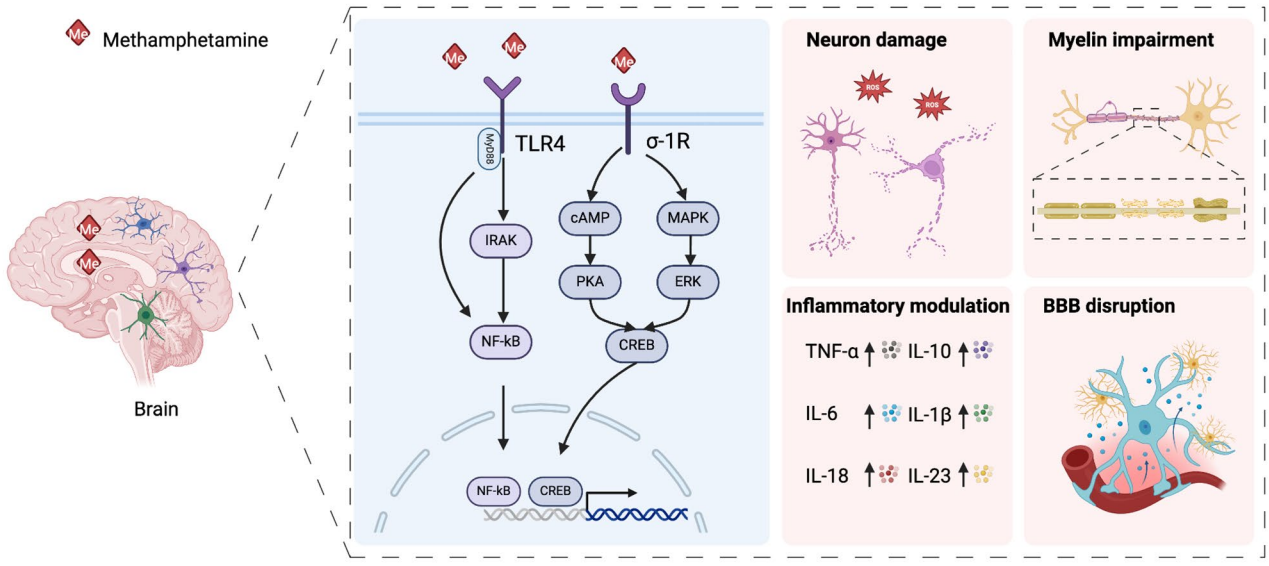

Fig. 1 The key pathways involved in METH-induced neuroinflammation. METH exposure activates glia cells through TLR4 and σ-1R, leading to downstream signaling through the MyD88/IRAK/NF-κB, cAMP/PKA and MAPK/ERK pathways. This activation results in the release of inflammatory cytokines, BBB disruption, myelin dysregulation, and neuronal damage. σ-1R: Sigma-1 Receptors; TLR4: Toll-Like Receptor 4; MyD88: Myeloid Differentiation Primary Response 88; IRAK: Interleukin-1 Receptor-Associated Kinase; NF-κB: Nuclear Factor-kappa B; cAMP: Cyclic Adenosine Monophosphate; PKA: Protein Kinase A; MAPK: Mitogen-Activated Protein Kinase; ERK: Extracellular Signal-Regulated Kinase; ROS: Reactive Oxygen Species; BBB: Blood-Brain Barrier; TNF-a: Tumor Necrosis Factor Alpha; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-1b: Interleukin-1 beta; IL-18: Interleukin-18; IL-23: Interleukin-23. Images created with BioRender

morphological changes and proliferation in the nucleus accumbens (NAc) [26, 27]. In vitro study have shown that this activation is marked by the production of pro-inflammatory cytokines (e.g., TNF-α) and anti-inflammatory cytokines (e.g., IL-10), which seem to result from acute METH exposure [28]. Consistently, increased expression of the anti-inflammatory cytokine (e.g., IL-10) has also been observed in the prefrontal cortex (PFC) and hippocampus in a rat model of acute METH reinstatement [29]. However, chronic METH use results in prolonged activation of microglia and elevated levels of pro-inflammatory factors (e.g., IL-6 and TNF-α) in the brain reward systems, such as NAc and ventral tegmental area(VTA), through the cyclic adenosine monophosphate/protein kinase A/cAMP response element-binding protein (cAMP/PKA/CREB) signaling pathway, thereby sustaining a state of neuroinflammation [30–32]. Furthermore, microglia release reactive oxygen species (ROS) and reactive nitrogen species (RNS) in a cluster of differentiation 11b (CD11b) -dependent manner, which are cytotoxic to oligodendrocytes and neurons [33, 34]. Reactive species induce oxidative stress, mitochondrial dysfunction, and ultimately neuronal apoptosis, thereby contributing to altered drug-seeking behaviors [35–37]. Inhibition of activated microglia, for example with PLX5622 in the NAc, has been shown to mitigate these behaviors [32]. However, exposure to high doses of METH can result in microglial death [38]. Researches conducted both in vivo (hippocampus) and in vitro indicates that induction of autophagy or the administration of exogenous TNF-α or IL-6 can attenuate microglial apoptosis, suggesting the presence of an intrinsic negative feedback mechanism that regulates microglial activity, which may account for the inconsistent findings in research [39, 40].

Furthermore, vessel-associated microglia initially preserve the integrity of the BBB through the expression of the tight-junction protein Claudin-5 and by establishing physical contact with endothelial cells [41]. However, after long-time METH exposure, microglia engage in the phagocytosis of astrocytic end-feet, leading to vascular damage and the subsequent impairment of BBB function [41]. This dual role highlights the intricate involvement of microglia in both the preservation and impairment of BBB integrity [42–44]. Furthermore, these findings indicate that microglia act as intermediaries in the cross-talk between peripheral and central immune responses. Considering the current limitations of detection methodologies, future research should prioritize the dynamic observation of microglia to clarify their specific role in BBB damage, particularly in determining whether they exacerbate or ameliorate such damage.

Astrocyte

Similar to microglia, astrocytes are among the most abundant glial cells in the CNS, playing critical roles in maintaining the BBB, regulating neurotransmitter levels,

and supporting neuronal function [45]. METH exposure induces reactive astrogliosis, a process characterized by the proliferation and hypertrophy of astrocytes [46]. Both in vivo and in vitro experiments have demonstrated that reactive astrocytes release a multitude of cytokines and chemokines, including mitogen-activated protein kinase kinase 5 (MAPK5), G Protein-Coupled Receptor 65 (GPR65), and C-X-C motif chemokine ligand 5 (CXCL5), thereby contributing to the inflammatory milieu [47]. The release of these pro-inflammatory mediators can exacerbate BBB permeability, facilitating the infiltration of peripheral immune cells and inflammatory molecules into the CNS [12, 48]. Significant markers of BBB disruption include the downregulation of claudins, occludins, junctional adhesion molecules, and cytoskeleton-associated scaffolding proteins such as zonula occludens [20]. Additionally, METH-induced alterations in astrocyte function encompass the dysregulation of glutamate transporters, resulting in elevated extracellular glutamate levels [49]. This dysregulation precipitates excitotoxicity, a pathological condition characterized by neuronal damage and death due to the overactivation of glutamate receptors [50]. Furthermore, METH stimulates astrocyte activation and the excessive release of glutamate, which in turn significantly activates microglia through the IL-10-cell division cycle 42 (Cdc42) signaling pathway. This observation suggests a crosstalk between microglia and astrocytes [32, 51].

Region-specific activation of glial cells induced by METH has been linked to behavioral sensitization, a phenomenon where the behavioral response to a consistent drug dose intensifies with repeated exposure [52]. Research has demonstrated significant correlations between the extent of METH-induced behavioral sensitization and the impact of astrocytes [53]. Specifically, enhanced glial fibrillary acidic protein (GFAP) immunoreactivity in the striatum, along with increased astrocyte proliferation and migration, has been observed [54, 55]. However, current research on the effects of METH on astrocytes predominantly relies on in vitro studies, which lack in vivo recordings of astrocyte activity. This limitation restricts temporal resolution and impedes a comprehensive understanding of astrocyte dynamics. Further investigation is required to elucidate how astrocytes contribute to the rewarding properties of addictive drugs, sensitization to drug effects, withdrawal, and the loss of behavioral control characteristic of these disorders, both in the short and long term.

Oligodendrocyte

Oligodendrocytes are responsible for the synthesis and maintenance of the myelin sheath that encases axons, thereby facilitating the rapid saltatory conduction of action potentials [56]. In addition to their myelinating role, oligodendrocytes secrete various neurotrophins, including nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 [57]. In vitro study has shown that METH exhibits concentration- and time-dependent cytotoxic effects on oligodendrocytes [58]. METH induces apoptosis by upregulating pro-apoptotic proteins such as BCL2-Associated X (Bax) and DP5 in vitro or by promoting the accumulation of α-synuclein in the corpus callosum of chronic METH mice models [58, 59]. This process results in structural damage to myelin, a reduction in myelin-associated proteins, and compromised neuroprotective functions. Despite these findings, research focusing on oligodendrocytes in the context of METH exposure remains sparse. Future investigations should utilize advanced technological methodologies, such as multi-omics approaches (genomics, transcriptomics, proteomics) and artificial intelligence to further elucidate these mechanisms.

