1521-0103/379/3/372–385$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

https://doi.org/10.1124/jpet.121.000767
J Pharmacol Exp Ther 379:372–385, December 2021

Minireview

Methamphetamine Dysregulation of the Central Nervous System and Peripheral Immunity

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Received May 28, 2021; accepted September 16, 2021

ABSTRACT

Methamphetamine (METH) is a potent psychostimulant that increases extracellular monoamines, such as dopamine and norepinephrine, and affects multiple tissue and cell types in the central nervous system (CNS) and peripheral immune cells. The reinforcing properties of METH underlie its significant abuse potential and dysregulation of peripheral immunity and central nervous system functions. Together, the constellation of METH's effects on cellular targets and regulatory processes has led to immune suppression and neurodegeneration in METH addicts and animal models of METH exposure. Here we extensively review many of the cell types and mechanisms of METH-induced dysregulation of the central nervous and peripheral immune systems.

SIGNIFICANCE STATEMENT

Emerging research has begun to show that methamphetamine regulates dopaminergic neuronal activity. In addition, METH affects non-neuronal brain cells, such as microglia and astrocytes, and immunological cells of the periphery. Concurrent disruption of bidirectional communication between dopaminergic neurons and glia in the CNS and peripheral immune cell dysregulation gives rise to a constellation of dysfunctional neuronal, cell, and tissue types. Therefore, understanding the pathophysiology of METH requires consideration of the multiple targets at the interface between basic and clinical neuroscience.

1. Introduction

With overdose deaths escalating 1789% from 1999 to 2017 (Clink, 2017), the potent psychostimulant methamphetamine (METH) potentiates multiple mechanisms that lead to abuse potential and health harm. METH pushes biologic systems into hyperactivation, creating a spiral of dysfunction afflicting not only the central nervous system (CNS) (Kish, 2008) but also multiple cell and tissue types in the periphery (Martin et al., 1971; Kaye et al., 2007). Thereby, METH users experience a constellation of impairments (Fig. 1) associated with the CNS and peripheral immune dysfunction, cardiovascular disease (Kaye et al., 2007), and immune dysregulation (Gaskill et al., 2014) involved in amplifying transmission of infectious disease (Galindo et al., 2012; Salamanca et al., 2015). Direct effects of methamphetamine by self-evaluation include arousal, acute improvement of mood and cognition, increased blood pressure, and respiratory rate (Harris et al., 2003; Newton et al., 2005; Mendelson et al., 2006).

First synthesized in 1893 by Nagai Nagayoshi (Nagai, 1893), METH, an amphetamine-class drug, was rapidly recognized for its stimulatory properties. Among these, METH promotes wakefulness and impairs inhibitions, which led to its extensive use during World War II (Defalque and Wright, 2011; Rasmussen, 2011). Today, METH is used clinically for obesity and attention deficit disorder with hyperactivity under the trade name Desoxyn (Drugs@FDA: FDA-approved drugs, n.d.). Despite its clinical efficacy, METH negatively affects multiple systems, exhibiting a host of side effects.

METH exerts its effects primarily through increasing extracellular monoamine neurotransmitters by multiple mechanisms (Sulzer et al., 2005; Xie and Miller, 2009; Saha et al., 2014; Lin et al., 2016; Miller et al., 2021). Although METH

Douglas Miller and Adithya Gopinath are supported by National Institutes of Health National Institute of Neurological Disorders and Stroke [Grant T32-NS082128]. Adithya Gopinath is also supported by National Center for Advancing Translational Sciences [Grant TL1TR001428] and [Grant UL1TR001427]. Dr. Habibeh Khoshbouei is supported by National Institute on Drug Abuse [Grant R01-DA026947] and National Institute of Neurologic Disorders and Stroke [Grant R01-NS071122]. Dr. Luis R. Martinez is supported in part by National Institute of Allergy and Infectious Diseases [Grant R01-AI145559].

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

https://dx.doi.org/10.1124/jpet.121.000767.

ABBREVIATIONS: BBB, blood-brain barrier; CaMKII, calmodulin kinase II; CNS, central nervous system; DAT, dopamine transporter; DC, dendritic cell; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; METH, methamphetamine; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; NK, natural killer; PKC, protein kinase C; ROS, reactive oxygen species; TAAR1, trace amine-associated receptor-1; TLR, toll-like receptor; TNF, tumor necrosis factor; VMAT2, vesicular monoamine transporter 2.

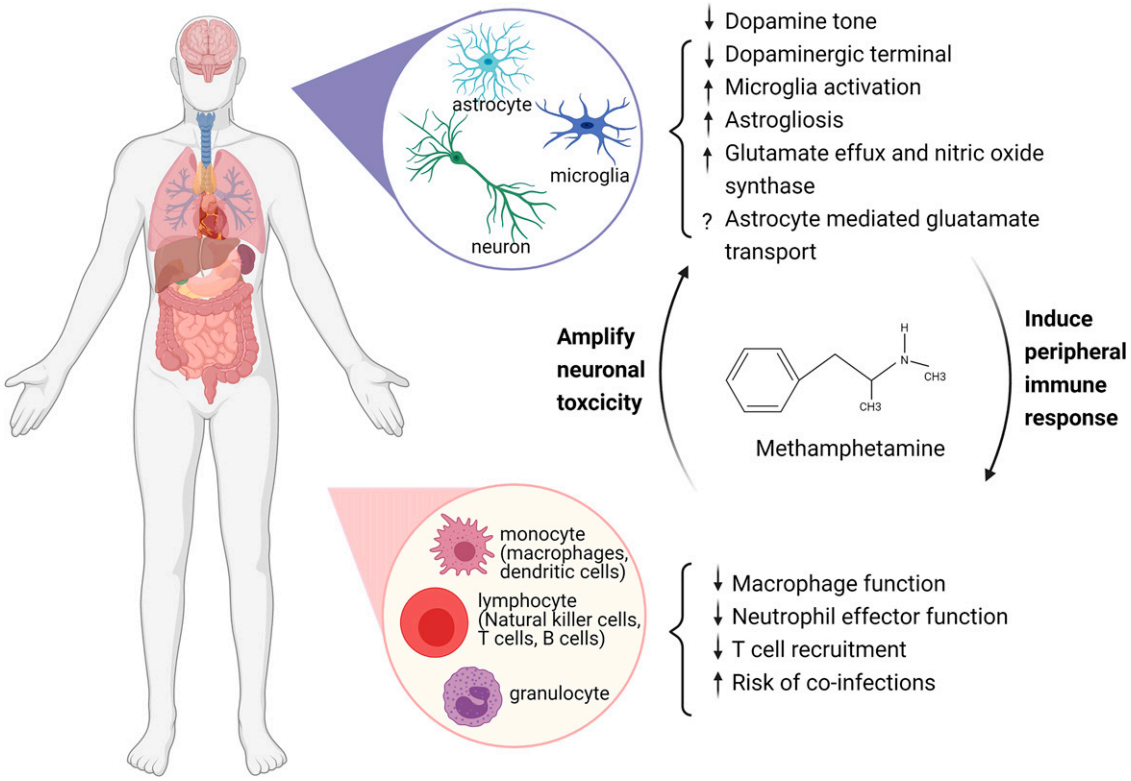

Fig. 1. Central and peripheral targets of methamphetamine-induced dysregulation of neuronal and immunologic cells.

affects serotonin and norepinephrine (and epinephrine) release (Kuczenski et al., 1995; Miller, 2011), dopamine accumulation remains central to the vast molecular cascades of METH use and abuse.

