

Review Article

Role of microglia in methamphetamine-induced neurotoxicity

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Abstract: Methamphetamine (Meth) is an addictive psychostimulant widely abused around the world. The chronic use of Meth produces neurotoxicity featured by dopaminergic terminal damage and microgliosis, resulting in serious neurological and behavioral consequences. Ample evidence indicate that Meth causes microglial activation and resultant secretion of pro-inflammatory molecules leading to neural injury. However, the mechanisms underlying Meth-induced microglial activation remain to be determined. In this review, we attempt to address the effects of Meth on human immunodeficiency virus (HIV)-associated microglia activation both *in vitro* and *in-vivo*. Meth abuse not only increases HIV transmission but also exacerbates progression of HIV-associated neurocognitive disorders (HAND) through activation of microglia. In addition, the therapeutic potential of anti-inflammatory drugs on ameliorating Meth-induced microglia activation and resultant neuronal injury is discussed.

Keywords: Drug abuse, methamphetamine, microglia, neuroinflammation, neurotoxicity

Introduction

Methamphetamine (Meth) is a highly-abused psychostimulant and the second most widely used illicit drug worldwide (after cannabis) [1]. Chronic abuse eventually leads to the neurotoxic regimen, which induces the psychological and behavioral abnormalities, such as increased aggressive behavior and craving for the drug [2-5]. The long-term neurotoxic effects of Meth are well established by neuroimaging studies and psychological tests and confirmed in both rodents and non-human primates [6-8]. Although the primary target of Meth is dopaminergic terminal, the neuropathological changes are not only limited in the striatum. A broader scope of the neural injury has been observed in human subjects with a decreased volume of the hippocampus and the hypertrophy in white matter [9]. Repeated administration of Meth also impaired cognitive function, which could be partially explained by current dopamine-based neurotoxic mechanisms [10-13], suggesting other mechanisms may be involved in Meth-associated neuropathology. Increasing evidence indicate that neuroinflammation fea-

tured by microglial activation plays an important role in Meth-induced neurotoxicity (**Figure 1**). The notion is supported by recent studies that anti-inflammatory drug ibudilast attenuated Meth dependence and Meth-induced neural injury [14-17].

Studies have shown that microgliosis is an early response to Meth abuse and such a response lasts for a long time even after abstinence [18, 19]. Over-activated microglia are found in multiple brain regions in individuals with Meth abuse, but not in those with cocaine use [19, 20]. The time-course, dose-response, and pharmacological profiles of Meth-induced microglial activation indicate that over-activated microglia are not merely a response subsequent to nerve terminal damage, but a specific pharmacological marker of Meth-induced neurotoxicity [18, 21]. As microglia are regulated by a variety of inhibitory signals such as CX3CL1, CD200, CD22, or CD172 [22-24], the impact of repeated Meth administration on inhibitory signaling molecules in central nervous system (CNS) were investigated as the potential therapeutic targets [25, 26]. On the other hand, since the