Together, the complex interactions among microglia, astrocytes, and cytokine signaling pathways are pivotal in driving the neuropathological alterations associated with MUD, highlighting the critical need for targeted neurobiological interventions [60]. Key cytokines such as IL-10, IL-6, and TNF-α are potential targets in this approach. However, the widespread sources of cytokine secretion make it difficult to target specific cell types within particular brain regions, leading to variable outcomes in different researches. Future research should focus on identifying the specific signaling pathways that activate the central immune system in response to METH.

Role of the peripheral immune system in MUD

MUD is not limited to the central nervous system; it also affects multiple peripheral tissues and organs, resulting in a broad spectrum of physiological symptoms and long-term health complications [61]. Chronic METH use has been demonstrated to affect the liver, spleen, gastrointestinal tract, and lymph nodes [62]. These effects frequently lead to systemic inflammation, and cellular damage across various organ systems, thereby diminishing the body's resilience to infections and other stressors.

Peripheral immune organ damage

METH profoundly impacts peripheral immune organs, including the spleen, liver, gut, and lymph nodes (Fig. 2) [63]. Chronic METH use causes structural and functional alterations in these organs, compromising the body's immune competence [64, 65]. For example, the spleen, a critical organ for filtering blood and mounting immune responses, is particularly vulnerable to METH-induced damage [66]. Acute METH exposure results in elevated levels of pro-inflammatory factors (IL-1β, IL-6) and anti-inflammatory factors (IL-10) in peripheral blood [67]. METH use has been associated with splenomegaly

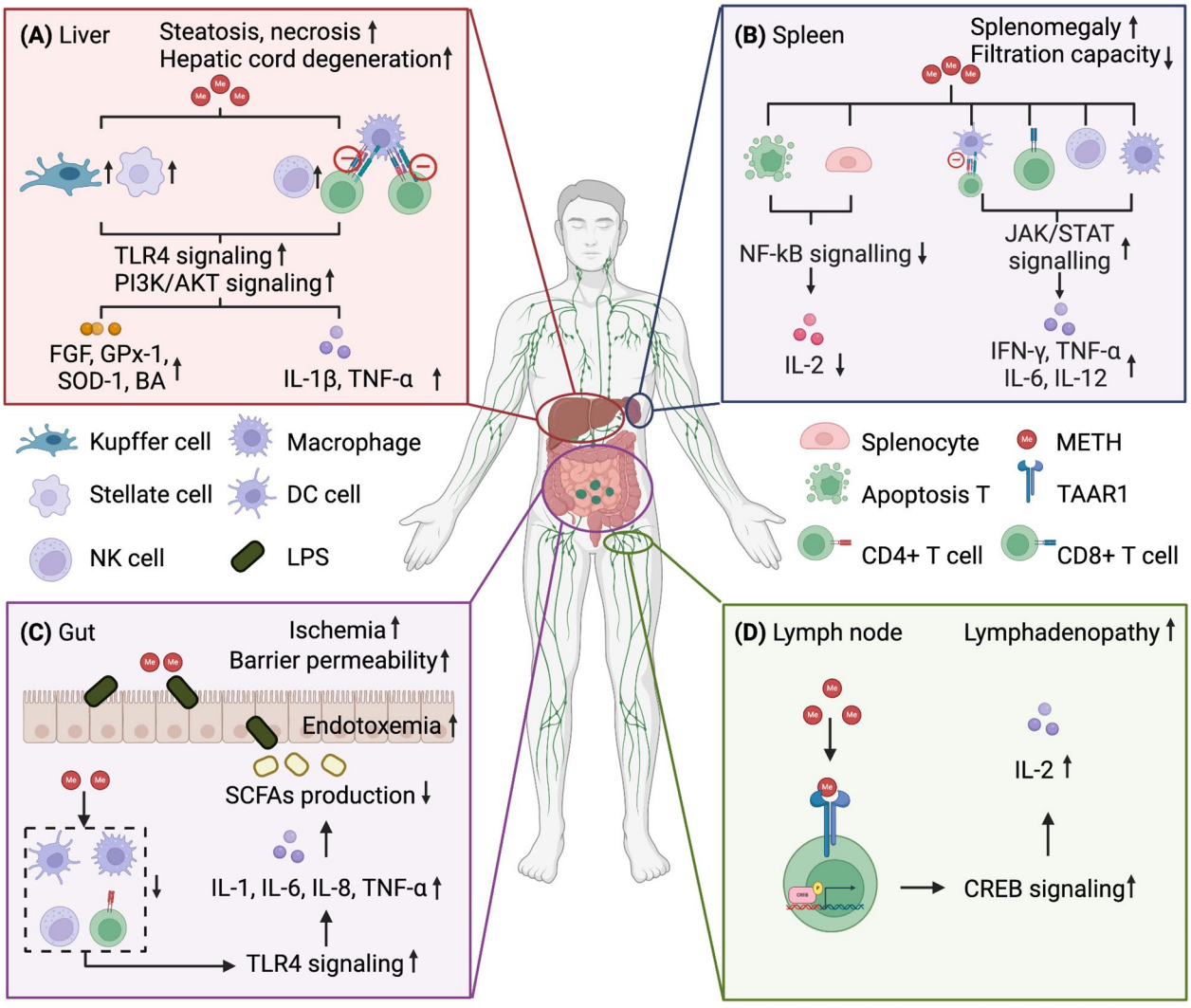

Fig. 2 Mechanism of impaired peripheral immune organs by METH. METH induces toxic effects on immune organs include (**A**) liver, (**B**) spleen, (**C**) gut and (**D**) lymph node. (**A**) METH exposure is associated with enhanced steatosis, fibrosis, and necrosis, and it induces hepatic cord degeneration. METH upregulates the activity of Kupffer cells and stellate cells through TLR4 and PI3K/AKT signaling pathways, resulting in increased levels of FGF, GPx-1, SOD-1, and BA. Furthermore, METH impairs macrophage antigen presentation by reducing their capacity to activate CD4 + and CD8 + T cells, and it promotes NK cells to produce pro-inflammatory cytokines including IL-1β, TNF-α. (**B**) METH exposure results in splenomegaly and impaired filtration capacity. Additionally, it induces apoptosis in T cells and splenocytes and inhibits the production of IL-2. METH exposure also promotes the production of IFN-γ, TNF-α, IL-6, and IL-12 through the activation of T cells, NK cells, and macrophages. (**C**) METH exposure induces acute ischemia and compromises barrier permeability. It also upregulates LPS levels and downregulates SCFAs through TLR4 signaling, thereby causing endotoxemia. Furthermore, METH exposure results in immunosuppression, characterized by the downregulation of DCs and NK cells. Additionally, it upregulates proinflammatory cytokines, including IL-1, IL-6, IL-8, and TNF-α, which are released by macrophages and CD4 + T cells. (**D**) METH also induces lymphadenopathy through TAAR1/CREB signaling and promoted the upregulation of IL-2. METH, methamphetamine; TLR4, toll-like receptor 4; PI3K/AKT, phosphatidyl-inositol 3-kinase/serine-threonine kinase; FGF, fibroblast growth factor; GPx-1, glutathione peroxidase-1; SOD-1, superoxide dismutase-1; BA, bile acid; NK, natural killer; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; CCL5, C-C motif chemokine ligand 5; IL-2, interleukin-2; IFN-γ, interferon-γ; IL-1, interleukin-1; IL-6, interleukin-6; IL-12, interleukin-12; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; DC, dendritic cell; IL-8, interleukin-8; TAAR1/CREB, trace amine-associated receptor 1/ cAMP response element-binding protein. Images created with BioRender

(enlarged spleen) and disruption of normal splenic architecture, impairing its ability to filter pathogens and regulate immune cell populations [19, 68]. This dysfunction leads to immune dysregulation, particularly in the distribution of T cells, NK cells, macrophages, and neutrophils, as observed through immunofluorescence staining [32, 69]. Chronic METH exposure induces decreased interleukin-2 (IL-2) production by splenocytes [70]. Additionally, elevated levels of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ), TNF-α, IL-6, and IL-12, along with reduced levels of anti-inflammatory cytokines such as IL-10, contribute to a sustained

inflammatory response, thereby exacerbating tissue damage [68, 69].

The liver plays a critical role in detoxifying harmful substances and regulating immune responses. Acute or large dose of METH exposure has been linked to increased steatosis [71–73], hepatic cord degeneration [72], and necrosis [74]. This damage not only disrupts the liver's detoxification processes but also impairs its ability to produce key proteins and molecules, such as acute-phase reactants, IL-1β, TNF-α and C-C motif chemokine ligand 5 (CCL5), essential for an effective immune response. This dysfunction contributes to immunosuppression [75, 76]. METH-induced hepatotoxicity can lead to inflammation and apoptosis via the TLR4/MyD88/TNF receptor associated factor 6 (Traf6) and phosphatidyl-inositol 3-kinase/serine-threonine kinase (PI3K/AKT) pathways, impairing liver function and damaging Kupffer cells and other immune cells [77, 78]. Specifically, METH enhances the activity of Kupffer cells and hepatic stellate cells, increasing their production of pro-inflammatory cytokines (including IL-1β and TNF-α), oxidative stress, and fibrosis, with upregulated expression of fibroblast growth factor (FGF), superoxide dismutase-1 (SOD-1), and glutathione peroxidase-1 (GPx-1) [79]. Several studies have explored the metabolic mechanisms behind METH-induced liver damage. Findings show increased serum levels of aspartate aminotransferase, low-density lipoprotein, and triglycerides, alongside elevated malondialdehyde and nitric oxide levels in the serum, liver, and brain [80, 81]. Interestingly, MUD patients exhibited lower plasma concentrations of total bile acids, cholic acid, and chenodeoxycholic acid, with the most significant decline observed after 3 months of abstinence, followed by gradual recovery over the next year [82]. Bile acids, which are cholesterol-derived molecules, are primarily synthesized in the liver and subsequently released into the small intestine to facilitate digestion. In addition to their digestive functions, bile acids possess immunomodulatory properties and have been shown to impair lymphocyte function, Kupffer cell phagocytosis, interferon responses, and the activity of natural killer cells [83]. These findings suggest the presence of potential immune-metabolic mechanisms that warrant further investigation in future research.