METH toxicity is mainly dose-dependent. METH is administered at relatively low doses (5–20 mg) clinically (Cruickshank and Dyer, 2009). Under such circumstances, METH generally leads to an acute increase in extracellular dopamine, which subsequently improves mood and cognitive functions, such as attention and learning (Nieoullon, 2002). However, METH-induced increases in mesolimbic dopamine release also produce behavioral reinforcing effects, leading to sustained self-administered consumption of high METH doses over time. Under sustained and high doses (>50 mg) (Cruickshank and Dyer, 2009), METH can produce severe cellular toxicity and long-term change in both CNS and peripheral nervous system, and these alterations are also exacerbated by the relatively long, ~12-hour half-life of the drug in the human (Cho et al., 2001). Herein, we review the vast literature, starting with structural interactions with the dopamine transporter and moving through central nervous and peripheral immunity systems afflicted in METH use disorder.

2. METH in the CNS

2.1 Entry of METH into the Brain

Metabolized to amphetamine in the liver by CYP2D6 (Wu et al., 1997; Li et al., 2010), amphetamines and derivatives, such as METH, are small molecules with high lipophilicity (Cho and Segal, 1994; Gulaboski et al., 2007), enabling their rapid diffusion across the blood-brain barrier (BBB) (de la Torre et al., 2012; Turowski and Kenny, 2015). Additionally, METH is a substrate for organic cation transporters (Wagner et al., 2017, 2018), which are expressed on BBB endothelial cells, further increasing transport of METH across the BBB (Turowski and Kenny, 2015). Furthermore, METH increases body temperature and alters the functional properties of the BBB (Bowyer et al., 1994; Bowyer and Ali, 2006; Kiyatkin and Sharma, 2009). Specifically, METH modulates endothelial cell tight junction and adherin networks comprised of proteins like matrix metalloproteinase-9, claudin-5, occludin, and vascular endothelial-cadherin (Martins et al., 2011; Gonçalves et al., 2017) that become increasingly permeable as the BBB breaks down, leading to METH accumulation in the brain parenchyma (Martins et al., 2011).

After crossing the BBB into the CNS, METH activates reward circuitry by increasing dopamine neurotransmission in the mesolimbic and mesocortical pathways (Abi-Dargham et al., 2003; Völlm et al., 2004; Filip et al., 2005). Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging in healthy human subjects found an increase in striatal dopamine release within hours after low-dose AMPH administration (0.3 mg/kg i.v.). Specifically, the dopamine response in the ventral striatum correlates with self-reported euphoria, alertness, and restlessness scores (Laruelle et al., 1995; Drevets et al., 2001). The mesolimbic pathway, which originates from the ventral tegmental area and projects to nucleus accumbens, amygdala, and hippocampus, critically regulates METH-related memories and reinforcement learning responses, such as conditioned place preference (Keleta and Martinez, 2012). The mesocortical pathway, which includes the ventral tegmental area projection to the prefrontal cortex, could lead to compulsive drug

administration seen in illicit users (Volkow and Fowler, 2000). The increase of dopamine transmission in different cortical and subcortical regions produces subsequent behavioral reinforcement and impulsivity associated with drug abuse, leading to sustained high-dose self-administration over time. This user-driven high-dose METH exposure ultimately leads to cumulative cytotoxicity, which we review in detail in the subsequent sections.

2.2 Neuronal Entry of METH through Biogenic Amine Transporters and Intracellular Mechanisms of METH-Induced Neuronal Dysfunction

Once in the brain, METH modulates the activity and reactivity of neurons. As with its passage across the BBB, the passage of METH across cell membranes inside the CNS is facilitated by METH's small size and lipophilicity. However, the similarity of the chemical structure of METH to endogenous biogenic amines facilitates METH to traffic across the membrane through neurotransmitter transporters, such as dopamine transporter, norepinephrine transporter, and serotonin transporter (Raiteri et al., 1977; Fischer and Cho, 1979). Inside neurons, METH perturbs multiple neuronal processes that affect function and health, stimulate oxidative stress pathways, and induce excitotoxicity and apoptosis (Shaerzadeh et al., 2018).

2.2.1 Regulation of Neurotransmission. Monoaminergic neurons using neurotransmitters, such as dopamine, norepinephrine, and serotonin, are the direct targets of METH within the CNS (Sulzer et al., 2005). To facilitate neurotransmission, these neurons package neurotransmitters into synaptic vesicles via vesicular monoamine transporter 2 (VMAT2) (Erickson et al., 1992; Eiden et al., 2004). Packaged vesicles undergo fusion with the plasma membrane during neuronal activity, enabling monoamines to diffuse into the synaptic cleft where they activate proximal receptors or diffuse via volume transmission to affect distal targets (Grace and Bunney, 1984; Agnati et al., 1995; Cragg et al., 2001; Beckstead et al., 2004; Rice and Patel, 2015) before the cessation of the signal by the monoamine transporters (Sulzer et al., 2005; Foster et al., 2006; Cheng and Bahar, 2015; Gaskill et al., 2017; Bu et al., 2021).

METH regulates monoaminergic neurons via multiple mechanisms, in which dopaminergic neurotransmission have been most extensively studied (Kuczenski and Segal, 1994; Bennett et al., 1998; Sulzer et al., 2005; Shaerzadeh et al., 2018). METH competes with dopamine uptake via the dopamine transporter. After the entry into the neurons, METH increases intracellular calcium levels, alters the activity of kinases (Kantor and Gnegy, 1998; Khoshbouei et al., 2004; Foster et al., 2006; Goodwin et al., 2009; Xie and Miller, 2009; Lin et al., 2016), phosphatases (Foster et al., 2002, 2006; Elliott and Beveridge, 2005) or trace amine-associated receptor-1 (TAAR1) activity (Xie and Miller, 2007, 2009), and stimulates the reverse transport of dopamine (dopamine efflux) through the dopamine transporter. METH-stimulated dopamine efflux leads to a rapid increase in extracellular dopamine levels in the brain (Mantle et al., 1976; Wall et al., 1995; Jones et al., 1999; Khoshbouei et al., 2003; Binda et al., 2005; Kahlig et al., 2005; Sulzer et al., 2005; Fog et al., 2006; Goodwin et al., 2009; Saha et al., 2014; Lin et al., 2016; Sambo et al., 2017; Miller et al., 2021). Additionally, METH interferes with the vesicular storage of dopamine in synaptic vesicles. Synaptic vesicles exhibit a lower pH than the cytosol, as established by ATP-driven transport of protons into the vesicle (Johnson, 1988). The amine/proton antiporter VMAT2 enables dopamine transport into the vesicle while transporting protons to the cytosol (Eiden and Weihe, 2011). The similarity of METH to the structure of dopamine facilitates competition through VMAT2 (Sulzer, 2011; Freyberg et al., 2016), disrupting the pH gradient necessary for dopamine transport into the synaptic vesicles (Freyberg et al., 2016) and stimulation of the reserpine binding site on VMAT2 to prevent further dopamine vesicular packaging (Peter et al., 1994; Pifl et al., 1995; Sulzer et al., 1995; Brown et al., 2000; Fleckenstein et al., 2007; Eiden and Weihe, 2011; German et al., 2015). In addition, METH affects the firing properties of dopaminergic neurons (Ingram et al., 2002; Branch and Beckstead, 2012; Lin et al., 2016) in a concentration-dependent manner (Branch and Beckstead, 2012), further increasing extracellular dopamine. Inside neurons, METH activity significantly increases cytosolic dopamine, dopamine efflux, and firing activity of dopamine neurons and reduces uptake and vesicular packaging, leading to elevated dopamine signaling not found in natural stimuli (Di Chiara and Imperato, 1988). As a result, METH affects neurotransmission and creates homeostatic burdens in neurons, leading to the activation of neurotoxic pathways.

