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Neuroimmune Basis of Methamphetamine Toxicity

Jennifer M. Loftis^{*,†,‡,1} and Aaron Janowsky^{*,†,‡,§}

^{*}Research & Development Service, Portland VA Medical Center, Portland, Oregon, USA

[†]Department of Psychiatry, Oregon Health & Science University, School of Medicine, Portland, Oregon, USA

[‡]Methamphetamine Abuse Research Center, Oregon Health & Science University, Portland, Oregon, USA

[§]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon, USA

Abstract

Although it is not known which antigen-specific immune responses (or if antigen-specific immune responses) are relevant or required for methamphetamine's neurotoxic effects, it is apparent that methamphetamine exposure is associated with significant effects on adaptive and innate immunity. Alterations in lymphocyte activity and number, changes in cytokine signaling, impairments in phagocytic functions, and glial activation and gliosis have all been reported. These drug-induced changes in immune response, particularly within the CNS, are now thought to play a critical role in the addiction process for methamphetamine dependence as well as for other substance use disorders. In Section 2, methamphetamine's effects on glial cell (e.g., microglia and astrocytes) activity and inflammatory signaling cascades are summarized, including how alterations in immune cell function can induce the neurotoxic and addictive effects of methamphetamine. Section 2 also describes neurotransmitter involvement in the modulation of methamphetamine's inflammatory effects. Section 3 discusses the very recent use of pharmacological and genetic animal models which have helped elucidate the behavioral effects of methamphetamine's neurotoxic effects and the role of the immune system. Section 4 is focused on the effects of methamphetamine on blood–brain barrier integrity and associated immune consequences. Clinical considerations such as the combined effects of methamphetamine and HIV and/or HCV on brain structure and function are included in Section 4. Finally, in Section 5, immune-based treatment strategies are reviewed, with a focus on vaccine development, neuroimmune therapies, and other anti-inflammatory approaches.

1. INTRODUCTION

The toxic effects of methamphetamine have been recognized for decades. Only recently, however, the role of the immune system in methamphetamine's neurotoxic effects has been examined in detail. A number of molecular and cellular mechanisms are triggered following exposure of cells or animals to methamphetamine, and the cascade of events from exposure to neurotoxicity involves cellular components from receptors to immune system activation and inflammation, to energy metabolism. The term "neurotoxicity" can be ambiguous due to the array of methods and perspectives that are used to address methamphetamine's effects. Here, the term is used to describe a condition that follows exposure to methamphetamine, which initiates a cascade of events resulting in altered behavior or cellular function *in the absence of drug*. This distinguishes neurotoxicity from intoxication and effects that occur simultaneously with drug exposure. This chapter reviews some of the more recent findings related to the mechanisms involved in the neuroimmune basis for methamphetamine toxicity.

2. PART 1

2.1. Microglia and astrocytes

Methamphetamine affects glial cell (e.g., microglia and astrocytes) activity, and glial cell activity can modulate the neurotoxic and addictive effects of methamphetamine. Microglia are the major antigen-presenting cells in brain and when activated, they secrete an array of signaling molecules (e.g., proinflammatory cytokines and chemokines) that can cause neuronal damage. Astrocytes are the most numerous and diverse glial cells in the CNS, with a variety of functions including, but not limited to, maintenance of brain homeostasis, storage and distribution of energy substrates, synaptogenesis, and brain defense. Like microglia, astrocytes can also secrete a number of signaling molecules that play a putative role in methamphetamine-induced neurotoxicity, such as pro- and anti-inflammatory cytokines including interleukins (ILs), interferons (IFNs), and tumor necrosis factors (TNFs), as well as chemokines (e.g., macrophage inflammatory proteins and monocyte chemoattractant proteins) (Whitney, Eidem, Peng, Huang, & Zheng, 2009). Activation of microglia and astrocytes are normal compensatory reactions to brain injury, but excess neuroinflammation can lead to further brain damage. Indeed, repeated or neurotoxic (i.e., high dose) methamphetamine exposure induces alterations in glial cell functions that contribute to a complex cascade of events, leading to neuroinflammation, neuronal damage, and behavioral impairments (Fig. 7.1). Table 7.1 provides a review of studies that describe acute and chronic effects of methamphetamine exposure on peripheral and central immune function.