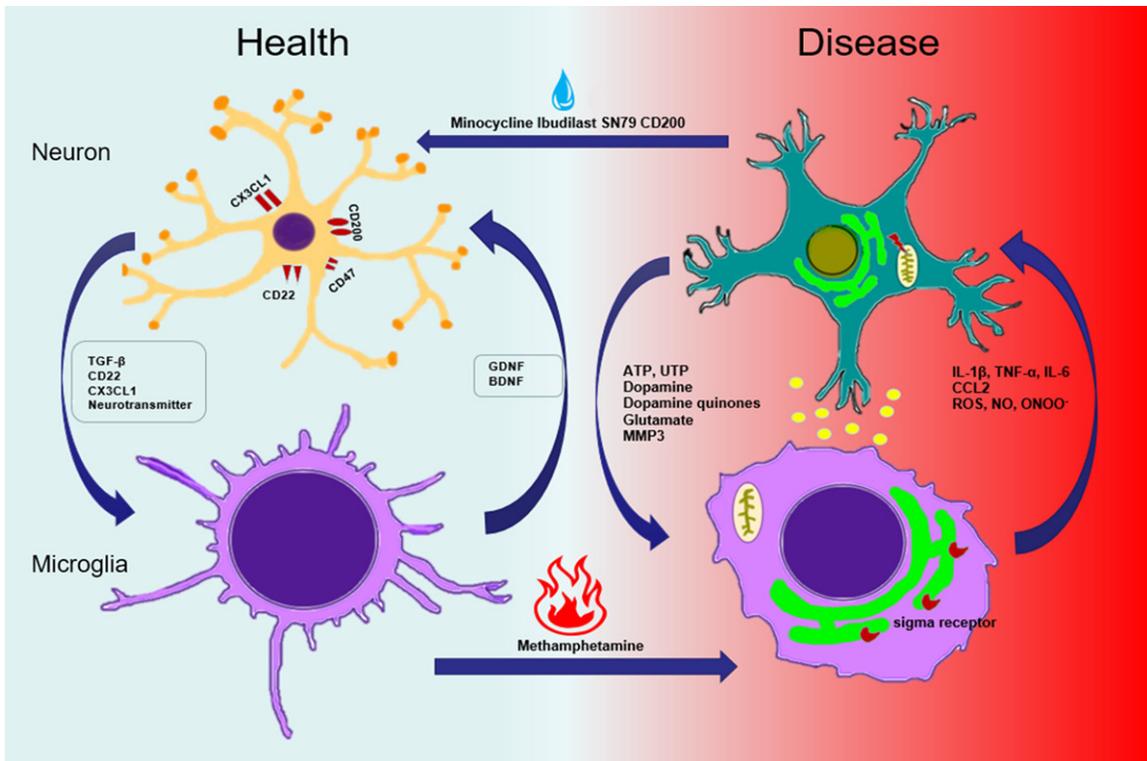


Figure 1. Schematic diagrams illustrating the roles played by microglia in health and disease (Meth abuse) conditions. In health, microglia activation is restricted by neuronal immunosuppressive signals. In turn, the microglia secretes neurotrophic factors to support the neuronal function. In Meth abuse condition (disease), however, Meth causes neuronal cell damage, especially the dopaminergic neuronal terminals. The damaged neurons release danger-associated signals leading to microglia activation. The activated microglia produces proinflammatory substances (neurotoxins), exacerbating Meth-associated neurotoxic activity. Thus, inhibition of microglia activation and resultant production of proinflammatory substances could be an important strategy for therapeutic intervention.

release of neurotoxins including pro-inflammatory cytokines and super oxidative factors are the primary neuronal toxic mediators of microglia [27], the production of these pro-inflammatory mediators after Meth treatment was analyzed [28]. However, the results on the immune modulatory effects of Meth are inconsistent. While its suppressive role was reported in most studies in the peripheral immune system [29-32], Meth was primarily considered as a pro-inflammatory mediator in the CNS [33-35]. A recent study on cultured microglia showed that Meth had limited impacts on microglia production of proinflammatory cytokines indicating the biological and molecular intricacy of this drug [36]. Further investigations on potential roles of the other CNS-specific factors and neuronal danger-associated molecular patterns (DAMPs) are needed. Meth dependence is one of the most common co-morbid conditions among the HIV-infected population [37]. In comparison with the independent effect of

Meth abuse or HIV infection, the combined action of HIV infection and Meth dependence resulted in more severe impairment on neurocognition [38-40]. Studies on the interactions between Meth and HIV proteins in animal models have demonstrated their synergistic effects on cognitive deficits [40, 41] and altered behaviors [42, 43]. However, the precise mechanisms underlying Meth exacerbation of HAND remain unclear. It has been shown that Meth-taking patients with HIV encephalitis (HIVE) exhibited a significant microgliosis, but not astrogliosis [44], suggesting that enhanced microglial activation underlies the cross-talk of HIV-1 infection and Meth dependence. Moreover, Meth abuse enhances opportunistic microbial brain infection [45, 46] and increases lipopolysaccharide (LPS)-mediated human macrophage production of proinflammatory cytokines [47]. LPS was found to potentiate Meth-associated neurotoxicity [48]. Based on these results, whether chronic Meth abuse could enhance

the pre-existing neuroinflammation and promote the progression of another comorbid disease are emerging topics that are worthy of further investigation.

Acute and chronic consequences of Meth abuse

Meth is a synthetic lipophilic drug that is blood brain barrier (BBB) permeable [49]. It derived from amphetamine, but with higher binding affinity to monoamine transporters [50]. Meth administration induces a remarkable outflow of monoamines from synaptic vesicles to cytosol on presynaptic neuron [51-53]. By reverse transportation and freely diffusion, Meth induces potent efflux of dopamine to postsynaptic site causing strong and long-lasting euphoric effect. A comparable dopamine dynamic study suggested that single injection of Meth on the concentration of 2.5 mg/kg induced around 5 times of dopamine release compared to cocaine on 40 mg/kg [54]. Because it is easy to synthesize and is much more potent on psychostimulant effect than other stimulants, Meth has already widely abused all around the world.