2.2.2 Intracellular Calcium, Oxidative Stress, and Neurotoxicity. Concordant with changes in neurotransmission, METH rapidly increases intracellular calcium (Yu et al., 2016; Sambo et al., 2017). Whereas intracellular calcium is critical to neurotransmitter release (Berridge, 1998; Beckstead et al., 2004; Neher and Sakaba, 2008; Borisovska et al., 2013) and monoamine transporter-mediated efflux (Gnegy et al., 2004), METH induces calcium release from intracellular stores (Yorgason et al., 2020) in addition to entry from extracellular milieu (Suzuki et al., 1992; Johnson et al., 2000; Uramura et al., 2000; Yu et al., 2016; Sambo et al., 2017). Calcium increases create burdens on cellular homeostasis that initiate oxidative stress pathways, excitotoxicity, and apoptosis.

In a series of papers, Wagner et al. (1980, 1985) showed that pretreatment with the antioxidant ascorbic acid–attenuated METH-induced dopamine depletion. Later, De Vito and Wagner showed that oxygen-free radical inhibitors also lessened the effects of METH-induced neuronal losses. Specifically, the inhibition of superoxide dismutase, a potent enzyme that catalyzes superoxide radicals to dioxygen (O_2) (McCord and Fridovich, 1969), exacerbates METH-stimulation of oxidative stress (De Vito and Wagner, 1989). In the following decades, the hypothesis that METH increases oxidative stress burden in the CNS has been extensively examined with consistent reproducibility (Cadet et al., 1994; Cubells et al., 1994; Ogawa et al., 1994; Jayanthi et al., 1998; Yamamoto and Zhu, 1998; Gluck et al., 2001; Quinton and Yamamoto, 2006; Tata and Yamamoto, 2007; Kita et al., 2009; Chandramani Shivalingappa et al., 2012; Shin et al., 2012; Solhi et al., 2014; McDonnell-Dowling and Kelly, 2017). Consequently, in addition to disrupted calcium homeostasis and oxidative stress, METH induces excitotoxicity and apoptosis in dopamine neurons (Cubells et al., 1994; Cadet et al., 1997b; Sattler and Tymianski, 2000; Deng et al., 2001, 2002; Quinton and Yamamoto, 2006; Cadet and Krasnova, 2009; Chandramani Shivalingappa et al., 2012; Shin et al., 2012; Kim et

al., 2020). Although METH enters neurons through the monoamine transporters, its affinity is higher for the catecholamine transporters [dopamine transporter (DAT) and norepinephrine transporter] than indoleamine transporter (serotonin transporter) (Howell and Negus, 2014). As a therapeutic option in treating substance abuse, DAT inhibitors exhibit more efficacy in preclinical assays of stimulant self-administration than other monoamine transporters and nondopaminergic targets (Fleckenstein et al., 2000; Sulzer et al., 2005; Howell and Negus, 2014; German et al., 2015). Therefore, we next extensively examine the structural and functional properties of DAT and METH regulation of DAT activity.

2.3 Structural Interactions with DAT

DAT is an integral membrane protein expressed in dopaminergic neurons and the primary target of amphetamines, such as METH, in the CNS. The electrochemical gradient of the membrane facilitates the DAT-coupled transport of Na^+ ions into the intracellular space, thus regulating dopamine neurotransmission in time and space. Multiple studies revealed that chronic use of METH in humans leads to a significant reduction of DAT at the striatum and the prefrontal cortex, which correlates with motor and cognitive impairment (Sekine et al., 2001; Volkow et al., 2001c; Sekine et al., 2003; McCann et al., 2008). Recent advances in structural and molecular biology have made significant progress in elucidating the mechanism of amphetamine modulation of DAT and dopamine neurotransmission. In this section, we will discuss the three central mechanisms through which METH modulates DAT activity: 1) competitive binding to the substrate-binding site, 2) internalization of membrane DAT, and 3) DAT-mediated dopamine efflux.

The recent resolution of drosophila DAT structure, combined with in silico modeling, permits the elucidation of structural dynamics of DAT and the direct comparison of the binding dynamics between dopamine and other psychostimulants (Penmatsa et al., 2013; Cheng and Bahar, 2015; Wang et al., 2015). The transport cycle starts with the binding of Na^+ ions, which breaks the bond between critical residues of the extracellular gate to reveal the primary binding site (S1) located at the transmembrane helices, forming an outward-facing open state. The binding of the substrate at S1 then prompts the closure of the extracellular gate to create a closed conformation, which is followed by the opening of the intracellular gate triggered by the dislocation of Na^+ ion. The transporter then opens up and becomes inward-facing, which allows the release of the substrate into the intracellular space.

The S1 site for dopamine binding also functions as an orthosteric site for psychostimulants, notably amphetamines. Unlike cocaine, whose binding to the S1 site prevents the conformational change of the transporter and arrests it in the outward-facing conformation (Beuming et al., 2008; Xue et al., 2015), amphetamine-class drugs, such as METH, bind to the S1 site with a geometry almost identical to dopamine, allowing the normal conformational change that leads to the reuptake of amphetamines into the intracellular space (Wang et al., 2015). The competitive binding of the S1 site by METH leads to a deficiency in dopamine reuptake. Moreover, intracellular METH could activate the TAAR1, a G-protein–coupled receptor, leading to DAT-mediated dopamine efflux and DAT endocytosis (Xie and Miller, 2007, 2009).