2.1.1 Microglia—The role of microglia in mediating methamphetamine's effects has been appreciated since the late 1990s when it was reported that following methamphetamine exposure microglia participate more in necrosis–phagocytosis of neuronal debris than in restoration of neuronal processes (Escubedo et al., 1998). Subsequently, glial cell activation associated with methamphetamine exposure has been well documented with significant contributions made from a number of laboratories (e.g., Asanuma, Miyazaki, Higashi, Tsuji, & Ogawa, 2004; Fantegrossi et al., 2008; Guilarte, Nihei, McGlothan, & Howard, 2003;

Hebert & O'Callaghan, 2000; Thomas, Francescutti-Verbeem, Liu, & Kuhn, 2004; Thomas, Walker, Benjamins, Geddes, & Kuhn, 2004). Microglial activation appears to be an early step in the process of methamphetamine-induced neurotoxicity, especially following exposure to high doses of methamphetamine (Thomas, Francescutti-Verbeem, & Kuhn, 2008b; Thomas, Francescutti-Verbeem, et al., 2004; Thomas, Walker, et al., 2004). Although, in some brain regions (e.g., caudate–putamen) microglial activation may not occur until 1 day or more after exposure to high-dose methamphetamine (Bowyer, Robinson, Ali, & Schmued, 2008). Neurotoxic regimens of methamphetamine exposure result in reactive microglia and increased inflammatory gene expression, particularly in striatum—but evidence of methamphetamine-induced microgliosis has also been observed in other brain regions [e.g., cerebellum and hippocampus (Escubedo et al., 1998); somatosensory and piriform cortices and periaqueductal gray (LaVoie, Card, & Hastings, 2004)].

Methamphetamine activates microglia in a dose-dependent manner and via a time course that is generally concurrent with damage to the dopaminergic system (Thomas, Walker, et al., 2004). As a possible target for methamphetamine's effects on microglia, the microglial-specific fractalkine receptor (CX3CR1) [a mediator of 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP)-induced neurodegeneration of dopamine neurons (Cardona et al., 2006)] was evaluated for a role in methamphetamine-induced microglial activation and neurotoxicity. Using mice in which the *CX3CR1* gene was deleted (*CX3CR1* knock-out mice), Thomas, Francescutti-Verbeem, and Kuhn (2008a) determined that CX3CR1 signaling does not modulate methamphetamine-induced neurotoxicity or microglial activation. Specifically, methamphetamine exposure had similar effects in both the *CX3CR1* knock-out mice and in the wild-type control mice (e.g., microglial activation, increases in body temperature, and reductions in dopamine) (Thomas et al., 2008a).

Once activated, microglia contribute to and potentially perpetuate methamphetamine-induced neuroinflammation and neurodegeneration through inflammatory processes, including the production of proinflammatory cytokines (e.g., TNF- α , IL-1 β , and IL-6), or through oxidative mechanisms (Clark, Wiley, & Bradberry, 2013; Yamamoto & Raudensky, 2008) (Fig. 7.1). For example, the excess dopamine resulting from methamphetamine exposure produces dopamine quinones (DAQs) which can activate microglia. Kuhn, Francescutti-Verbeem, and Thomas (2006) demonstrated that DAQs cause time-dependent activation of cultured microglial cells. Importantly, microarray analysis of the effects of DAQs on microglial gene expression indicated that many of the genes differentially regulated by DAQs were those associated with inflammation and neurotoxicity, including cytokines, chemokines, and prostaglandins. Thus, following methamphetamine exposure, the generation of DAQs may induce early activation of microglial cells and increased expression of inflammatory signaling cascades. Of note, one study reported a global pattern of microglial activation and microgliosis in individuals with a history of methamphetamine addiction, which appeared to persist for at least 2 years into abstinence (Sekine et al., 2008).