The instant effects of Meth include increased attention, activity, and wakefulness; decreased fatigue and appetite; euphoria and rush experience. Hyperthermia and irregular heartbeat are two most prominent toxic effects of hyperthermia and irregular heartbeat overdose [49]. On the other hand, chronic use of Meth induces a series of negative consequences including addiction, anxiety, confusion, insomnia, mood disturbances, and violent behaviors [55]. In addition to these psychotic symptoms, chronic abusers are often associated with cognitive deficits ranging from impaired pulse control, working memory and decision-making [56-58]. These symptoms are accompanied by the Meth-induced neuropathological changes including the damage to dopamine and serotonin axons, loss of gray matter, hypertrophy of the white matter, and microgliosis. Neuroimaging studies with specific probes implicated a monoamine transporter reduction and dopaminergic terminal degeneration [59, 60]. Moreover, magnetic resonance imaging (MRI) studies indicated that Meth-associated neurodegeneration was not restricted to the striatum [9, 61]. Considerable shrinkage of hippocampi, gray matter, cingulate cortex, limbic cortex and paralimbic cortex was observed in recreational abusers

[9]. Multiple neurotoxic events are associated with Meth abuse including oxidative stress, excitotoxicity, hyperthermia, mitochondrial dysfunction, endoplasmic reticulum stress, and neuroinflammatory responses. Here, we primarily focus on neuroinflammation associated with microglial activation.

Microgliosis: a neurotoxic marker of Meth addiction

Microglial activation is characterized by proliferation, morphologically change, migration and inflammatory secretion profiles [62]. It is well-established that the activation of microglia is relative to neurodegenerative diseases, brain injury and toxicant-induced damage to the CNS [63]. In animal model injected with Meth, microgliosis was found in multiple brain areas [64]. A human study validated the remarkable microglial activation in all brain regions using positron emission tomography (PET) with a specific radiotracer [19]. The dose- and time-response of Meth-induced microglial activation performed on Meth-administrated rat indicated that microglial response preceded both terminal neuronal degeneration and astrocyte activation [18]. As it is difficult to differentiate infiltrated monocyte/macrophage with activated microglia by immunohistochemistry staining, the possibility that Meth increases the trafficking of peripheral immune cells into the brain needs to be further proved. The irradiated mice were rescued with bone marrow transplantation from "green mice", a transgenic mouse line with an enhanced GFP (eGFP) expression in all tissues except for erythrocytes and hair. To determine if Meth increases the peripheral monocyte infiltration, the peripheral monocytes in the brain with eGFP were detected after Meth administration. Two days after four injections of neurotoxic regimen of Meth (5 mg/kg) and/or physiological saline in with a 2-h interval, the brains were harvested, fixed and the sectioned. The stratum sections were examined under fluorescent microscope. While the resident microglia were significantly activated in the striatum, no infiltrated eGFP-expressing cells (migrated hematopoietic cells) were detected [25]. Although this study suggests that there is no evidence of transmigration of peripheral hematopoietic cells cross the BBB in response to Meth administration, the role of BBB impairment in Meth-induced neuroinflammation is still in debate. The alteration of BBB

permeability was found shortly after Meth administration and lasted long in multiple brain areas including stratum, amygdala, and hippocampus [65, 66]. Moreover, Meth application was found to induce the oxidative stress in cultured primary human brain microvascular endothelial cells (BMVEC) [67]. The impairment of barrier function of BBB was determined both *in vivo* using fluorescent tracer and *in vitro* via transendothelial electrical resistance (TEER) test. The application of Meth diminished the tightness of BMVEC monolayers by decreasing the expression of cell membrane-associated tight junction proteins and thus, enhanced the monocyte transendothelial migration [67]. The increased monocyte passage through the endothelial cells monolayer can be blocked by a specific inhibitor of Arp 2/3 complex, indicating that actin cytoskeletal dynamics play an important role in Meth-induced transendothelial monocyte migration [68]. Taken together, although the Meth-induced microglial activation is validated in both animal models and human abusers, it is still controversial whether Meth-associated inflammatory response is mediated by the resident microglia other than the peripheral immune cells infiltration.