METH also significantly impacts the gastrointestinal (GI) system [84]. Firstly, the rapid and prolonged release of norepinephrine following METH use causes arterial vasoconstriction, leading to acute intestinal ischemia. Common GI symptoms among METH users include abdominal cramping, severe constipation or diarrhea, and tissue dehydration due to the vasoconstriction [84]. Additionally, METH alters the gut microbiota, disrupting gut homeostasis by triggering TLR4-related colonic inflammation, disturbing microbial composition, and reducing microbiota-derived short-chain fatty acids (SCFAs) [85]. Beyond the GI tract, chronic METH use has also been linked to lymphadenopathy, altering the cellular makeup of lymph nodes and impairing immune responses, thereby increasing vulnerability to infections [86]. Research has shown that METH activates trace amine-associated receptor 1 (TAAR1) in vitro, affecting crucial T cell functions such as cAMP activation and IL-2 production, suggesting that TAAR1 may play a significant role in METH-induced immune response [87].

In conclusion, METH has a profound impact on peripheral immune organs, causing structural and functional impairments that compromise the body's overall immune competence. However, due to the wide range of damage markers and the limited time points for data collection, current research lacks adequate temporal and spatial resolution. To address this, future studies should incorporate advanced technologies, such as real-time ultrasound imaging and other non-invasive in vivo monitoring tools, to assess peripheral organ damage more accurately. Additionally, advanced algorithms should be employed to develop clinical diagnostic models that can better identify and predict METH-induced immune dysfunction.

Cellular and molecular mechanisms

As mentioned above, METH exposure significantly alters the cellular composition of key immune cells, including macrophages, dendritic cells (DCs), T cells, B cells, and NK cells [88–91]. For example, chronic METH use has immune-suppressive effects on antigen-presenting cells, such as macrophages and DCs, and reduces T cell proliferative activity [13]. Given that innate and adaptive immune cells predominantly circulate in the peripheral blood, this section will focus on the mechanisms involving these immune cells and molecules.

T cells, a critical component of the adaptive immune system, exhibit various cytotoxic and immune-modulating functions upon activation. The two main T-cell subtypes are CD3 + CD8 + T cells, responsible for cell-mediated cytotoxicity and cytokine release, and CD3 + CD4 + T cells, which can be further classified into pro- and anti-inflammatory subtypes [92]. Among immune cells, METH's effects on T cells have been most extensively studied. METH-induced T cell activation has been shown to involve several transcription factors, such as NF-κB, CREB, and nuclear factor of activated T cells 1(NFAT1) [19, 93]. Moreover, METH impairs T cell proliferation by inhibiting the Cyclin-dependent kinase 2(CDK2)–cyclin E complex proteins [94]. However, research on CD4 + and CD8 + T cell changes following METH exposure is inconsistent, with some studies reporting reduced activation of both cell types, while others reported a decrease in CD4 + T cells and an increase

in CD8 + T cells [66, 70, 86]. These discrepancies may stem from variations in drug administration methods or detection time points. METH also induces T cell apoptosis through mechanisms like mitochondrial dysfunction, reactive oxygen species production, and oxidative stress [95, 96]. Although limited, some studies suggest that METH directly targets TAAR1 on T cells, leading to activation and IL-2 production [87]. Furthermore, in vitro studies have demonstrated that acute METH exposure results in an elevated secretion of anti-inflammatory cytokines, specifically IL-4 and IL-10, by CD4 + T cells [97]. Conversely, in chronic METH exposure mouse models, an increase in the levels of the pro-inflammatory cytokines (e.g., IL-6) and a decrease in the levels of the anti-inflammatory cytokines (e.g., IL-4 and IL-10) by CD4 + T cells were observed [98]. These findings suggest that the duration and pattern of METH exposure may have a significant impact on the immune response effects of T cells. Further research is required to fully understand how METH triggers T cell activation and damage, as well as the regulatory factors involved.

Macrophages, a key component of the innate immune system, play a vital role in maintaining homeostasis and responding to infections [91, 99, 100]. METH exposure has been found to induce macrophage apoptosis by activating autophagy pathways such as activating protein-1/ steroid receptor activator (AP-1/SRC) and releasing pro-inflammatory factors like IL-1β and TNF-α [101–103]. Dendritic cells, which orchestrate T cell immune responses, also show METH-induced dysfunction. METH may inhibit lysosomal-autophagosomal degradation, creating a low pH environment that hinders normal antigen processing and presentation, leading to immunosuppression [104]. B cells, though less studied in the context of METH, are also affected [61]. Research in C57BL/6 mice has shown that METH disrupts B cell activation in response to both T cell-dependent and T cell-independent antigens [105]. Seven days post-antigenic challenge, METH enhances B cell infiltration into pulmonary and splenic tissues and disrupts IgM expression on B cell surfaces, impairing antibody-mediated immunity. Additionally, B cells exposed to METH exhibit impaired proliferation due to the activation of NF-κB, signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase - extracellular signal-regulated kinase (MAPK-ERK), and apoptosis pathways [106, 107].

Overall, MUD induces significant alterations in both peripheral immune organs and cellular mechanisms. Damage to organs such as the spleen, liver, and lymph nodes undermines the body's ability to mount effective immune responses. Future studies should explore the extent to which METH disrupts the relationship between auto-reactive antibodies and organ injury.

Interaction of central and peripheral immune systems in MUD

The interplay between the central and peripheral immune systems in MUD involves complex feedback mechanisms that exacerbate both neuroinflammation and systemic immune dysregulation. Signals continuously exchange between the CNS and peripheral immune organs, creating a self-reinforcing cycle that worsens the pathological effects of MUD. This section will elaborate on the following two aspects separately: the regulation of the peripheral immune systems by the central immune systems and how the peripheral systems affect the central immune systems (Fig. 3).

How does the central system regulate the peripheral system?

Immune factors (such as cytokines and chemokines) from the CNS have diverse effects on the peripheral immune system [108]. Cytokines released by activated microglia and astrocytes, such as CCL2, TNF-α, and IL-1β, can penetrate the systemic circulation, disrupting the BBB and increasing cerebral blood flow and vascular permeability [18, 109, 110]. These molecules reach peripheral immune organs, such as the spleen, liver, and gut, triggering immune activation and dysregulation. The spleen and liver, which naturally filter blood-borne molecules, are particularly vulnerable to damage from METH-induced cytokine surges. For instance, studies show that chemokines produced by microglia influence the recruitment and function of peripheral monocytes, exacerbating peripheral inflammation [111–115]. Other inflammatory signaling pathways, such as NF-κB, receptor-interacting serine/threonine-protein kinase (RIPK), MAPK, ERK, c-Jun N-terminal kinase (JNK), and Janus kinase (JAK), are also activated, contributing to sustained peripheral inflammation [116]. In addition, cytokines like IL-33 from microglia stimulate peripheral immune responses, such as T cell activation in the spleen through the growth stimulation expressed gene 2 (ST2) signaling pathway, further linking central and peripheral immune systems [117].

METH withdrawal exacerbates this central-peripheral communication by targeting brain regions involved in stress response, such as the hypothalamus and amygdala. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and the vagus nerve (VN) triggers the release of stress hormones like glucocorticoids, which modulate immune activity [118]. VN activation also directly affects peripheral organs, such as the spleen and liver, further influencing immune responses [119]. This complex network of humoral and neural pathways regulates inflammatory cytokine production in peripheral immune cells, including T cells, monocytes, and macrophages. Upon activation, the VN can modulate various peripheral