2.1.2 Astrocytes—For astrocytes, methamphetamine's effects are mediated, in part, by changes in: (1) transcription factor pathways, (2) astrocytic cytokine receptors, (3) excitatory amino acid transporters (EAATs), and (4) glucose uptake mechanisms (Abdul Muneer,

Alikunju, Szlachetka, & Haorah, 2011). Methamphetamine can activate astrocytes and induce astrogliosis (e.g., in striatum) via activation of the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling cascade (Hebert & O'Callaghan, 2000; Robson et al., 2014)—a pathway that is similarly thought to contribute to astrogliosis following exposure to other neurotoxic substances (MPTP) (e.g., Sriram, Benkovic, Hebert, Miller, & O'Callaghan, 2004) and one that may promote the persistence of reactive gliosis following toxicant exposure (Hebert & O'Callaghan, 2000). For example, Friend and Keefe (2013) reported that astrocytes (but not microglia) remain reactive for at least 30 days following methamphetamine exposure. Consistent with a role for inflammatory signaling in maintaining methamphetamine's activation of astrocytes, mice treated with a neurotoxic regimen of methamphetamine (i.e., four doses of 5 mg/kg administered every 2 h) show significant increases in oncostatin M receptor expression (an astrocytic receptor, Tamura, Morikawa, & Senba, 2003, for the proinflammatory IL-6-type cytokine oncostatin M) (Robson et al., 2014). Methamphetamine also alters EAATs on astrocytes [particularly type 2, EAAT-2 (reviewed in Cisneros & Ghorpade, 2012)] putatively via the production of reactive oxygen species (ROS) (Vaarmann, Gandhi, & Abramov, 2010). These changes in transporter expression could compromise the ability of EAATs to remove extracellular glutamate from the synapse (Cisneros & Ghorpade, 2012; Lau & Tymianski, 2010), thus contributing to methamphetamine-induced excitotoxicity and neurotoxic immune activation [a.k.a. inflammotoxicity (Wilhelm, Hashimoto, Roberts, & Loftis, 2014)].

2.2. Inflammatory signaling

A growing literature demonstrates that methamphetamine exposure and activation of microglia and astrocytes (as well as other cell types) alters peripheral and central immune functions (In, Son, Rhee, & Pyo, 2005; In et al., 2004; Liang et al., 2008; Martinez et al., 2009; Ye et al., 2008) and that immune factors such as cytokines (e.g., IL-1 β , IL-6, and TNF- α), chemokines [e.g., monocyte chemoattractant protein-1 (MCP-1)], and adhesion molecules play a critical role in the development and persistence of methamphetamine-induced neuronal injury and neuropsychiatric impairments (Clark et al., 2013; Loftis et al., 2011; Yamamoto, Moszczynska, & Gudelsky, 2010; Yamamoto & Raudensky, 2008). In an astrocytic cell line, methamphetamine exposure for 3 days increases IL-6 and IL-8 RNA levels by 4.6 ± 0.2 fold and 3.5 ± 0.2 fold, respectively (Shah et al., 2012). Consistent with these findings, mice treated with methamphetamine show brain region-specific increases in the expression of proinflammatory cytokines (e.g., IL-1 β) up to 3 weeks after methamphetamine exposure (Loftis et al., 2011). In a rigorous study designed to evaluate whether or not deletion of the TNF- α gene in mice affects addictive-like behavior, including methamphetamine self-administration, motivation to self-administer methamphetamine, and cue-induced reinstatement of methamphetamine-seeking behavior, Yan, Nitta, Koseki, Yamada, and Nabeshima (2012) measured methamphetamine self-administration and reinstatement of drug-seeking behavior in TNF- α knock-out and wild-type mice. The authors observed an upward shift of dose responses to methamphetamine self-administration under a fixed ratio schedule of reinforcement in the TNF- α knockout as compared with wild-type mice, indicating that mice lacking TNF- α administered more methamphetamine than controls. Similarly, TNF- α knock-out mice also had a higher breaking point under a progressive ratio schedule of reinforcement, suggesting that TNF- α can also influence

motivation to self-administer drug. Taken together, these findings demonstrate that TNF- α signaling affects methamphetamine self-administration and motivation to obtain the drug. However, TNF- α did not appear to contribute to methamphetamine-associated cue-induced relapsing behavior (Yan et al., 2012).