To determine the mechanism of microglial activation, various experimental groups were designed to mimic selected pharmacological elements of Meth action [21]. As another psychostimulant with high binding affinity with plasma dopamine transporter, cocaine failed to trigger microglial activation in Meth administered rat [21]. Also, the administration of cocaine was found less relative to long-term neurotoxicity [20, 69]. The involvement of dopamine receptors in Meth-induced microglial activation was also evaluated. However, neither D1 nor D2 receptor agonist replicated Meth-induced microglial activation, which suggested that microglial activation was independent of Meth-induced release of dopamine [21]. Furthermore, the levorotary enantiomer of Meth (L-Meth), a molecular sharing the most receptor targets with Meth but with much less binding affinities, failed to activate microglia. Because L-Meth is much less neurotoxic compared to dextrorotary enantiomer [70], its failure in inducing microglial activation further suggests that Meth-induced neuroinflammation is an essential event in the Meth neurotoxic cascade. On the other hand, the factors that mitigate neurotoxicity of Meth such as lower ambient temperature and NMDA receptor antago-

nists also reduce microgliosis along with their neuroprotective effects [18, 71]. Moreover, the tolerance of Meth toxicity is also associated with attenuated microglial activation. After a neurotoxic challenge with Meth, tolerance was developed to the subsequent neurotoxic effects of Meth [72-74]. Although the second Meth stimulation induced the same extent of hyperthermia and astrocyte activities, microglial activation was blunted [75, 76]. Thus, attenuated microglial activation was considered as an important mechanism underlying the reduced Meth-induced neurotoxicity. In contrast, classical immunogen LPS administration significantly increased the microglial activation and potentiated the Meth-induced neurotoxicity [48, 77]. While the astrocytes remain reactive even 30 days after Meth administration, microglial activation subsides within 7 days, which was more reflecting the acute Meth-induced neurotoxicity [76]. Based aforementioned evidence, microglial activation could be an important indicator of Meth-induced toxicity.

Although *in vivo* experiments demonstrate a solid link between neurotoxicity and microglia-mediated neuroinflammation [78], limited studies have been done on Meth effects on cultured microglia. While Meth receptors on microglia remain to be determined, it is unclear whether Meth-induced microglial activation is a receptor-mediated effect. Therefore, testing enantiomers on isolated microglia may, at least in part, address this question because of the different binding affinities of the dextrorotary/levorotary forms to certain receptors. Since activated microglial primarily contribute to neuronal injury by releasing various neurotoxic factors, many studies focus on the activation of inflammatory signaling pathway and subsequent production of neurotoxins after Meth exposure. A latest study evaluated mRNA levels of inflammatory-associated genes on cultured microglia stimulated by various concentrations of Meth [36]. Proinflammatory cytokines upregulated *in vivo* were found unchanged in Meth-treated microglial cultures [36]. The inflammatory responses on both whole brain microglia and isolated striatum microglia are consistent, which means there is no regional specificity of microglia activation. Moreover, the IL-1 β level and cell viability were found decreased after administration of 1 mM Meth [36]. This was consistent with previous experiments on cultured microglia, which

showed the apoptotic effect of Meth in 500 μ M, and could be reversed by TNF α and IL-6 through IL-6 receptor and JAK-STAT3 pathway [79]. While most of the studies indicate that there is less possibility for Meth to stimulate the pro-inflammatory response directly, a study performed on CHME-5 cell line (Human fetal microglial immortalized with large T antigen of simian virus 40) suggested that Meth could reactivate HIV transcription in an NF- κ B-dependent manner. The NF- κ B reporter assay (Luciferase System) and the p65 ELISA of nuclear extracts were used to examine the activity of this cellular transcription factors. The activation of NF- κ B was observed in CHME-5 cell treated with 500 μ M Meth. The activation effect of Meth started as early as 0.5 h and lasted for 24 h. Moreover, the I κ B dominant-negative construct, which lacked the phosphorylation site and could not be dissociated from NF- κ B, blocked the Meth-induced activation [80]. It is worth to note that the concentration of Meth used in those experiments was more than 500 μ M, which was too high to represent the condition of long-term recreational users. On the other hand, the activation of microglia might also be a consequence of the neuronal release of DAMPs that stimulated by application of Meth. High mobility group box-1 (HMGB1) was found upregulated after Meth administration and mediated the neuroinflammatory response in multiple brain areas [36]. Another candidate neuronal DAMP that might mediate Meth-induced microglial activation is DA-quinones (DAQ). The excess outflow of dopamine induced by Meth could be self-oxidized to DAQ that might play an obligatory role in various Meth-induced neurotoxic effects [81, 82], because researchers found DAQ causes a time-dependent activation of cultured microglia. Gene expression study analyzed 101 genes alteration, in which inflammation cytokines, chemokines, and prostaglandins were upregulated, whereas protective neuronal genes were downregulated [81]. The critical roles of dopamine and its oxidative form in Meth-induced microglial activation were further demonstrated by the disruption of DA release from the newly synthesized pool *in vivo*, which abrogated the microgliosis [83]. Thus, the excessive release of dopamine from vesicles and outflow outside neuronal terminals might function as neuronal DAMPs that could be sensed by regional microglia and initiates the neurotoxic signal cascades [83]. Despite the aforemen-

tioned progresses the patterns and mechanisms of microglia activation in the brain need to be further investigated.