2.4 Regulation of DAT Activity and Membrane Association

METH induces the reversal of the transport cycle, leading to DAT-mediated dopamine efflux through a phosphorylation-dependent mechanism (Sulzer et al., 1995; Khoshbouei et al., 2004; Kahlig et al., 2005; Foster et al., 2006). DAT undergoes both basal and protein kinase C (PKC)-mediated phosphorylation on its N terminals (Foster et al., 2002). METH increases DAT phosphorylation in heterologous cell lines and rodent striatal tissues (Cervinski et al., 2005). Conversely, either inhibition of PKC activity or truncation of DAT N terminus could block DAT efflux (Kantor and Gnegy, 1998; Khoshbouei et al., 2004). Other than PKC, calmodulin kinase II (CaMKII) was also shown to interact with the DAT C terminus and regulate phosphorylation of serine residues on the N terminus (Fog et al., 2006; Steinkellner et al., 2014). Acute inhibition with CaMKII inhibitor KN93 significantly reduced amphetamine-induced dopamine efflux in mouse striatum measured by chronoamperometry (Fog et al., 2006). However, whether METH could directly lead to CaMKII activation is unknown. METH treatment significantly increases Ca^{2+} influx in primary neuronal cultures either through DAT dependent mechanism or by acting on L-type voltage-gated calcium channels and stimulates CaMKII (Chen et al., 2016; Sambo et al., 2017). Paradoxically, in vivo METH injection in rats instead inhibits CaMKII activity in various brain regions, including the parietal cortex, striatum, and midbrain (Akiyama and Suemaru, 2000; Suemaru et al., 2000). The difference between in vivo and in vitro studies highlights a profound systemic effect of METH on calcium homeostasis with a complex downstream influence beyond DAT regulation.

Sigma-1 receptor, a chaperone protein residing on the endoplasmic reticulum, was also shown to regulate METH-induced DAT efflux (Sambo et al., 2017; Hedges et al., 2018). Sigma receptor activation significantly attenuated METH-induced DAT-mediated efflux measured by amperometry in midbrain neuronal culture but had no effects on DAT-mediated efflux on its own. Interestingly, sigma-1 receptor antagonist BD-1063 also significantly reduced METH-induced dopamine efflux in striatal slices (Hedges et al., 2018). At a higher concertation, BD-1063 blocks DAT; therefore, the conflicting results could be due to the concentration of BD-1063 used in this study or indirect mechanism of sigma-1 receptor downregulation since the latter study did not examine the effect of BD-1063 treatment alone in striatal dopamine release and DAT efflux. However, similar to the data shown in Sambo et al., at the concentrations specific for the sigma-1 receptor, the sigma-1 agonist SA 4503 attenuated METH-mediated hyperactivity at a low dose but enhanced it at higher doses (Rodvelt et al., 2011) potentially because of an off-target effect of the drug.

As an integral plasma membrane protein, endocytic trafficking dynamically regulates DAT surface expression. Multiple studies have demonstrated that amphetamines can robustly drive DAT internalization in heterologous and endogenous systems (Fleckenstein et al., 1997; Saunders et al., 2000; Gulley et al., 2002; Hall et al., 2014; Wheeler et al., 2015; Fagan et al., 2020). Amphetamine treatment significantly activates RhoA and Rac1 in mouse midbrain slices (Wheeler et al., 2015). Conversely, amphetamine-induced DAT internalization can be prevented by inhibiting RhoA through PKA (Wheeler et al., 2015). Activation of RhoA and Rac1 defines

an endocytic route that is clathrin-independent and dynamin-dependent (Chi et al., 2013). Accordingly, pharmacological inhibition of dynamin also blocks amphetamine-induced DAT internalization (Kahlig et al., 2006). Repeated administration of METH in mice also increases the expression of piccolo, a presynaptic cytoskeletal matrix protein. Interestingly, piccolo negatively regulates METH-induced DAT internalization, possibly through sequestering membrane phosphatidylinositol 4,5-bisphosphate (Cen et al., 2008).

Another mechanism through which METH may regulate DAT trafficking and DAT-mediated efflux is through DAT oligomerization. DAT assumes different quaternary structures ranging from monomers to oligomers (Hastrup et al., 2003; Sorkina et al., 2018; Jayaraman et al., 2021), and the formation of oligomers could enhance both DAT internalization and dopamine efflux (Khoshbouei et al., 2004; Sorkina et al., 2018). Multiple administration of METH in rats selectively enhances oligomerization of DAT but not D2 receptors in rat striatum, whereas in heterologous cells overexpressing DAT, dispersion of DAT oligomers by dopamine and amphetamine can be demonstrated by Western blot and fluorescence resonance energy transfer imaging (Chen and Reith, 2008; Siciliano et al., 2018).

Although METH affects multiple systems throughout the body, the CNS is most notoriously linked to METH use disorder. METH intake alters cognitive systems by inducing feelings of euphoria and wakefulness directly through altered dopaminergic signaling. As METH exerts many effects through DAT, dopaminergic neurons are the primary source of DAT within the CNS, making dopaminergic neurons especially vulnerable. METH users exhibit depleted striatal dopamine levels (Wagner et al., 1980), reduced striatal DAT levels (Volkow et al., 2001c), and dopamine-associated cognitive dysfunctions (Paulus et al., 2002; McCann et al., 2008). Furthermore, repeated or long-term abuse of METH leads to addiction (Meade et al., 2015), memory deficits (Reichel et al., 2011; Fitzpatrick et al., 2020), paranoia (Leamon et al., 2010), and increases the likelihood of dopaminergic neurodegenerative disease such as Parkinson disease (Callaghan et al., 2012; Lappin et al., 2018). Many of these effects persist even in prolonged abstinence (McCann et al., 1998; Volkow et al., 2001b). Specifically, METH damages dopaminergic neurons by inducing oxidative stress (Cubells et al., 1994), DNA damage (Cadet et al., 1997a; Deng et al., 2001; Cadet et al., 2002), excitotoxicity, excitability (Abekawa et al., 1994; Battaglia et al., 2002; Branch and Beckstead, 2012; Lin et al., 2016), and activation of apoptotic pathways (Cadet et al., 1997b; Deng et al., 2002; Larsen et al., 2002). Although dopaminergic neurons are the primary direct target of METH in the CNS, METH use interferes with multiple brain regions, nondopaminergic neurons, and non-neuronal cells.

2.5 Other Cellular Targets of METH in the CNS

2.5.1 Nonmonoaminergic Neurons. In vivo microdialysis in animal studies reveals that METH injections also induce glutamate efflux (Stephans and Yamamoto, 1995). Glutamate release could subsequently activate N-methyl-D-aspartate (NMDA) receptor and nitric oxide synthase. Indeed, METH administration causes overexpression of neuronal nitric oxide synthase both in vivo and in vitro (Sheng et al., 1996; Deng and Cadet, 1999). Nitric oxide generation in the CNS after METH exposure may in turn augment dopamine release and production of reactive oxygen species and lead to neurotoxicity (Bowyer et al., 1995). In addition, pharmacological or genetic ablation of nitric oxide synthase could reduce methamphetamine-induced neurotoxicity and modulate METH-induced behavioral sensitization (Di Monte et al., 1996; Itzhak and Ali, 1996; Itzhak, 1997). As a corollary, pretreatment with NMDA receptor antagonist MK-801 also suppressed the behavior sensitization effect of METH (Ohno and Watanabe, 1995). These studies highlight an essential role of glutamate and nitric oxide in the toxic effects of methamphetamine in the brain.