Interestingly, IFN- γ (another proinflammatory cytokine) injected systemically prior to repeated methamphetamine exposure protects against methamphetamine-induced neurotoxicity (as measured by a reduction in striatal dopamine transporters) and hyperthermia, putatively through intracerebralmolecular pathways (Hozumi et al., 2008). Thus, of the altered immune factors, some cytokines appear to facilitate or promote methamphetamine-induced toxicities but others may slow or prevent the development of adverse drug effects. Taken together, these observations describe a critical role for CNS immune signaling in methamphetamine neurotoxicity and dependence. More research is needed to elucidate the specific signaling pathways [e.g., STAT3, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (Wires et al., 2012)] and cell types (e.g., microglia, astrocytes, and vascular endothelial cells) that induce and perpetuate these neuroinflammatory processes—particularly because these immune effects can impact addictive and related behavioral responses.

2.3. Molecular/cellular: receptors and transporters

2.3.1 Neurotransmitter modulation of methamphetamine's inflammatory effects—Methamphetamine alters the disposition of a number of neurotransmitters and high doses cause reductions in a number of cell types, especially in the striatum. Loss of dopaminergic, GABAergic, and cholinergic cells has been described (Zhu, Xu, & Angulo, 2006). However, glial cells are also involved in neurotoxic reactions to methamphetamine, and receptors for neurotransmitters have been found on various cell types that are involved in immune response. Methamphetamine-induced alterations in neurotransmitter availability can affect receptor-mediated second messenger systems and downstream events inside the cell. Recent evidence for possible roles of methamphetamine in altering neurotransmitter-linked changes in intermediates of the immune response is described here.

As opposed to its indirect effects on neurotransmitter receptors via its actions as a serotonin, norepinephrine, dopamine, and vesicular monoamine (2) transporter substrate (Eshleman, Calligaro, & Eldefrawi, 1993; Sulzer et al., 1995; Wilhelm, Johnson, Lysko, Eshleman, & Janowsky, 2004), methamphetamine and its analogs, including methylenedioxymethamphetamine (MDMA), are direct agonists at trace amine associated receptor 1 (TAAR1). Endogenous agonists for the TAAR1 include tyramine and octopamine, as well as other neurotransmitter precursors and metabolites (Borowsky et al., 2001; Bunzow et al., 2001). TAAR1 mRNA and mRNA for other TAARs have been identified on mouse B and NK cells, and in stimulated human peripheral blood lymphocytes (Nelson, Tolbert, Singh, & Bost, 2007). In addition, TAAR1 protein has been characterized in rhesus monkey peripheral blood mononuclear cells (Panas et al., 2012). This latter report also characterized the effects of methamphetamine on phosphorylation of protein kinase A (PKA) and protein kinase C (PKC) activity in peripheral blood mononuclear cells as well as in rhesus monkey immortalized B lymphocytes. Generally, methamphetamine increased