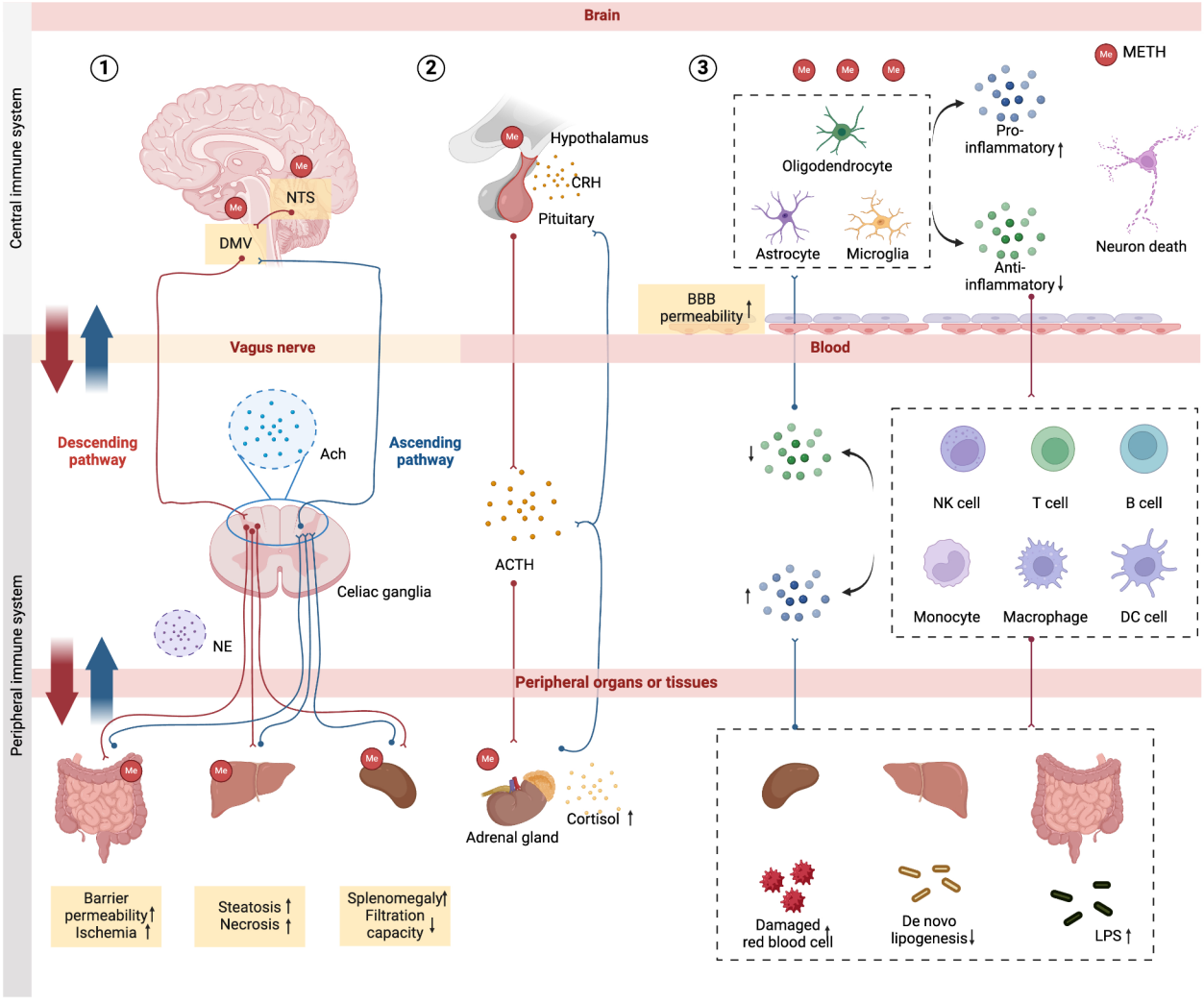

Fig. 3 Interaction of peripheral immune systems and central immune systems in METH addiction. METH addiction induces systemic damage through three potential mechanisms. Firstly, METH exposure activates the vagus nerve in the NTS and the DMV, leading to the release of acetylcholine and norepinephrine. This activation results in dysfunction of peripheral immune organs, including the gut, liver, and spleen, potentially creating a positive feedback loop. Secondly, chronic METH exposure activates the HPA axis, inducing the release of cortisol, which causes immunosuppression, representing a negative feedback mechanism. Thirdly, METH directly and indirectly damages the BBB, activating immune cells and promoting the production of cytokines and chemokines, which can directly impact peripheral organs. METH, methamphetamine; NTS, nucleus tractus solitarius; DMV, dorsal motor nucleus of the vagus; HPA, hypothalamic-pituitary-adrenal; BBB, blood-brain barrier; Ach, acetylcholine; NE, norepinephrine; CRH, corticotropin releasing hormone; ACTH, adreno-cortico-tropic hormone; LPS, lipopolysaccharides. Images created with BioRender

immune organs, including the spleen, liver, and gut. Recent research demonstrated that transcutaneous auricular VN stimulation (taVNS) reduced infarct volume and promoted angiogenesis in rats [120]. Additionally, the hypothalamus plays a central role in the autonomic nervous system by coordinating the neuroendocrine (glucocorticoid) response and cholinergic pathways. This coordination inhibits the release of inflammatory cytokines from peripheral T cells, monocytes, and macrophages, while promoting the release of anti-inflammatory mediators, such as IL-10 [121]. Similarly, norepinephrine (NE) released from dense neural networks throughout the brain and from peripheral organs, such as the spleen, induces significant anti-inflammatory phenotypes in lymphocytes, monocytes, and macrophages [122]. Additionally, the release of catecholamines from nerve endings can stimulate the release of acetylcholine (ACh) from splenic T memory cells, thereby inhibiting inflammation [123].

Collectively, these findings suggest an altered immune landscape under METH exposure in which immune cells, including T cells, macrophages, and DCs, may become hyperactive. This hyperactivation can exacerbate systemic inflammation, thereby contributing to chronic

conditions [124]. Moreover, the spleen and liver's capacity to filter blood and regulate immune cell populations becomes compromised under prolonged inflammatory states, resulting in altered immune responses that further impact the CNS [19, 62].

How does the peripheral system affect the central system?

METH also induces significant alterations in peripheral immune organs, which subsequently affect the CNS [125]. On one hand, METH can directly damage the BBB, allowing peripheral immune organs to promote neuroinflammation by secreting small molecules that pass through the BBB. On the other hand, peripheral immune organs can secrete inflammatory factors that reach the central nervous system through the bloodstream, exacerbating BBB damage and triggering neuroinflammation. For instance, METH-induced gut dysbiosis facilitates the translocation of bacterial endotoxins, such as LPS, into the bloodstream. These endotoxins are capable of traversing the compromised BBB, thereby directly activating central immune cells and exacerbating neuroinflammation [84, 126]. METH also induces hepatotoxicity, resulting in hepatocyte injury and a decrease in immune regulatory proteins. The impaired liver cannot detoxify or produce essential immune-regulatory factors effectively, thereby exacerbating peripheral inflammation and indirectly impacting CNS health through the release of inflammatory mediators such as TNF-α, IL-6, and IL-1β [127, 128]. Hepatic damage also results in increased plasma ammonia concentrations, which contribute to oxidative stress and inflammation. This systemic inflammatory response can compromise the integrity of the BBB via mechanisms involving matrix metalloproteinase-9 (MMP-9), thereby increasing BBB permeability and facilitating the infiltration of peripheral inflammatory cells into the brain [129].

Furthermore, the activation and migration of peripheral immune cells may further compromise the integrity of the BBB. The resulting damage to these barriers facilitates the entry of peripheral inflammatory cells into the CNS, leading to the accumulation of additional inflammatory mediators within the CNS [130]. For instance, activated macrophages exacerbate inflammation by releasing pro-inflammatory cytokines and chemokines, which recruit T cells that sustain inflammation through the production of IL-17 [131]. Subsequently, under the influence of chemokines, leukocytes infiltrate the damaged brain tissue, thereby exacerbating inflammation. The proportion and distribution of M1 and M2 microglia also undergo alterations, with anti-inflammatory M2 microglia regaining predominance. Microglia and macrophages facilitate the clearance of cellular debris. This inflammatory cycle progressively deteriorates the pathological state of the CNS, culminating in neural damage and potential neurodegenerative changes. Moreover, blocking the infiltration of C-C Motif Chemokine Receptor 2 (CCR2+) monocytes into the brain has shown neuroprotective effects, reducing BBB disruption and central inflammation [132].

Besides positive feedback regulation, the interactions between the central and peripheral immune systems also include negative feedback regulation [133, 134]. For example, the release of anti-inflammatory cytokines, such as IL-10, from specific microglial and peripheral immune cells functions to mitigate excessive inflammation [135]. Nevertheless, in the context of MUD, these regulatory mechanisms are frequently overwhelmed by the substantial pro-inflammatory response. This impairment may diminish the effectiveness of negative feedback mechanisms, thereby permitting a pro-inflammatory state to prevail [136]. Consequently, the central immune system influences the peripheral immune system, and activation of the peripheral immune system reciprocally promotes central immune activation. These interactions exacerbate the pathological progression of MUD, contributing to relapse and associated symptoms [137, 138].

Nonetheless, the causal relationship between these systems remains contentious. Given the constraints of contemporary research methodologies, the majority of available immunological evidence is cross-sectional, rendering the identification of the primary initiating factor and the dynamic evolution of the immune response ambiguous. Future investigations must aim to elucidate the critical immunological determinants that drive the progression of SUD. Nonetheless, it is evident that the BBB, serving as a conduit between the peripheral and central immune systems, plays a pivotal role in this process and will be a central focus of forthcoming research endeavors.

Future directions

Examining MUD through the lens of central-peripheral immune system interactions provides a novel perspective, indicating potential therapeutic strategies that target this bidirectional communication. Nonetheless, significant gaps and challenges persist in comprehensively understanding the mechanisms of central-peripheral immune interactions (Fig. 4).