The microglia neurotoxicity was initially demonstrated *in vitro* with primary cultured microglia. After challenge with proinflammatory stimuli such as LPS, IFN β , or TNF α , the supernatants were transferred to cultured neurons, and the neuronal apoptosis was observed [84]. Ever since these experiments, it has been well established that the toxic microglial secretory products are the major mediators of microglia-induced neurotoxicity [85-88]. For this reason, it is critical to examine whether the proinflammatory factors, released by microglia in response to Meth, are toxic to neurons. It was shown that microglia-associated factors, for example, IL-1 α , IL-6, CCL2, and TNF α , were upregulated in mice with a single low-dose regimen of Meth [89]. The microglial-mediated proinflammatory responses were attenuated by minocycline, a selective inhibitor of microglial activation [89]. However, the experiment using mice with genetic deficiency in IL-1 α , IL-6, and CCL2 did not show neuroprotection against Meth [89]. Only the mice lack of the TNF1/2 receptors showed attenuated neurotoxicity, indicating that TNF- α is a critical factor in Meth-induced neurotoxicity. Thereby, it is hypothesized that the failure of minocycline in neuroprotection against Meth-associated neuronal damages could be attributed to its incomplete inhibition of TNF- α signaling pathway [89]. Currently, neuroprotective effects targeting microglial activation on Meth-related neurotoxicity in an animal model is controversial [89-92]. The disparity between these mixed results probably attribute to the differences in the dosing regimen or the time of anti-inflammatory drug administration. However, lack of specific selectivity against downstream pathway(s) might also contribute to these ambiguous results. Further studies on identification and inhibition of more specific molecular targets mediating microglia-mediated neuroinflammation are imperative.

Microglia: a potential intersecting point for Meth and HIV

Despite the successfulness of highly active antiretroviral therapy (HAART), 50% of the HIV-infected individuals still suffer from HIV-associated neurological disorder (HAND) [93].

The persistent neuroinflammation was found in HAND patients, even in the HAART era [94-97]. A neuroimaging study revealed that the degree of neuroinflammation marked by the activated microglia inversely correlated with the executive function even in the patient receiving HAART [98]. Meth abuse is prevalent among HIV-infected patients, and the interaction between Meth abuse and HIV pathogenesis is an interesting research topic for many neurovirologists [37, 99, 100]. In comparison to their independent effects, Meth exposure combined with HIV infection produces severer impairment on neurocognition [38, 39]. Studies on the interactions between HIV proteins and Meth in animal models have further demonstrated their synergistic effects on cognitive dysfunctions [40, 41] and altered behaviors [42, 43]. However, the precise mechanisms for Meth exacerbation of HAND are still not fully understood. More significant microgliosis was observed in Meth-taking patients with HIV, while astrogliosis was not changed [44]. Thus, enhanced microglial activation could be the intersecting point for the cross-talk of HIV infection and Meth dependence. Because neurons are refractory to the HIV infection, the activated microglia are most likely the contributors to neuronal damages and cognitive dysfunctions due to the release of neurotoxic substances [101]. On the one hand, Meth is associated with increased entry of virus into CNS system, which could be attributed to several potential mechanisms including increased peripheral viral load [102], reduced adherence to antiretroviral therapy [103], and disruption of the blood-brain barrier (BBB) [65, 104]. Furthermore, Meth can regulate the HIV replication by targeting HIV-associated cellular factors [105, 106]. The potential of dopamine to promote HIV replication is corroborated in rat and monkey models with administration of L-DOPA [107, 108]. However, the dopamine concentrations used in the above studies were very high; it is questionable whether such high dopamine concentrations could be found in Meth abusers [109].