expression of the phosphorylated enzymes in PHA-treated cells. TAAR1-mediated stimulation of PKA and PKC phosphorylation appears to be necessary but not sufficient, i.e., PHA is also required for phosphorylation. In fact, it appears that PHA is required to increase the expression of TAAR1, which precedes methamphetamine stimulation of TAAR1 and subsequent phosphorylation of PKA and PKC. The authors also reported methamphetamine-induced increases in nuclear factor of activated T cells, part of the calcium response pathway, and an increase in cyclic AMP-response element binding protein (CREB) pathway in rhesus monkey TAAR1-transfected cells. Thus, methamphetamine stimulation of TAAR1 in lymphocytes appears to play an important role in lymphocyte function preceding immune response. Babusyte, Kotthoff, Fiedler, and Krautwurst (2013) subsequently demonstrated that activation of T-cell and B-cell TAAR1 (and 2) by endogenous ligands such as phenethylamine results in altered cytokine expression. Although the effects of methamphetamine were not examined, similar results could be expected. Reports also indicate that malignant B cells, including a Burkitt's lymphoma cell line are sensitive to TAAR1 agonists, which reduce their viability (Wasik, Millan, Scanlan, & Barnes, 2012). Clearly, TAAR1 receptors on lymphocytes are involved in cell function and cellular response. However, it is not clear that TAAR1-mediated cellular mechanisms in neurons and lymphocytes are shared.

Glutamate receptors have also been implicated in the behavioral effects of methamphetamine (Achat-Mendes, Platt, & Spealman, 2012; Crawford, Roberts, & Beveridge, 2013; Herrold, Voigt, & Napier, 2013), and there are some data to indicate the role of specific glutamate receptors in neurotoxicity. Metabotropic glutamate receptor 5 (mGluR5) appears to play a role in the methamphetamine-induced change in immune response signaling. Shah et al. (2012) reported that exposure of the SVGA astrocyte cell line to methamphetamine caused a dose-dependent increase in mRNA and protein for the proinflammatory cytokines IL-6 and IL-8, as well as translocation of the nuclear subunit of NF κ B, and the effects are most likely due to activation of Akt/PI3K pathways. Importantly, the effects of methamphetamine on IL-6 and IL-8 expression were reduced in the presence of 2-methyl-6-(phenylethynyl)pyridine (MPEP), an mGluR5 antagonist. The authors proposed a model consistent with direct stimulation of mGluR5 by methamphetamine. Additional studies suggest that mGluR5 regulates methamphetamine-induced dopamine release and the neurotoxic effects of methamphetamine on dopaminergic neurons, as MPEP also blocks the reduction in dopamine that is caused by high-dose methamphetamine, as well as methamphetamine-induced dopamine release (Gołembowska, Konieczny, Wolfarth, & Ossowska, 2003).

The involvement of ionotropic *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtypes of glutamate receptors have also been implicated in methamphetamine-induced neurotoxicity by experimental results indicating that the NMDA receptor antagonist (dl)-amino-5-phosphonovaleric acid (AP5) or the AMPA receptor antagonist dinitroquinoxaline-2,3-dione (DNQX) prevent methamphetamine-induced c-fos expression and dopamine depletion, possibly as a result of reducing corticostriatal input (Gross, Duncker, & Marshall, 2011). Calcium release has been implicated in the mechanism of action of glutamate and

methamphetamine neurotoxicity: NMDA + methamphetamine-induced neurotoxicity could be reduced by exposure of hippocampal slices in culture to the endoplasmic reticulum-bound sigma-1 receptor antagonist BD1047 which is coupled to calcium-mediated signal cascades (Smith, Butler, & Prendergast, 2010). Thus, evidence suggests both direct and indirect roles for glutamate receptors in methamphetamine-induced neurotoxic events.

A number of reports implicate the $\alpha 7$ subtype of nicotinic cholinergic receptor in the neurotoxic effects of methamphetamine. In the rat, 6-hydroxydopamine model of Parkinson's disease, the $\alpha 7$ receptor agonist, 3-[(2,4-dimethoxy)benzylidene]-anabaseine dihydrochloride, reduces 6-hydroxydopamine-induced cell loss and the elevation of markers of neurotoxicity (Suzuki et al., 2013). The possibility that $\alpha 7$ receptors play a similar role in methamphetamine-induced neurotoxicity is supported by evidence that the $\alpha 7$ antagonist methyllycaconitine (MLA) prevents methamphetamine-induced neurotoxic events including decreases in cellular dopamine and in dopamine transporter expression, and methamphetamine-induced glutamate release (Northrop, Smith, Yamamoto, & Eyerman, 2011). The effect may be mediated by ROS, since MLA blocks methamphetamine-induced ROS production (Escubedo, Camarasa, Chipana, García-Ratés, & Pubill, 2009; Escubedo, Chipana, Pérez-Sánchez, Camarasa, & Pubill, 2005; Pubill et al., 2005). Therefore, the data support the hypothesis that methamphetamine indirectly causes release of the glutamate that is involved in methamphetamine-induced neurotoxicity. Although methamphetamine affects a number of receptors, including specific nicotinic cholinergic receptor subtypes, in its toxic effects, the role of muscarinic cholinergic receptors in methamphetamine's cellular effects has not been described in detail.