A significant challenge lies in the fact that, despite the identification of notable markers in MUD (such as IL-1β and TNF-α), the precise molecular mechanisms underlying the bidirectional communication remain insufficiently elucidated. It is mainly due to the inherent limitations of current animal models, they cannot completely replicate the immunodynamics processes associated with patients suffering from MUD, thereby hindering the translational potential of these studies. Future research should prioritize the development of robust cross-species models

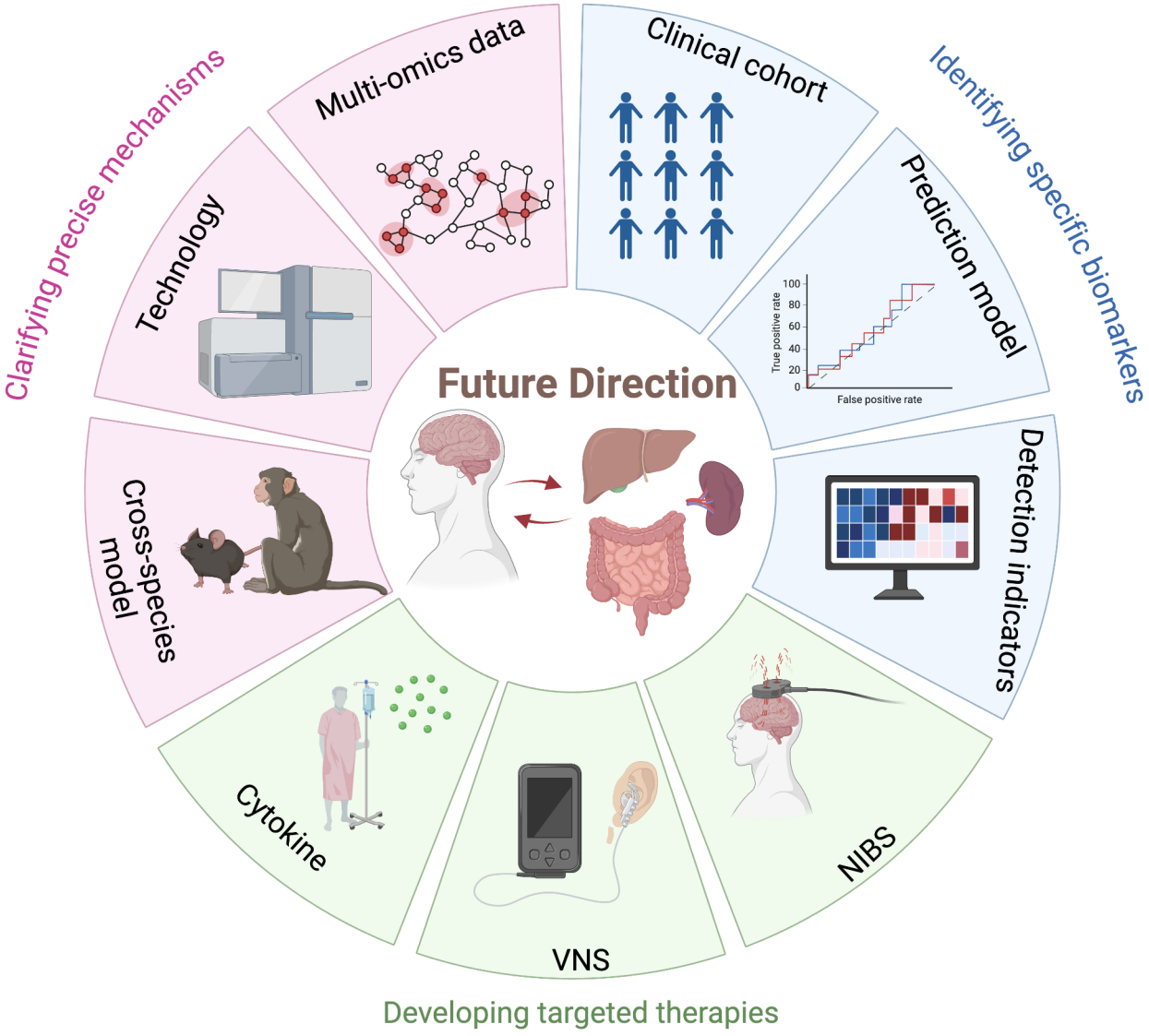

Fig. 4 Framework for future research. Further research should focus on advancing the understanding of the precise mechanisms, identification of specific biomarkers, and development of targeted therapies in animal and human studies. VNS: Vagus Nerve Stimulation; NIBS: Non-Invasive Brain Stimulation; Images created with BioRender

of MUD to elucidate causal relationships and signaling mechanisms.

Another challenge is although the current research has identified certain molecules related to SUD, these biomarkers have not undergone sufficient validation and cannot serve as reliable clinical tools for predicting addiction risk. The majority of biomarker research is still in the experimental phase, with insufficient validation by large-scale population samples, particularly in assessing reproducibility and reliability under diverse conditions. Furthermore, because the progression of MUD may involve various mechanisms, single biomarker alone cannot fully represent the progression. Currently, there is insufficient research on how biomarkers change dynamically during the development of MUD. Consequently, future research should involve longitudinal clinical cohort studies and employ advanced algorithms to identify and predict critical indicators. Given recent advancements in multi-omics technologies, including genomics, transcriptomics, and proteomics, and the rise of artificial intelligence, there is increasing potential to use these tools to deeply analyze interaction mechanisms and identify potential biomarkers.

Conclusions

Together, this review discusses how MUD induces systemic inflammation, involving central immune cells such as microglia and astrocytes, as well as peripheral

immune cells like macrophages and T/B cells. The interplay between these two immune systems is mediated by the regulation of the BBB and VN. They establish a feedback mechanism that exacerbates the detrimental consequences of MUD. Future research need to focus on utilizing advanced technologies to identify biomarkers and develop targeted immunotherapies.

Acknowledgements
This work was supported by Brain Science and Brain-Like Intelligence Technology (2021ZD0202105, 2022ZD0211100); National Nature Science Foundation (82130041, 82171484).

Author contributions
S.S. contributed to the conception, design, data collection, and drafting of the manuscript. Y.S. contributed to the data collection. Both S.S. and Y.S. designed and created the figures with BioRender. G.Z. contributed to critically supervising and revising the manuscript. M.Z. contributed to the conception, design, supervision, and revision of the manuscript. All authors read and approved the final paper.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
This study did not involve human or animal subjects, and thus, no ethical approval was required.

Conflict of interest
The authors declare no conflicts of interest.

Competing interests
The authors declare no competing interests.

Received: 13 December 2024 / Accepted: 7 February 2025
Published online: 15 February 2025