Although METH directly targets dopaminergic neurons, dysregulated spatial-temporal dopamine signaling affects nondopaminergic neurons in multiple brain regions. Dopaminergic neurons project throughout the brain, providing input to local neurons and distal regions. Consequently, METH exposure alters both nondopaminergic neuronal networks (Volkow and Morales, 2015; Miller et al., 2019) as well as target regions, such as the GABAergic medium spiny neurons of the striatum (Volkow and Morales, 2015) and corticostriatal synapses (Bamford et al., 2008). In addition to METH-induced striatal dysregulation, both the hippocampus (Thompson et al., 2004; Swant et al., 2010; North et al., 2013; Dean et al., 2015) and cortex (Volkow et al., 2001a; Thompson et al., 2004; Kohno et al., 2014) exhibit deteriorated neural signaling, structural abnormalities, and functional connectivity. In sum, METH dysregulates the activity of both dopaminergic and nondopaminergic neurons and affects multiple brain regions (Volkow and Morales, 2015). However, METH dysregulation extends beyond neural cell types within the CNS.

2.5.2 Microglia. The two principal homeostatic regulators and neural protectors in the CNS, the specialized phagocytic cells, microglia, and the abundant astrocytes, also suffer the consequences of METH abuse. Microglia rapidly respond to homeostatic disturbances and neurotoxicity and are thus referred to as "sensors of pathology" (Shaerzadeh et al., 2018) and specifically sense dopamine neurotransmission through dopamine receptors (Kettenmann et al., 2011). High doses of METH promote microglial activation (Thomas et al., 2004; Fantegrossi et al., 2008). Surprisingly, microglial activation can occur before the onset of pathology (LaVoie et al., 2004), reinforcing the notion of their sensitivity to homeostatic disturbances, such as neuronal loss (Miller et al., 2018). Similarly, in METH users, microglia are involved in METH-induced wakefulness (Wisor et al., 2011). Despite responding to METH-induced dyshomeostasis, microglia are also susceptible to damage by METH. Human and mouse microglial cell lines exhibit increased mitochondrial apoptotic pathway markers (Sharikova et al., 2018) and the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway cell death pathway (Coelho-Santos et al., 2012) after METH exposure. METH reduces the distribution and expression of toll-like receptor (TLR) 4 on the surface of microglia after exposure to bacterial lipopolysaccharide (LPS) (Vargas et al., 2020). In addition, METH dysregulates the TLR4/MD2 complex signaling pathways, alters the activation of NF-κB, and lowers the synthesis of proinflammatory cytokines by microglia after LPS stimulation. Notably, microglial cells treated with METH and sensitized with LPS showed significant cellular morphologic alterations, including enlarged nuclei and ruffled surface. Furthermore, microglia have been implicated in tolerance to METH (Thomas and Kuhn, 2005), albeit with less-understood mechanisms (Shaerzadeh et al., 2018).

2.5.3 Astrocytes. Like microglia, astrocytes sense neural activity, modulate homeostasis (Schipke and Kettenmann, 2004), and participate in METH use disorder (Narita et al., 2008). In adult animals, METH exposure often leads to loss of TH-positive terminals and increased glial fibrillary acidic protein (GFAP)–containing astrocytes in the striatum (Hess et al., 1990; Broening et al., 1997). De Vito and Wagner (1989) initially hypothesized that loss of dopamine terminals increases the oxidation of dopamine and forms free radicals, leading to astrogliosis. However, Pu and Vorhees (1993) later observed that upregulation of GFAP–containing astrocyte could occur in the absence of depletion of TH-positive terminals after METH exposure in younger animals, suggesting METH could have a direct effect on astrocytes. Indeed, acute exposure to METH in primary cortical astrocytes induces oxidative stress (Lau et al., 2000) and leads to profound changes in the transcriptional signature (Bortell et al., 2017). Some of the most enriched pathways include upregulation of MAP2K5 gene clusters, which contributes to neuroprotection of dopaminergic neurons in response to oxidative stress (Cavanaugh et al., 2006) and upregulation of IL2RG, Antigen peptide transporter 2 (TAP2), and IL1RN, which promote inflammatory responses.

Astrocytes regulate extrasynaptic glutamate tone via transporter-mediated uptake and efflux (Anderson and Swanson, 2000). In addition to the dopamine system, METH also alters glutamatergic transmission in the corticostriatal pathway (Schwendt et al., 2012; Parsegian and See, 2014). Astrocytes express functional TAAR1, a primary METH target. Concomitant exposure to METH and HIV-1 significantly increased TAAR1 mRNA level and reduced glutamate clearance (Cisneros and Ghorpade, 2014). Surprisingly, METH self-administration does not influence GLT1 expression or glutamate reuptake in nucleus accumbens core (Sidiropoulou et al., 2001; Siemsen et al., 2019). This observation contrasts with cocaine self-administration, which promptly reduced GLT-1 expression and glutamate uptake (Knackstedt et al., 2010). However, METH self-administration decreased contacts between astrocytes and presynaptic neurons (Siemsen et al., 2019), possibly inducing connexin internalization in astrocytes and reducing gap junction communication between astrocytes and neurons (Castellano et al., 2016). Glutamatergic excitability in the corticostriatal pathway hypothetically underlies relapse in drug abuse (Ernst and Chang, 2008), and astrocytes could be a potential therapeutic target. More research is needed to confirm the effect of METH and the mechanisms involved in astrocyte-mediated glutamate reuptake.

3. Effects of METH on Peripheral Host Immunity

The medical complications involved in dependence are likely due to accumulation of METH in most body organs. Previous work found that METH accumulates differentially in human body organs; concentrations are particularly high in the kidneys and lungs, whereas the stomach, pancreas, liver, and spleen were intermediate, and the brain and heart were notably lower than other tissues (Volkow et al., 2010). The use of METH impairs both innate and adaptive immunity (In et al., 2005). METH exposure modifies the cellular components of macrophages, granulocytes, dendritic cells (DCs), T cells, B cells, and natural killer (NK) cells, indicating that the mechanisms of immunosuppression are complex (Harms et al., 2012). In addition, infection with HIV (Ellis et al., 2003), hepatitis (Gonzales et al., 2006), tuberculosis (Mankatittham et al., 2009), and other transmissible diseases (Galindo et al., 2012) is exacerbated by METH use. Contaminated needles and syringes used to inject METH enable spread of infectious diseases to multiple users (Ellis et al., 2003). Here, we discuss up-to-date data on the negative effects of METH on peripheral host innate and adaptive immunity and highlight areas for future investigations.

3.1 Innate Immunity

3.1.1 Macrophages/Monocytes. Macrophages recognize immunoreactive IgG that accumulates in the amygdala and hippocampal pyramidal cell region of the mouse brain, resulting in intense degeneration due to rapid phagocytosis of neurons. A single injection of a physiologic dose (5 mg/kg) of the METH followed by bacterial LPS stimulation demonstrates rapid peripheral migration of these leukocytes to the CNS of C57BL/6 mice (Salamanca et al., 2015). METH enables macrophage polarization from M0 to M1. It augments the production of nitric oxide and proinflammatory cytokines. Particularly, METH treatment increases tumor necrosis factor (TNF)-α, IL-12, and IL-1β, whereas anti-inflammatory cytokine IL-10 release decreases in coculture with neurons, which intensify the neurotoxic effects (Li et al., 2018). METH users suffer from hyperthermia (body temperature $>40.5^{\circ}$C), resulting in BBB permeability (Bowyer and Ali, 2006). METH modifies macrophage mitochondrial function and temperature-associated signaling pathways and increases their production of reactive oxygen species (ROS) (Sanchez-Alavez et al., 2020). These data suggest that METH-exposed peripheral macrophages mediate the amplification of neuronal toxicity and degeneration.