Recently, common molecular targets for Meth and HIV intersecting effects gain more attention. It has been suggested that voltage-gated potassium channels (Kv) are involved with neuronal damage and microglial function [110]. HIV protein Tat and gp120 were reported to increase the outward potassium current and proinflammatory cytokines release, resulting in neu-

rotoxic activity [111, 112]. The potassium channels on microglia were also associated with Meth neurotoxicity [113]. Thus, it is worth to investigate further whether Meth application could potentiate the Tat- or gp120-induced microglial inflammatory response through specific potassium channels. In addition, some microglia-associated proinflammatory cytokines that are crucial for the progression of Meth- and HIV-induced neuropathological changes are also needed to be further investigated [114-117]. The enhanced TNF α secreted by microglia after Meth stimulation might be responsible for the increased HIV replication [118], NMDA receptor neurotoxicity [119], and BBB disruption [120]. Likewise, upregulated IL-1 β and IL-8 expression may also contribute to the Meth and HIV-associated neurotoxic activities [116, 117] as demonstrated by their compromising effects on Long-term potentiation (LTP) and cognitive function [121, 122].

Meth and neuronal immunosuppressive signals

The neuronal cells are vulnerable to the potential detrimental immune reactions. Except for a few limited brain areas, most neurons are incompetent in regenerating themselves [123]. Thus, in addition to the physical isolation by blood brain barrier, neurons express multiple immune suppressive signals to provide a restricted and immunosuppressed microenvironment, which rapidly turns down uncontrolled microglial activation to prevent secondary neuronal damage [22]. Those signals may be secreted by neurons including TGF- β , CX3CL1, and CD22 or expressed on the membrane such as CD200 and CD47. Among these suppressive signals exchanging between the neuron and glial cells, CX3CL1-CX3CR1 and CD200-CD200R are two most well-studied axes in Meth-associated neuronal dysfunction [25, 26]. Ample evidence shows CX3CL1 is the most prominent neuron-derived signal that restricts microglial activation after harmful environmental stimulation [124]. Mice homozygous with CX3CR1-deficient have been widely studied in various neurodegenerative models. Mice with deficient CX3CL1-CX3CR1 signaling showed an enhanced microglial activation, resulting in greater neurotoxicity [125]. In Meth-induced neurotoxicity, while the genes of many inflammatory molecules were found upregulated, the expression levels of CX3CR1 and CX3CL1 did

not change [126]. Unlike the hypersensitivity of the neurons to MPTP-induced neurotoxicity in a CX3CR1 knockout mouse model, the level of Meth-induced hyperthermia and dopaminergic terminal damage were not enhanced in CX3CR1 deficient mice [25]. It is still unclear, however, if the overexpressed exogenous CX3CL1 could downregulate Meth-induced microglial activation. Thus, although current evidence supports that microglial activation and neuronal damage induced by Meth are not mediated by CX3CR1 signaling, the therapeutic potential of this signaling axis needs further investigation.

Another well-studied neuronal immunosuppressive signal in Meth-induced neurotoxicity is CD200. The neuroprotective roles of CD200 against microglia-induced neurotoxicity were reported in multiple neurodegenerative disease models [127, 128]. Consistently, CD200 exerts protective effects on Meth neurotoxicity via decreasing microglial activation [26]. The Fc region of CD200 (CD200-Fc) was tested on neuron-microglia co-culture system and on rats before Meth treatment [26]. CD200-Fc has been proved *in vitro* that it suppressed the microglial activation and secretion of inflammatory cytokines (IL-1 β and TNF α) [26]. Meanwhile, the Meth-induced striatal neurotoxicity was also attenuated by the CD200-Fc application [26]. However, the Meth-associated microglial activation and neuronal damage were not completely blocked by CD200-Fc, indicating the insufficiency of the solo neuronal suppressive signal. Also, because Meth-induced neuronal damages are consisted of multifactorial and complicated processes, the inhibition of microglial activation might not be enough to reverse the toxicity of Meth completely. Lastly, it is still challenging to deliver the antibody drugs into the specific brain areas. Thus, improved delivery systems must facilitate developing the immunosuppressive neuronal signals administration as a therapeutic strategy [129].

Therapeutic studies of Meth-induced neural injury

Currently, the emerging cures for Meth addiction are cognitive behavioral therapy and inpatient treatment. However, the therapeutic effect is barely satisfied. Only 33% of Meth users finished 16 weeks of outpatient counseling and merely 45% patients achieved 3 weeks of Meth abstinence [130]. Even inpatient treatment can

reach only 30% long-term abstinent [131]. The reason for this high relapse rate is the Meth-induced neuropsychiatric impairments [132, 133]. Long-term abuse of Meth causes structural damages to multiple brain areas followed by the impairment of the cognitive and psychiatric functions [134-136]. The Meth abstainers with brain dysfunctions are more likely to relapse [3, 58]. This feedback loop is the major obstacle to the current therapy for Meth dependence. However, with limited successfulness of drug development based on neurotransmitter systems, alternative therapeutic strategies are needed. Because the neuroinflammation plays a critical role in Meth-induced neurotoxicity, overactivated microglia seems to be a promising target for therapeutic approaches.