References

1. Jones CM, Compton WM, Mustaquim D. Patterns and characteristics of methamphetamine use among adults - United States, 2015–2018. MMWR Morb Mortal Wkly Rep. 2020;69(12):317–23.
2. Shaerzadeh F, Streit WJ, Heysieattalab S, Khoshbouei H. Methamphetamine neurotoxicity, microglia, and neuroinflammation. J Neuroinflammation. 2018;15(1):341.
3. 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.
4. Gipson CD, Rawls S, Scofield MD, Siemsen BM, Bondy EO, Maher EE. Interactions of neuroimmune signaling and glutamate plasticity in addiction. J Neuroinflammation. 2021;18(1):56.
5. Crews FT, Zou J, Qin L. Induction of innate immune genes in brain create the neurobiology of addiction. Brain Behav Immun. 2011;25(Suppl 1Suppl 1):S4–12.
6. Zhu Y, Yan P, Wang R, Lai J, Tang H, Xiao X, et al. Opioid-induced fragile-like regulatory T cells contribute to withdrawal. Cell. 2023;186(3):591–e60623.
7. Li H, Watkins LR, Wang X. Microglia in neuroimmunopharmacology and drug addiction. Mol Psychiatry. 2024.
8. Coller JK, Hutchinson MR. Implications of central immune signaling caused by drugs of abuse: mechanisms, mediators and new therapeutic approaches for prediction and treatment of drug dependence. Pharmacol Ther. 2012;134(2):219–45.
9. Lin C, Wang X. Microglia in drug addiction: a perspective from neuroimmunopharmacology. Zool Res. 2024;45(3):704–6.
10. Wang X, Northcutt AL, Cochran TA, Zhang X, Fabisiak TJ, Haas ME, et al. 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):3622–34.
11. Zhang Y, Lv X, Bai Y, Zhu X, Wu X, Chao J, et al. Involvement of sigma-1 receptor in astrocyte activation induced by methamphetamine via up-regulation of its own expression. J Neuroinflammation. 2015;12:29.
12. Huang J, Ding J, Wang X, Gu C, He Y, Li Y, et al. Transfer of neuron-derived alpha-synuclein to astrocytes induces neuroinflammation and blood-brain barrier damage after methamphetamine exposure: involving the regulation of nuclear receptor-associated protein 1. Brain Behav Immun. 2022;106:247–61.
13. Kalayasiri R, Dadwat K, Thika S, Sirivichayakul S, Maes M. Methamphetamine (MA) use and MA-induced psychosis are associated with increasing aberrations in the compensatory immunoregulatory system, interleukin-1alpha, and CCL5 levels. Transl Psychiatry. 2023;13(1):361.
14. Pronovost GN, Hsiao EY. Perinatal interactions between the Microbiome, immunity, and neurodevelopment. Immunity. 2019;50(1):18–36.
15. Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. Physiol Rev. 2019;99(3):1325–80.
16. Bekkering S, Dominguez-Andres J, Joosten LAB, Riksen NP, Netea MG. Trained immunity: reprogramming innate immunity in Health and Disease. Annu Rev Immunol. 2021;39:667–93.
17. Salter ML, Lau B, Go VF, Mehta SH, Kirk GD. HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users. Clin Infect Dis. 2011;53(12):1256–64.
18. Wu H, Zhang Z, Ma Y, Chen F, Xiong P, Xie Z, et al. Dynamic immune and exosome transcriptomic responses in patients undergoing psychostimulant methamphetamine withdrawal. Front Cell Neurosci. 2022;16:961131.
19. Hernandez-Santini AC, Mitha AN, Chow D, Hamed MF, Gucwa AL, Vaval V, et al. Methamphetamine facilitates pulmonary and splenic tissue injury and reduces T cell infiltration in C57BL/6 mice after antigenic challenge. Sci Rep. 2021;11(1):8207.
20. Pimentel E, Sivalingam K, Doke M, Samikkannu T. Effects of drugs of abuse on the blood-brain barrier: a brief overview. Front Neurosci. 2020;14:513.
21. Plein LM, Rittner HL. Opioids and the immune system - friend or foe. Br J Pharmacol. 2018;175(14):2717–25.
22. Khan RS, Lalor PF, Thursz M, Newsome PN. The role of neutrophils in alcohol-related hepatitis. J Hepatol. 2023;79(4):1037–48.
23. Dang J, Tiwari SK, Agrawal K, Hui H, Qin Y, Rana TM. Glial cell diversity and methamphetamine-induced neuroinflammation in human cerebral organoids. Mol Psychiatry. 2021;26(4):1194–207.
24. Prinz M, Jung S, Priller J. Microglia Biology: one century of evolving concepts. Cell. 2019;179(2):292–311.
25. Nayak D, Roth TL, McGavern DB. Microglia development and function. Annu Rev Immunol. 2014;32:367–402.
26. Kusui Y, Izuo N, Tokuhara R, Asano T, Nitta A. Neuronal activation of nucleus accumbens by local methamphetamine administration induces cognitive impairment through microglial inflammation in mice. J Pharmacol Sci. 2024;154(3):127–38.
27. Zhang X, Wang Y, Wang H, Li H, Zhang T, Peng Y, et al. 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):1607–13.
28. Fernandes NC, Sriram U, Gofman L, Cenna JM, Ramirez SH, Potula R. Methamphetamine alters microglial immune function through P2X7R signaling. J Neuroinflammation. 2016;13(1):91.
29. Karimi-Haghighi S, Dargahi L, Haghparast A. Cannabidiol modulates the expression of neuroinflammatory factors in stress- and drug-induced reinstatement of methamphetamine in extinguished rats. Addict Biol. 2020;25(2):e12740.
30. Karimi-Haghighi S, Chavoshinezhad S, Mozafari R, Noorbakhsh F, Borhani-Haghighi A, Haghparast A. Neuroinflammatory response in reward-Associated psychostimulants and opioids: a review. Cell Mol Neurobiol. 2023;43(2):649–82.
31. Wang B, Chen T, Wang J, Jia Y, Ren H, Wu F, et al. 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;56:168–78.
32. Vilca SJ, Margetts AV, Hoglund L, Fleites I, Bystrom LL, Pollock TA, et al. Microglia contribute to methamphetamine reinforcement and reflect persistent

transcriptional and morphological adaptations to the drug. Brain Behav Immun. 2024;120:339–51.
33. Marin-Teva JL, Dusart I, Colin C, Gervais A, van Rooijen N, Mallat M. Microglia promote the death of developing Purkinje cells. Neuron. 2004;41(4):535–47.
34. Di Liberto G, Pantelyushin S, Kreutzfeldt M, Page N, Musardo S, Coras R, et al. Neurons under T cell attack coordinate phagocyte-mediated synaptic stripping. Cell. 2018;175(2):458–71. e19.
35. Pramanik A, Das S, Khanna GL. Differential effects of performance-enhancing drugs 'Methamphetamine' and 'hCG' on ex-vivo cultured primary blood mononuclear cells of male athletes. Pharmacol Rep. 2020;72(4):1047–57.
36. Krasnova IN, Justinova Z, Cadet JL. Methamphetamine addiction: involvement of CREB and neuroinflammatory signaling pathways. Psychopharmacology. 2016;233(10):1945–62.
37. Sharikova AV, Quaye E, Park JY, Maloney MC, Desta H, Thiyagarajan R, et al. Methamphetamine induces apoptosis of Microglia via the intrinsic mitochondrial-dependent pathway. J Neuroimmune Pharmacol. 2018;13(3):396–411.
38. Buchanan JB, Sparkman NL, Johnson RW. Methamphetamine sensitization attenuates the febrile and neuroinflammatory response to a subsequent peripheral immune stimulus. Brain Behav Immun. 2010;24(3):502–11.
39. Zhang Y, Shen K, Bai Y, Lv X, Huang R, Zhang W, et al. Mir143-BBC3 cascade reduces microglial survival via interplay between apoptosis and autophagy: implications for methamphetamine-mediated neurotoxicity. Autophagy. 2016;12(9):1538–59.
40. Coelho-Santos V, Goncalves J, Fontes-Ribeiro C, Silva AP. Prevention of methamphetamine-induced microglial cell death by TNF-alpha and IL-6 through activation of the JAK-STAT pathway. J Neuroinflammation. 2012;9:103.
41. Haruwaka K, Ikegami A, Tachibana Y, Ohno N, Konishi H, Hashimoto A, et al. Dual microglia effects on blood brain barrier permeability induced by systemic inflammation. Nat Commun. 2019;10(1):5816.
42. Bowyer JF, Sarkar S, Tranter KM, Hanig JP, Miller DB, O'Callaghan JP. Vascular-directed responses of microglia produced by methamphetamine exposure: indirect evidence that microglia are involved in vascular repair? J Neuroinflammation. 2016;13(1):64.
43. Chen Z, Jalabi W, Hu W, Park HJ, Gale JT, Kidd GJ, et al. Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. Nat Commun. 2014;5:4486.
44. Choi BR, Johnson KR, Maric D, McGavern DB. Monocyte-derived IL-6 programs microglia to rebuild damaged brain vasculature. Nat Immunol. 2023;24(7):1110–23.
45. Santello M, Toni N, Volterra A. Astrocyte function from information processing to cognition and cognitive impairment. Nat Neurosci. 2019;22(2):154–66.
46. Navaei F, Fathabadi FF, Moghaddam MH, Fathi M, Vakili K, Abdollahifar MA, et al. Chronic exposure to methadone impairs memory, induces microgliosis, astrogliosis and neuroinflammation in the hippocampus of adult male rats. J Chem Neuroanat. 2022;125:102139.
47. Bortell N, Basova L, Semenova S, Fox HS, Ravasi T, Marcondes MC. Astrocyte-specific overexpressed gene signatures in response to methamphetamine exposure in vitro. J Neuroinflammation. 2017;14(1):49.
48. Surnar B, Shah AS, Park M, Kalathil AA, Kamran MZ, Ramirez Jaime R, et al. Brain-accumulating nanoparticles for assisting astrocytes to reduce human immunodeficiency virus and drug abuse-Induced Neuroinflammation and oxidative stress. ACS Nano. 2021;15(10):15741–53.
49. Goncalves J, Leitao RA, Higuera-Matas A, Assis MA, Coria SM, Fontes-Ribeiro C, et al. Extended-access methamphetamine self-administration elicits neuroinflammatory response along with blood-brain barrier breakdown. Brain Behav Immun. 2017;62:306–17.
50. Yu C, Narasipura SD, Richards MH, Hu XT, Yamamoto B, Al-Harthi L. HIV and drug abuse mediate astrocyte senescence in a beta-catenin-dependent manner leading to neuronal toxicity. Aging Cell. 2017;16(5):956–65.
51. Canedo T, Portugal CC, Socodato R, Almeida TO, Terceiro AF, Bravo J, et al. Astrocyte-derived TNF and glutamate critically modulate microglia activation by methamphetamine. Neuropsychopharmacology. 2021;46(13):2358–70.
52. Thomas DM, Dowgiert J, Geddes TJ, Francescutti-Verbeem D, Liu X, Kuhn DM. Microglial activation is a pharmacologically specific marker for the neurotoxic amphetamines. Neurosci Lett. 2004;367(3):349–54.
53. Armstrong V, Reichel CM, Doti JF, Crawford CA, McDougall SA. Repeated amphetamine treatment causes a persistent elevation of glial fibrillary acidic protein in the caudate-putamen. Eur J Pharmacol. 2004;488(1–3):111–5.
54. Narita M, Miyatake M, Shibasaki M, Tsuda M, Koizumi S, Narita M, et al. Long-lasting change in brain dynamics induced by methamphetamine: enhancement of protein kinase C-dependent astrocytic response and behavioral sensitization. J Neurochem. 2005;93(6):1383–92.
55. Snider SE, Hendrick ES, Beardsley PM. Glial cell modulators attenuate methamphetamine self-administration in the rat. Eur J Pharmacol. 2013;701(1–3):124–30.
56. Lopez-Muguruza E, Matute C. Alterations of Oligodendrocyte and Myelin Energy Metabolism in multiple sclerosis. Int J Mol Sci. 2023;24(16).
57. Poyhonen S, Er S, Domanskyi A, Airavaara M. Effects of neurotrophic factors in glial cells in the Central Nervous System: expression and Properties in Neurodegeneration and Injury. Front Physiol. 2019;10:486.
58. Genc K, Genc S, Kizildag S, Sonmez U, Yilmaz O, Tugyan K, et al. Methamphetamine induces oligodendroglial cell death in vitro. Brain Res. 2003;982(1):125–30.
59. Ding J, Huang J, Xia B, Hu S, Fan H, Dai J, et al. Transfer of alpha-synuclein from neurons to oligodendrocytes triggers myelin sheath destruction in methamphetamine administration mice. Toxicol Lett. 2021;352:34–45.
60. Shi S, Chen T, Zhao M. The crosstalk between neurons and Glia in Methamphetamine-Induced Neuroinflammation. Neurochem Res. 2022;47(4):872–84.
61. Miller DR, Bu M, Gopinath A, Martinez LR, Khoshbouei H. Methamphetamine Dysregulation of the Central Nervous System and Peripheral immunity. J Pharmacol Exp Ther. 2021;379(3):372–85.
62. Davidson M, Mayer M, Habib A, Rashidi N, Filippone RT, Fraser S, et al. Methamphetamine induces systemic inflammation and anxiety: the role of the Gut-Immune-Brain Axis. Int J Mol Sci. 2022;23:19.
63. Volkow ND, Fowler JS, Wang GJ, Shumay E, Telang F, Thanos PK, et al. Distribution and pharmacokinetics of methamphetamine in the human body: clinical implications. PLoS ONE. 2010;5(12):e15269.
64. Zamanian RT, Hedlin H, Greuenwald P, Wilson DM, Segal JI, Jorden M, et al. Features and outcomes of methamphetamine-associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2018;197(6):788–800.
65. Abdullah CS, Remex NS, Aishwarya R, Nitu S, Kolluru GK, Traylor J, et al. Mitochondrial dysfunction and autophagy activation are associated with cardiomyopathy developed by extended methamphetamine self-administration in rats. Redox Biol. 2022;58:102523.
66. Mata MM, Napier TC, Graves SM, Mahmood F, Raeisi S, Baum LL. Methamphetamine decreases CD4 T cell frequency and alters pro-inflammatory cytokine production in a model of drug abuse. Eur J Pharmacol. 2015;752:26–33.
67. Kobeissy FH, Shakkour Z, Hayek SE, Mohamed W, Gold MS, Wang KKW. 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):158–68.
68. Wu XL, Li X, Li Y, Kong LP, Fang JL, Zhou XS, et al. The overexpression of Thioredoxin-1 suppressing inflammation induced by methamphetamine in spleen. Drug Alcohol Depend. 2016;159:66–71.
69. Peerzada H, Gandhi JA, Guimaraes AJ, Nosanchuk JD, Martinez LR. Methamphetamine administration modifies leukocyte proliferation and cytokine production in murine tissues. Immunobiology. 2013;218(8):1063–8.
70. In SW, Son EW, Rhee DK, Pyo S. Methamphetamine administration produces immunomodulation in mice. J Toxicol Environ Health A. 2005;68(23–24):2133–45.
71. Halpin LE, Yamamoto BK. Peripheral Ammonia as a mediator of Methamphetamine Neurotoxicity. J Neurosci. 2012;32(38):13155–63.
72. Halpin LE, Gunning WT, Yamamoto BK. Methamphetamine causes acute hyperthermia-dependent liver damage. Pharmacol Res Perspect. 2013;1(1):e00008.
73. Merchant K, Schammel C, Fulcher J. Acute Methamphetamine-Induced hepatic and pancreatic ischemia. Am J Forensic Med Pathol. 2019;40(3):285–8.
74. Kamijo Y, Soma K, Nishida M, Namera A, Ohwada T. Acute liver failure following intravenous methamphetamine. Vet Hum Toxicol. 2002;44(4):216–7.
75. Shima N, Miyawaki I, Bando K, Horie H, Zaitsu K, Katagi M, et al. Influences of methamphetamine-induced acute intoxication on urinary and plasma metabolic profiles in the rat. Toxicology. 2011;287(1–3):29–37.
76. Zhou JT, Xu Y, Liu XH, Cheng C, Fan JN, Li X et al. Single-cell RNA-seq reveals that Methamphetamine inhibits Liver immunity with involvement of dopamine receptor D1. Genomics Proteom Bioinf. 2024.
77. Li JH, Liu JL, Li XW, Liu Y, Yang JZ, Ma HS, et al. Maternal inulin supplementation ameliorates prenatal methamphetamine exposure-induced hepatotoxicity and restores gut microbiota in mouse offspring. Ecotoxicol Environ Saf. 2024;269:115769.