Microbial CNS translocation and monocyte activation predict mortality in METH users with treated HIV (Carrico et al., 2018). METH enhances HIV infection of macrophages, acts as a cofactor in the pathogenesis of the virus by being a primary source, and accelerates the progression of AIDS in HIV-infected users (Liang et al., 2008). METH use downregulates TLR-9 expression (Cen et al., 2013; Burns and Ciborowski, 2016) and impairs intracellular innate antiviral type I interferon (IFN) mechanisms in macrophages, contributing to phagocytic cell susceptibility to HIV infection (Wang et al., 2012). Macrophages exposed to METH and infected with HIV gp-120 mediate the synthesis of matrix metalloproteinase (MMP)-9 after LPS challenge. MMP-9 is responsible for the remodeling of the extracellular environment facilitating the migration of monocytes/macrophages to the CNS (Reynolds et al., 2011). Cultures of monocytes incubated with METH and HIV-Tat promote the release of the MMP activator urokinase plasminogen activator, which may contribute to CNS inflammation and neuroAIDS by stimulating the activation of matrix-degrading proteinases through Gi/Go-coupled signaling (Conant et al., 2004). METH stimulates the production of dopamine in the CNS, and this neurotransmitter increases the infection of macrophages with HIV by upregulation of the virus coreceptor chemokine receptor type 5 (CCR5) regardless of the initial viral load (Gaskill et al., 2014; Basova et al., 2018). The effects of METH on the synthesis of dopamine in the CNS, HIV neuropathogenesis, and immunomodulation and how all these factors may contribute to neuroinflammation and neuronal

toxicity/degeneration need further elucidation to manage the complexity of substance abuse and AIDS.

Macrophages are essential for modulating the effector function of neutrophils. METH intake by mice substantially increases the presence of macrophages in necrotic spleens, and tissue injury is associated with increased quantities of proinflammatory cytokines, IFN-γ, TNF-α, IL-6, IL-12, and ROS (Peerzada et al., 2013). Reduced number of macrophages in the liver of METH-treated mice resulted in hepatocellular atrophy likely due to abundant recruitment of neutrophils to hepatic tissue, releasing elevated levels of ROS and causing extensive tissue damage (Peerzada et al., 2013). In human blood and murine organs, observed levels of METH were found to cause apoptotic death in macrophages, causing users to be more susceptible to infectious disease (Aslanyan et al., 2019). METH can exacerbate hepatitis C virus infection and replication in human hepatocytes (Ye et al., 2008) because users show low numbers of macrophages and a mixed Th1-Th2 phenotype immune response (Peerzada et al., 2013). METH may reduce the macrophage response, which may increase users' susceptibility to disease and contribute to severe medical conditions, such as acquisition of blood-borne diseases.

METH also modifies macrophage antimicrobial functions, such as nitric oxide and TNF-α production (In et al., 2004). Acidic organelles within macrophages are alkalized by METH, which inhibits phagocytosis and killing of major AIDS-associated yeast-like fungal pathogens, *Candida albicans*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* (Tallóczy et al., 2008; Martinez et al., 2009; Patel et al., 2013). For instance, METH-mediated immunosuppression during histoplasmosis is characterized by altered cytokine secretion in the lungs of infected mice, abnormal processing of *H. capsulatum* within macrophages, and Macrophage-1 antigen (MAC-1) receptor immobilization on the macrophage surface, which participates in phagocytosis (Martinez et al., 2009). Incubation of macrophages with METH increases the MYD88-dependent TLR4 pathway and decreases macrophage phagocytic capacity (Pramanik et al., 2020). Activation of TLR4 by METH after TLR4 binds to Myeloid Differentiation factor 2 (MD2), its coreceptor, exacerbates neuroinflammation (Wang et al., 2019). METH was found to impair complex signaling pathways, such as TLR4/MD2, activation of NF-κB, and proinflammatory mediator production in microglial cell lines in context of LPS stimulation (Vargas et al., 2020). Similarly, dysregulation of antigen presentation and diminished processing capacity of macrophages have been observed during METH exposure (Harms et al., 2012). In tissue culture, macrophages exposed to METH displayed increases in TNF-α levels without increases in IL-1β and IL-8 in addition to TNF-α upon LPS stimulation (Liu et al., 2012). Macrophages excised from mice injected with METH demonstrate reduced skin tissue mobilization, phagocytosis, antigenic processing, nitric oxide production, and bacteria killing (Mihu et al., 2015). These alterations to the innate immunity by METH compromise inflammatory responses and the microbicidal functions of these phagocytic cells, making users prone to infection.

IgM induces macrophage effector responses against opportunistic pathogens in the context of METH abuse. IgM and complement promote phagocytosis and the microbicidal functions of macrophages against *C. neoformans* in the presence of the drug by upregulating the actin polymerization regulator protein GTPase-RhoA and complement receptor 3 expression on their surface, respectively (Aslanyan et al., 2017). Cryptococci incubated with IgM, complement, and METH exhibited more cells per aggregate, a conceivable justification for their more significant ingestion by phagocytes. IgM augmented fungicidal action by macrophages by preventing the alkalization of the phagosome and inducing intracellular nitric oxide synthesis. In contrast, METH inhibits IgG1-mediated phagocytosis of *C. neoformans* by macrophages and microglia, likely because of lowered expression of membrane-bound Fcγ receptors (Aslanyan et al., 2019). Nitric oxide production by macrophages during interactions with fungi was associated with diminished amounts of TNF-α. The conflicting results obtained in these studies suggest that investigating the role of METH on the molecular and cellular immunity of users and their susceptibility to acquiring infectious diseases would provide significant insight.

3.1.2 Granulocytes. The effect of METH on granulocytes is limited, although these leukocytes are highly associated with tissue damage if they are not cleared quickly. Neutrophils are recruited to the injury site within minutes after infection or trauma and are the hallmark of acute inflammation. METH impairs human neutrophil function (Mihu et al., 2015). This recreational drug has a detrimental impact on neutrophil migration, phagocytosis, respiratory burst, and killing of bacteria in a mouse model of cutaneous wound infection (Mihu et al., 2015). Mice injected with METH for 21 days had significant neutrophil infiltration in the spleen and liver, resulting in necrosis and hepatocellular atrophy (Peerzada et al., 2013), respectively, likely associated with increased formation of free radicals (Wells et al., 2008). Furthermore, rats chronically treated with METH showed severe regional hemorrhage, partial acinal cell necrosis, acinal cells destruction, abundant neutrophil infiltration, interstitial vessel edema and dilation, and pancreatic fatty cell invasion (Ito et al., 1997). In this regard, a postmortem examination of a 53-year-old man whose death was certified as METH toxicity evinced diverticulum of the duodenum and neutrophilic infiltrate (Sakry and Kemp, 2020). Neutrophil involvement in METH-mediated acute kidney injury, a common condition observed in intoxication, is observed in approximately 10% of the cases (Isoardi et al., 2020). In addition, acute METH administration and LPS challenge stimulate the infiltration of macrophages and neutrophils into the CNS, which may have significant implications in users' neurotoxicity (DiCaro et al., 2019).