In recent years, exciting progresses have been made on developing an anti-inflammation strategy against microglia-mediated neuronal damages [137, 138]. Minocycline is the most lipophilic tetracycline antibiotic that is proved for an anti-inflammatory effect through inhibition of key inflammatory enzymes, like inducible nitric oxide synthase (iNOS) [139], Matrix metalloproteinases (MMPs) [140], cyclooxygenase-2 (COX2) [141] and Phospholipase A2 (PLA2) [142]. Minocycline blocked the microglial activation and attenuated the Meth-induced neurotoxicity [90, 143, 144]. After pretreatment of minocycline (40 mg/kg), the behavioral sensitization induced by repeated administration of Meth (3 mg/kg/day) was significantly attenuated [143]. Furthermore, the reduction of dopamine and dopamine transporter (DAT) after Meth are also rescued by application of minocycline [143]. A study performed on monkeys further confirmed the neuroprotective effect of minocycline against Meth [90]. A reduction of DAT after repeated administration of Meth (2 mg/kg) was observed by PET, with or without minocycline (200 mg). The treatment of minocycline, either pre- or post-Meth administration, significantly blocked the DAT reduction. [90]. Administration of minocycline was also effective for Meth-related psychotic disorders as revealed in a clinical case report from Japan [144]. However, only one patient was involved in that clinical study, which was insufficient to perform the statistical analysis. In the latest years, minocycline was found to block the rewarding effect of Meth and reduce the self-administrated amount of Meth on both experimental animal models and human studies

[145, 146]. Consecutive administration of minocycline (20-40 mg/kg) ameliorated the Meth-induced impairment of long-term memory [147]. Most importantly, minocycline attenuated the maintenance and reinstatement of Meth-seeking behaviors, which indicated that minocycline treatment might be able to reduce the craving and relapse for Meth addiction [148]. Taken together, minocycline might break the aforementioned feedback loop to help Meth-dependent individuals quit from relapse. However, we also noticed that there are some divergent views in this regard. In contrast to the researches mentioned above, there are some other studies suggesting that minocycline is unable to protect neurons from Meth challenge [89, 149]. The discrepancies may, at least in part, be attributed by different doses of Meth employed in these studies (10 mg/kg and 20 mg/kg). The total amount of Meth administered with multiple times was much higher in those other studies.

The interaction of the stress and Meth abuse has been well-studied. The unpredictable stress was not only considered as a potentiating factor but also a relapse inducer [16, 150]. Ketoprofen, an FDA-proved medication previously used to treat arthritis has recently been found to have a potential therapeutic effect on stress-induced inflammatory response in Meth-administrated rats [151, 152]. Moreover, persistent stress was also linked with increased microglial activation [153, 154]. To investigate the neuroinflammatory effects on stress-induced potentiation of Meth toxicity, the researchers examined the activity of cyclooxygenase (COX), a well-known neuroinflammatory mediator, in rats exposed to both stress and Meth. Their results showed that the COX inhibitor, ketoprofen, attenuated the enhanced monoaminergic toxicity induced by stress as well as Meth administration [155]. Further experiments demonstrated that an increased permeability of BBB induced by neuroinflammation might underlie the synergistic mechanism of stress and Meth. Ketoprofen, applied either during or post the treatment, significantly reduced the impairment of BBB [151]. Despite its therapeutic potential on synergistic effects of Meth and stress, ketoprofen, however, did not have a protective effect on Meth alone. This is consistent with a previous report regarding to the development of COX as a potential intervention target on Meth toxicity [156]. The current

results also suggest that neuroinflammation may exacerbate the existing monoaminergic damage, and thus, promote the disease progression [157].