78. Chen LJ, He JT, Pan M, Liu JL, Zhang KK, Li JH, et al. Antibiotics Attenuate Methamphetamine-Induced Hepatotoxicity by regulating oxidative stress and TLR4/MyD88/Traf6 Axis. Front Pharmacol. 2021;12:716703.
79. de Carvalho TG, Garcia VB, de Araujo AA, da Silva Gasparotto LH, Silva H, Guerra GCB, et al. Spherical neutral gold nanoparticles improve anti-inflammatory response, oxidative stress and fibrosis in alcohol-methamphetamine-induced liver injury in rats. Int J Pharm. 2018;548(1):1–14.
80. Fakharbad MJ, Moshiri M, Ommati MM, Talebi M, Etemad L. A review of basic to clinical studies of the association between hyperammonemia, methamphetamine. Naunyn Schmiedebergs Arch Pharmacol. 2022;395(8):921–31.
81. Koriem KM, Soliman RE. Chlorogenic and caftaric acids in liver toxicity and oxidative stress induced by methamphetamine. J Toxicol. 2014;2014:583494.
82. Ma Y, Wu H, Wang H, Chen F, Xie Z, Zhang Z, et al. Psychiatric comorbidities and Liver Injury are Associated with Unbalanced plasma bile Acid Profile during Methamphetamine Withdrawal. Front Endocrinol (Lausanne). 2021;12:801686.
83. Lee MH, Nuccio SP, Mohanty I, Hagey LR, Dorrestein PC, Chu H et al. How bile acids and the microbiota interact to shape host immunity. Nat Rev Immunol. 2024.
84. Prakash MD, Tangalakis K, Antonipillai J, Stojanovska L, Nurgali K, Apostolopoulos V. Methamphetamine: effects on the brain, gut and immune system. Pharmacol Res. 2017;120:60–7.
85. Zhang K, Chen L, Yang J, Liu J, Li J, Liu Y, et al. Gut microbiota-derived short-chain fatty acids ameliorate methamphetamine-induced depression- and anxiety-like behaviors in a Sigmar-1 receptor-dependent manner. Acta Pharm Sin B. 2023;13(12):4801–22.
86. Harms R, Morsey B, Boyer CW, Fox HS, Sarvetnick N. Methamphetamine administration targets multiple immune subsets and induces phenotypic alterations suggestive of immunosuppression. PLoS ONE. 2012;7(12):e49897.
87. Sriram U, Cenna JM, Haldar B, Fernandes NC, Razmpour R, Fan S, et al. Methamphetamine induces trace amine-associated receptor 1 (TAAR1) expression in human T lymphocytes: role in immunomodulation. J Leukoc Biol. 2016;99(1):213–23.
88. Lo Iacono L, Catale C, Martini A, Valzania A, Viscomi MT, Chiurchiu V, et al. From traumatic childhood to Cocaine abuse: the critical function of the Immune System. Biol Psychiatry. 2018;84(12):905–16.
89. Chilunda V, Weiselberg J, Martinez-Meza S, Mhamilawa LE, Cheney L, Berman JW. Methamphetamine induces transcriptional changes in cultured HIV-infected mature monocytes that may contribute to HIV neuropathogenesis. Front Immunol. 2022;13:952183.
90. Grosgebauer K, Salinas J, Sharkey M, Roach M, Pallikkuth S, Dilworth SE, et al. Psychosocial correlates of Monocyte activation and HIV persistence in Methamphetamine users. J Neuroimmune Pharmacol. 2019;14(1):16–22.
91. Macur K, Ciborowski P. Immune System and Methamphetamine: molecular basis of a relationship. Curr Neuropharmacol. 2021;19(12):2067–76.
92. Bettelli E, Korn T, Kuchroo VK. Th17: the third member of the effector T cell trilogy. Curr Opin Immunol. 2007;19(6):652–7.
93. Lee HS, Jeong GS. 6,7,4[Formula: see text]-Trihydroxyflavanone prevents Methamphetamine-Induced T Cell Deactivation by protecting the activated T cells from apoptosis. Am J Chin Med. 2021;49(1):95–111.
94. Potula R, Haldar B, Cenna JM, Sriram U, Fan S. Methamphetamine alters T cell cycle entry and progression: role in immune dysfunction. Cell Death Discov. 2018;4:44.
95. Sriram U, Hill BL, Cenna JM, Gofman L, Fernandes NC, Haldar B, et al. Impaired subset progression and polyfunctionality of T cells in mice exposed to Methamphetamine during chronic LCMV infection. PLoS ONE. 2016;11(10):e0164966.
96. Potula R, Hawkins BJ, Cenna JM, Fan S, Dykstra H, Ramirez SH, et al. Methamphetamine causes mitrochondrial oxidative damage in human T lymphocytes leading to functional impairment. J Immunol. 2010;185(5):2867–76.
97. Prasad A, Kulkarni R, Shrivastava A, Jiang S, Lawson K, Groopman JE. Methamphetamine functions as a novel CD4(+) T-cell activator via the sigma-1 receptor to enhance HIV-1 infection. Sci Rep. 2019;9(1):958.
98. Sriram U, Haldar B, Cenna JM, Gofman L, Potula R. Methamphetamine mediates immune dysregulation in a murine model of chronic viral infection. Front Microbiol. 2015;6:793.
99. Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. Annu Rev Immunol. 2015;33:643–75.
100. Locati M, Curtale G, Mantovani A. Diversity, mechanisms, and significance of macrophage plasticity. Annu Rev Pathol. 2020;15:123–47.
101. Aslanyan L, Ekhar VV, DeLeon-Rodriguez CM, Martinez LR. Capsular specific IgM enhances complement-mediated phagocytosis and killing of Cryptococcus neoformans by methamphetamine-treated J774.16 macrophage-like cells. Int Immunopharmacol. 2017;49:77–84.
102. Basova LV, Vien W, Bortell N, Najera JA, Marcondes MCG. Methamphetamine signals transcription of IL1beta and TNFalpha in a reactive oxygen species-dependent manner and interacts with HIV-1 Tat to decrease antioxidant defense mechanisms. Front Cell Neurosci. 2022;16:911060.
103. Barbaro JM, Sidoli S, Cuervo AM, Berman JW. Methamphetamine dysregulates Macrophage functions and Autophagy to mediate HIV Neuropathogenesis. Biomedicines. 2022;10(6).
104. Talloczy Z, Martinez J, Joset D, Ray Y, Gacser A, Toussi S, et al. Methamphetamine inhibits antigen processing, presentation, and phagocytosis. PLoS Pathog. 2008;4(2):e28.
105. Mitha AN, Chow D, Vaval V, Guerrero P, Rivera-Rodriguez DE, Martinez LR. Methamphetamine compromises the adaptive B cell-mediated immunity to antigenic challenge in C57BL/6 mice. Front Toxicol. 2021;3.
106. Park JH, Seo YH, Jang JH, Jeong CH, 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.
107. Piepenbrink MS, Samuel M, Zheng B, Carter B, Fucile C, Bunce C, et al. Humoral Dysregulation Associated with increased systemic inflammation among injection heroin users. PLoS ONE. 2016;11(7):e0158641.
108. Chan KL, Poller WC, Swirski FK, Russo SJ. Central regulation of stress-evoked peripheral immune responses. Nat Rev Neurosci. 2023;24(10):591–604.
109. Toborek M, Seelbach MJ, Rashid CS, Andras IE, Chen L, Park M, et al. Voluntary exercise protects against methamphetamine-induced oxidative stress in brain microvasculature and disruption of the blood-brain barrier. Mol Neurodegener. 2013;8:22.
110. Abdul Muneer PM, Alikunju S, Szlachetka AM, Murrin LC, Haorah J. Impairment of brain endothelial glucose transporter by methamphetamine causes blood-brain barrier dysfunction. Mol Neurodegener. 2011;6:23.
111. Mahad D, Callahan MK, Williams KA, Ubogu EE, Kivisäkk P, Tucky B, et al. Modulating CCR2 and CCL2 at the blood-brain barrier: relevance for multiple sclerosis pathogenesis. Brain. 2006;129(Pt 1):212–23.
112. Broekaart DWM, Anink JJ, Baayen JC, Idema S, de Vries HE, Aronica E, et al. Activation of the innate immune system is evident throughout epileptogenesis and is associated with blood-brain barrier dysfunction and seizure progression. Epilepsia. 2018;59(10):1931–44.
113. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. J Neurosci. 2009;29(7):2089–102.
114. Seleme MC, Kosmac K, Jonjic S, Britt WJ. Tumor necrosis factor Alpha-Induced recruitment of inflammatory mononuclear cells leads to inflammation and altered Brain Development in Murine Cytomegalovirus-infected Newborn mice. J Virol. 2017;91(8).
115. Paré A, Mailhot B, Lévesque SA, Juzwik C, Ignatius Arokia Doss PM, Lécuyer MA, et al. IL-1β enables CNS access to CCR2(hi) monocytes and the generation of pathogenic cells through GM-CSF released by CNS endothelial cells. Proc Natl Acad Sci U S A. 2018;115(6):E1194–203.
116. Vishwakarma S, Singh S, Singh TG. Pharmacological modulation of cytokines correlating neuroinflammatory cascades in epileptogenesis. Mol Biol Rep. 2022;49(2):1437–52.
117. Korhonen P, Kanninen KM, Lehtonen Š, Lemarchant S, Puttonen KA, Oksanen M, et al. Immunomodulation by interleukin-33 is protective in stroke through modulation of inflammation. Brain Behav Immun. 2015;49:322–36.
118. Fitzgerald PJ. Many drugs of abuse may be acutely transformed to dopamine, norepinephrine and epinephrine in vivo. Int J Mol Sci. 2021;22(19).
119. Garcia-Carmona JA, Georgiou P, Zanos P, Bailey A, Laorden ML. Methamphetamine withdrawal induces activation of CRF neurons in the brain stress system in parallel with an increased activity of cardiac sympathetic pathways. Naunyn Schmiedebergs Arch Pharmacol. 2018;391(4):423–34.
120. Ma J, Zhang L, He G, Tan X, Jin X, Li C. Transcutaneous auricular vagus nerve stimulation regulates expression of growth differentiation factor 11 and activin-like kinase 5 in cerebral ischemia/reperfusion rats. J Neurol Sci. 2016;369:27–35.
121. Wang Z, He D, Zeng YY, Zhu L, Yang C, Lu YJ, et al. The spleen may be an important target of stem cell therapy for stroke. J Neuroinflammation. 2019;16(1):20.
122. Thoppil J, Mehta P, Bartels B, Sharma D, Farrar JD. Impact of norepinephrine on immunity and oxidative metabolism in sepsis. Front Immunol. 2023;14:1271098.