In allergic inflammation, basophils, mast cells, and eosinophils are primary effector cells, and in innate and adaptive immunity. Chronic METH use increases the risk of cardiovascular (Islam et al., 1995) and hepatic (Maruta et al., 1997) lesions characterized by eosinophilic degeneration and disarray. METH contaminated with lead and intravenously administered by users interferes with liver function, lowers hematocrit values, and induces basophilic stippling of red blood cells (Allcott et al., 1987). Basophilic stippling observed through peripheral blood smear of erythrocytes indicates disturbed erythropoiesis and is characterized by the presence of numerous basophilic granules that are distributed through the cytoplasm. Additionally, METH regulates cytokine production by mast cells in LPS-treated mice via the dopamine-3 receptor (Xue et al., 2015). In mouse bone marrow, mast cell dopamine-3 receptors regulate TLR4 expression and also regulate mitogen-activated protein kinase (MAPK) and NF-κB signaling molecules induced by coexposure of METH and LPS (Xue et al., 2016). METH also impairs the activation of mast cells and cytokine production in the murine

intestine after sensitization with LPS (Xue et al., 2018). Although the presence of granulocytes may serve as markers for METH-associated complications, additional studies are required to understand their involvement and organ specificity in the setting of drug abuse.

3.1.3 Dendritic Cells. DCs are antigen-presenting cells that serve to present antigens to both innate and adaptive immune cells. DCs are front-line defenders against HIV and associated infections. Physiologic METH doses decrease DCs in mice after a 2-week injection regimen (Harms et al., 2012). DCs harbor HIV while facilitating the infection of T cells. METH enhances HIV replication in immature DCs. Additionally, proteins, such as Chemokine receptor 3 (CXCR3), galectin-1, peroxiredoxin, procathepsin B, and protein disulfide isomerase, are regulated by METH exposure (Reynolds et al., 2007). This substance of abuse also upregulates the expression of Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) on the surface of mature DCs (Nair et al., 2006; Nair and Saiyed, 2011). DCs treated with METH display differential expression of genes associated with HIV pathogenesis, including chemokine regulation, cytokinesis, apoptosis, cell cycle regulation and signal transduction mechanisms (Mahajan et al., 2006). Besides, METH enhances HIV infection in association with increments in the expression of coreceptors CXCR4 and CCR 5, which are mediated by upregulation of dopamine-2 receptors, downregulation of extracellular signal–regulated kinase 2 (ERK2), and the upregulation of p38 mitogen-activated protein kinase (MAPK) (Nair et al., 2009). METH also reduces the process of phagocytosis, collapses the acidic pH of phagolysosomes, and inhibits antigen presentation to splenic T cells by DCs (Tallóczy et al., 2008). Accumulating evidence indicates that METH exerts immunosuppressive effects on DCs, exacerbating AIDS pathology, and increasing the risk of users acquiring coinfections.

3.1.4 Natural Killer Cells. NK cells are cytotoxic lymphoid cells critical to the innate immunity in eliminating cancerous and virally infected cells without the assistance of antibodies or Major histocompatibility complex (MHC) molecules. Available data indicate the existence of biologic sex differences on the effect of METH in the response of NK cells. For instance, female cynomolgus monkeys injected with a single dose of 3 mg/kg of METH show elevated activity of NK cells after 6 hours. However, these cytotoxic lymphocytes reduce by 50% 24 hours postinjection compared with control animals, and this time interval variation is related to cortisone levels (Saito et al., 2006). Similarly, single and repeated injections of 5 mg/kg of METH decreased splenic NK cells and metabolic activity, especially in female mice (Saito et al., 2008). However, METH does not alter the blood viral load in simian immunodeficiency virus–infected monkeys, but this psychostimulant increases brain viral load while mediating the activation of NK cells and their production of TNF-α and IFN-γ (Marcondes et al., 2010). Additional studies investigating the impact of sex differences or viral infection on NK cell activation in METH users are necessary.

3.2 Adaptive Immunity

3.2.1 T Cells. T cells are important in coordinating immune responses because of their predictable activation and replication cycles and association with other adaptive immune responses (Anderton, 2006). The fundamental mechanisms defining the relationship between cells of the adaptive immune system and METH are presently limited. Nevertheless, the data strongly suggest that METH produces negative effects on adaptive immune responses, increasing host vulnerability to progressive diseases, in particular HIV (In et al., 2005; Martinez et al., 2009). METH causes tissue injury, induces apoptosis, and affects both cytotoxic T-cell and helper T-cell recruitment in mice undergoing immune challenge (Hernandez-Santini et al., 2021). Surface expression and distribution of CD3 and CD28 in human Jurkat T cells are diminished by METH (Hernandez-Santini et al., 2021). In addition, METH decreases IL-2 production in Jurkat T cells, indicating suppression of activation and proliferation of T lymphocytes (Hernandez-Santini et al., 2021).

Rodent models demonstrate that METH alters cell distributions in both thymus and spleen and modulates peripheral T-cell populations (In et al., 2005; Hernandez-Santini et al., 2021). High-dose METH administration induces apoptosis in the rat thymic and splenic lymphocytes and produces acute immunosuppression, potentially explaining why METH users experience higher rates of infection (Harms et al., 2012; Peerzada et al., 2013). For example, murine studies demonstrate that METH shifts cytokine response in retroviral infections (Yu et al., 2002; Liang et al., 2008), alters immune cell gene expression (Mahajan et al., 2006), and compromises thymic CD4+/CD8+ T-cell ratios (Yu et al., 2002; In et al., 2005). METH lowers T-cell recruitment into pulmonary tissue (Hernandez-Santini et al., 2021), interfering with T-cell proliferation and decreasing the ability of these lymphocytes to sustain a protective immune response against pathogens of the respiratory tract (Martinez et al., 2009). Likewise, METH-treated mice show elevated early IL-6 and IL-10 levels in tissue homogenates, which could imply the development of a maladaptive Th2 response against pathogenic microbes in the respiratory tract despite Th1 cytokine production (Peerzada et al., 2013). For example, individuals who are HIV-infected and abusing METH in Thailand showed a high risk of coinfection with *Mycobacterium tuberculosis* and progression of extrapulmonary tuberculosis due to low CD4+ T-cell counts (Mankatittham et al., 2009). Moreover, METH use interferes with the benefits of antiretroviral therapy in HIV-infected individuals by increasing their viral load compared with nonusers (Carrico et al., 2019).

An alternate explanation for compromised T-cell function involves that METH alters oxidative stress responses. T lymphocytes properties are significantly altered by oxidative stress. In response to antigenic stimulation during oxidative stress, T cells exhibit signal transduction suppression, reduced transcription factor activity, and diminished secretion of cytokine in various model systems (Flora et al., 2003; Shah et al., 2012). The capability of reactive oxidative free radicals to affect T-cell function has been demonstrated in humans under various pathologies, particularly AIDS, in which oxidative stress can impair the host capacity to control retroviral replication (Potula et al., 2010).