Sigma receptor (Sig-R), an endoplasmic reticulum protein, has two subtypes expressed in the brain (Sig-1R and Sig-2R) [158]. Meth binds to Sig-R with preferential binding affinity on Sig-1R (2-4 μ M), ten times higher than Sig-2R (16-47 μ M) [159]. Sig-1R has been implicated in the addiction and toxicity induced by Meth [160-164]. The adaptive upregulation of Sig-1R in the mid-brain was observed after 5 weeks of self-administrated with Meth [165]. Antagonists of Sig-1R block the Meth-induced neurotoxic effects [163] and prevent the development of behavioral sensitization to Meth [164]. In the CNS, Sig-1R is expressed in microglia [166]. A sigma receptor antagonist (SN79) was found to suppress microglial activation and proinflammatory cytokine release in vivo, which blocks the subsequent Meth-induced neurotoxicity. In vitro, inhibition of Sig-1R blocked the Meth-induced microglial apoptosis [167] and with pretreatment of Ditolyguanidine (DTG) or afoazole, sigma receptor agonists, the ATP-induced Ca^{2+} in microglia decreased and proinflammatory cytokine expression reduced [168]. Although these results suggest sigma receptor as a viable target, it is still too early to conclude that blocking Sig-1R reverse the Meth-induced toxicity by modulation of microglial activity. First, localization studies indicated that Sig-1R was not exclusively expressed in microglia [169]. Second, SN79 is also reported with attenuation of Meth-induced astrogliosis [170]. In cultured astrocyte, Sig-1R is involved in Meth-induced astrocyte activation in a positive feedback manner [171]. More studies focused on the exact biochemical relationship between Sig-1R and Meth in microglia are needed. The interaction of Sig-1R and inositol 1,4,5-triphosphate receptors (IP3Rs) on mitochondria-associated ER membrane (MAM) is worth to be investigated on cultured microglia treated with Meth. The potentiation of Ca^{2+} transmission between ER and mitochondria might play a role in Meth-induced microglial activation [172].

The most striking progress having been made recent years based on neuroinflammation is the use of ibudilast to treat Meth dependence. Ibudilast exerts its anti-inflammation effect by inhibition of phosphodiesterase-4 [173, 174].

Because its ability to cross the BBB and suppress the microglial activation, ibudilast has been thoroughly studied for potential efficacy on Meth addiction. To date, Ibudilast has been demonstrated to be effective in reducing the self-administration of Meth and rate of stress-induced Meth relapse [16, 146]. Moreover, it is also showed to modulate Meth-induced behavioral change [15]. The neuroprotective role of this drug has been attributed to its inhibition of inflammatory response [175]. Given the fact that Meth is prevalent in HIV-infected patients and microglia are one the most important common targets that mediate the rapid progression of HAND in HIV patients with Meth abuse, it is very meaningful that ibudilast also inhibits Tat-induced proinflammatory cytokines release from microglia [176]. Altogether, this pharmacotherapy is quite promising for Meth addiction and may block the potentiation effect of Meth on the pre-existing neurodegenerative disorders, such as HAND. Currently, using ibudilast for Meth dependence has completed the phase I clinical trial for drug safety, and now is undertaking the phase II clinical trial (NCT01860807).

Summary

Traditionally, inflammation has four common cellular and molecular hallmarks: upregulation of proinflammatory cytokines and chemokines, activation macrophages (and brain microglia), recruitment of leukocytes and tissue damage [177]. In the study of Meth-induced neuroinflammation, solid evidence demonstrate that administration of Meth could induce a substantial inflammatory response [33] as shown in **Figure 1**. Upregulated inflammatory mediators and proliferation of microglia were found highly correlated with subsequent Meth-induced neurotoxicity [18, 81]. The Meth-induced microglial activation temporally precedes the neuronal damage and response to Meth application in a dose-dependent manner, suggesting a specific causal relationship with Meth-induced neurotoxicity [18, 178]. In human abusers, overactivated microglia have been found in multiple brain areas, which exist for years even in Meth abstainers [19]. Taking together, these results indicate neuroinflammation is a potential target for Meth-induced neurotoxicity. Multiple pharmacotherapies targeting neuroinflammation have been carried out in experimental animals and demonstrated neuroprotective effects

against the Meth-induced neurotoxicity (**Figure 1**). However, because of the limited information on Meth's target receptors in microglia, the precise molecular mechanism(s) for these protective drugs are still not fully understood. Given the possibility that the inflammatory responses of microglia after Meth stimulation in vivo are a secondary response to the neuronal DAMPs (i.e., HMGB1 or Dopamine-quinone), it is worth to investigate whether Meth could interact with other neuronal toxic factors to enhance the microglial activation in a synergistic manner. All in all, identification of Meth specific molecular receptor(s) in microglia will allow us to develop more specific therapeutic strategies for not only eventually helping abusers quit from Meth, but also preventing or ameliorating Meth-induced neurotoxicity.

Disclosure of conflict of interest

None.

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Microglia and meth-induced neurotoxicity

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