123. Chamorro A, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. Nat Rev Neurol. 2012;8(7):401–10.
124. Sanchez-Alavez M, Bortell N, Basova L, Samad F, Marcondes MCG. Macrophages and brown adipocytes cross-communicate to modulate a thermogenic program following methamphetamine exposure. Int J Hyperth. 2020;37(1):1368–82.
125. Croese T, Castellani G, Schwartz M. Immune cell compartmentalization for brain surveillance and protection. Nat Immunol. 2021;22(9):1083–92.
126. Akinyemi DE, Chevre R, Soehnlein O. Neuro-immune crosstalk in hematopoiesis, inflammation, and repair. Trends Immunol. 2024;45(8):597–608.
127. Gopinath A, Riaz T, Miller E, Phan L, Smith A, Syed O, et al. Methamphetamine induces a low dopamine transporter expressing state without altering the total number of peripheral immune cells. Basic Clin Pharmacol Toxicol. 2023;133(5):496–507.
128. Zhang KK, Yang JZ, Cheng CH, Wan JY, Chen YC, Zhou HQ, et al. Short-chain fatty acids mitigate methamphetamine-induced hepatic injuries in a Sigma-1 receptor-dependent manner. Ecotoxicol Environ Saf. 2024;280:116538.
129. Northrop NA, Halpin LE, Yamamoto BK. Peripheral ammonia and blood brain barrier structure and function after methamphetamine. Neuropharmacology. 2016;107:18–26.
130. Li Y, Kong D, Bi K, Luo H. Related effects of Methamphetamine on the Intestinal Barrier via cytokines, and potential mechanisms by which methamphetamine may occur on the Brain-Gut Axis. Front Med (Lausanne). 2022;9:783121.
131. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol. 2014;5:491.
132. Varvel NH, Neher JJ, Bosch A, Wang W, Ransohoff RM, Miller RJ, et al. Infiltrating monocytes promote brain inflammation and exacerbate neuronal damage after status epilepticus. Proc Natl Acad Sci U S A. 2016;113(38):E5665–74.
133. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2016;138(4):984–1010.
134. Smiley CE, Wood SK. Stress- and drug-induced neuroimmune signaling as a therapeutic target for comorbid anxiety and substance use disorders. Pharmacol Ther. 2022;239:108212.
135. Silva AI, Socodato R, Pinto C, Terceiro AF, Canedo T, Relvas JB, et al. IL-10 and Cdc42 modulate astrocyte-mediated microglia activation in methamphetamine-induced neuroinflammation. Glia. 2024;72(8):1501–17.
136. Jia S, Guo X, Chen Z, Li S, Liu XA. The roles of the circadian hormone melatonin in drug addiction. Pharmacol Res. 2022;183:106371.
137. Wang Q, Guo X, Yue Q, Zhu S, Guo L, Li G, et al. Exploring the role and mechanism of gut microbiota in methamphetamine addiction using antibiotic treatment followed by fecal microbiota transplantation. Anat Rec (Hoboken). 2023;306(5):1149–64.
138. Yu Z, Chen W, Zhang L, Chen Y, Chen W, Meng S, et al. Gut-derived bacterial LPS attenuates incubation of methamphetamine craving via modulating microglia. Brain Behav Immun. 2023;111:101–15.

Publisher's note