Interestingly, METH alters intracellular calcium utilization in T lymphocytes followed by the production of oxidative free radicals that initiate mitochondrial damage and inhibit T-cell function (Potula et al., 2010). Mitochondria are a source of intracellular ROS and ATP, both of which are regulated by calcium. T-cell incubation with METH increases cytosolic calcium, though, and leads to the saturation of the electron

transport chain, contributing to significant synthesis of oxidative free radicals. This cascade eventually results in oxidative alteration of proteins, reduced ATP levels, and mitochondrial dysfunction in T cells (Potula et al., 2010). A compensatory downregulation of mitochondrial proteins from chronic METH treatment can provoke a durable imbalance in cellular redox, diminishing T cells' capacity to react to and control opportunistic pathogens (Potula et al., 2010; Chandramani Shivalingappa et al., 2012; Martins et al., 2013).

3.2.2 B Cells. METH accumulates in organs (Shiue et al., 1993; Fowler et al., 2007) and induces apoptosis (Iwasa et al., 1996) in the spleen, the organ responsible for humoral or antibody-mediated immunity through resident B cells. B cells perform multiple functions, such as antigen presentation, plasma cell differentiation, antibody production and release, and development of immune memory. METH alters blood and tissue antibody production during infection or antigenic challenge in rodents (In et al., 2005; Wey et al., 2008; Martinez et al., 2009). Mice injected with METH and infected with *H. capsulatum* have shown increased IgG2b levels in lethal histoplasmosis (Martinez et al., 2009). Chronic B-cell activation, excessive systemic inflammation, and increased HIV exposure accompany high IgG3 production in users that inject the drugs (Piepenbrink et al., 2016). METH attenuates the production of ovalbumin (the main component of egg white)-specific class of antibodies, including IgM, IgG1, and IgG2a in mice (Wey et al., 2008). The drug also reduces the production of IL-4 and IFN-γ in splenocytes isolated from METH-treated animals and exposed to ovalbumin ex vivo (Wey et al., 2008). The activation of B lymphocytes, which involves T cell–dependent and T cell–independent antigen, was recently explored in C57BL/6 mice to determine the effects of METH on antibody-mediated immunity to ovalbumin (T cell–dependent) and LPS (T cell–independent) (Mitha et al., 2021). Pulmonary and splenic tissue infiltration by B cells was enhanced by METH 7 days post–antigenic challenge. Considerable recruitment of B cells into pulmonary splenic tissues is not related to interaction with the antigen, thereby METH may function as the antigen. In support of this hypothesis, multiple studies have generated METH-specific antibodies and may provide a viable therapeutic agent to treat addiction to METH (Owens et al., 2011). Similarly, chronic use of METH exhibit increased B-cell infiltration and autoantibodies, leading to development of autoimmunity (Simonovska et al., 2016). For example, IgM and C3 complement accumulation in the renal system produce chronic kidney disease in long-term METH users (Jones and Rayner, 2015). Deposition of METH in lung and spleen tissue may be responsible for prolonged B-cell recruitment and elevated vulnerability of other immune cell subtypes to METH. Furthermore, METH may severely disrupt IgM distribution and expression on the B-cell surface, thereby negatively affecting the antibody-mediated immune response. Future studies should interrogate the extent to which METH dysregulates the relationship between autoreactive antibodies and organ injury as well as B-cell memory.

4. Conclusion and Future Perspectives

METH use is a challenge worldwide, and its impact on human health has recently begun to become elucidated. Although most of these studies have focused on the behavioral modifications this recreational drug causes in users, limited data exist describing its effects on peripheral immunity or the association between the CNS and peripheral inflammatory responses. Emerging evidence indicates a causal connection between METH and compromised immunity in users, animals, and mammalian cells. METH also destroys dopamine receptors in neurons, making chronic users insensitive to emotions or pleasure because of permanent defects to the reward system. However, the role of METH on peripheral cells carrying dopamine receptors has not been investigated. Hence, elucidating the specific mechanisms of METH abuse and CNS/peripheral immunity will involve using interdisciplinary techniques and appropriate animal and cellular systems to recreate the effects of this drug in human users.

METH use causes deleterious alterations to the CNS homeostasis. Brain damage has been associated with METH-induced hyperthermia (Marco et al., 2021) and oxidative stress (Kim et al., 2020), which are well known consequences of inflammation, suggesting that studies involving the peripheral-brain axis are imperative. For instance, T cells are particularly susceptible to METH (In et al., 2005; Potula et al., 2018), which may have potential implications in the modulation of the inflammatory response (Mata et al., 2015) in the CNS (Loftis and Janowsky, 2014) and peripheral organs, especially those in which METH accumulates for an extended time (Volkow et al., 2010). Thus, the identification of the underlying mechanisms by which METH affects innate and adaptive immunity will enhance the prospects of developing novel therapeutic and prophylactic interventions to manage the consequences of recreational METH use, possibly minimizing brain damage and addiction in chronic METH users. Although there is no medication available that counteracts the detrimental effects of METH, recent efforts have focused on the development of anti-METH immunotherapies, such as monoclonal antibodies and lipid-based vaccines, which act as pharmacokinetic antagonists, isolating METH and its metabolites from the CNS, diminishing the toxic effects of the drug (Peterson et al., 2014; Collins et al., 2016; Hambuchen et al., 2016). Similar approaches can be used to neutralize the effector functions of specific immune or resident cells and inflammatory mediators stimulated by METH that may cause alteration in behavior and tissues in humans. These existing challenges and potential goals are of considerable significance for multiple fields, including immunology, neuroscience, psychology, health care, and drug abuse.

Finally, METH abuse disorder is characterized by multisystem dysfunction within the CNS and peripheral targets. Current investigations are likely to be only the tip of the iceberg, such that numerous other diseases, especially neurodegenerative diseases, are likely to be significantly progressed and altered by METH use. Recent technical advances have enabled the tracking of neural activity in deep brain structures, particularly those rich in dopaminergic neurons, which are verified genetically (Mejias-Aponte et al., 2015; da Silva et al., 2018; Fernandes et al., 2020; Kremer et al., 2020), that are direct targets of METH in the CNS. Future work in these areas and those that receive input from or send projections to the ventral midbrain will elucidate many of the collective population properties that predispose and give rise to addiction or failures that lead to relapse. Furthermore, examination of brain regions and peripheral tissue types in acute ex vivo slice preparations or cultures of cell types of interest enable dissection of distinct intrinsic properties of these regions and how they

are affected by METH without confounding of extrinsic brain region input or ascending sensory signals (Miller et al., 2019, 2021).

METH likely affects multiple areas of the peripheral-brain axis and exerts dysregulation of a plethora of tissue types. As these separate areas become dysfunctions, untangling how these spiraling dysregulations affect each other, either compensatory or exacerbating, demonstrates the need for continued studies to understand the implications of METH addiction and immunity. Until the use of METH is severely reduced, the effects of METH on our society will be substantial.

Author Contributions

Wrote or contributed to the writing of the manuscript: Miller, Bu, Gopinath, Martinez, Khoshbouei.

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