Methamphetamine is a substrate for the dopamine transporter and causes neurotransmitter release (Eshleman et al., 2013), which may trigger drug-induced changes in behavior, but may not exert its neurotoxic effects via direct interaction with dopamine receptors. However, chronic changes in neurotransmitter interactions with receptors that accompany drug abuse can alter cellular function, and lymphocytes express a number of receptors that might be affected by methamphetamine (see also Table 7.1). In Section 3.1, effects of methamphetamine on signaling systems in brain are discussed.

3. PART 2

3.1. Animal models

Behavioral effects of methamphetamine's neurotoxic effects and the role of the immune system have been characterized using pharmacological and genetic models. Many of the genetic models involve knock-out animals. For instance, dopamine D1 knock-out mice have less hyperthermia, gliosis, and inducible nitric oxide synthase in the striatum and less dopaminergic cell loss in the substantia nigra in response methamphetamine, as compared to wild-type control mice (Ares-Santos et al., 2012), and dopamine D2 receptor knock-out mice have reduced hyperthermia, loss of striatal dopaminergic markers, as well as a reduction in other markers of neurotoxicity (Granado, Ares-Santos, et al., 2011). Nrf2 is a neuroprotective gene that attenuates the effects of oxidative stress and is involved in innate immune response in the CNS. Nrf2 knock-out mice have an exaggerated response to methamphetamine, including increased glial activation, and expression of TNF- α and IL-15

(Granado, Lastres-Becker, et al., 2011). Prodynorphin-deficient mice were less sensitive to the dopamine depleting effects of methamphetamine as compared to wild-type mice. The mechanism for this effect may be via anti-inflammatory effects of dynorphin, which is found in very high concentrations in the nigrostriatal pathway (Wang et al., 2012). Likewise, protein kinase C δ knock-out animals have reduced lipid peroxidation, protein oxidation, and behavioral deficits in response to methamphetamine. These studies were corroborated using pharmacological interventions, which also indicate increased tyrosine hydroxylase phosphorylation in response to methamphetamine (Shin et al., 2011, 2012).

Using pharmacological manipulations to reduce serotonin, Thomas, Angoa Pérez, Francescutti-Verbeem, Shah, and Kuhn (2010) demonstrated that serotonin may not play an essential role in methamphetamine neurotoxicity (reductions in dopaminergic cell markers such as dopamine, tyrosine hydroxylase, and the dopamine transporter). Importantly, this study also demonstrated that hyperthermia is not a prerequisite for toxicity, since depletion of serotonin is associated with increased hyperthermia. In experiments connecting the pharmacological effects of methamphetamine to its immunological effects, Buchanan et al. (2010b) demonstrated that a high-dose methamphetamine regimen increased the CNS cytokine response to subsequent i.p. administration of LPS, and also activated microglia.

4. PART 3

4.1. Blood–brain barrier and clinical considerations

4.1.1 Blood–brain barrier—The blood–brain barrier (BBB) is comprised of endothelial cells that line brain capillaries and contribute to supplying the brain with nutrients, regulating the transport of essential molecules (e.g., glucose and amino acids) to the brain, and protecting neural tissue from toxic substances—functions that collectively serve to maintain a stable environment. The BBB endothelial cells are surrounded by astrocytic perivascular endfeet which release specific factors, including transforming growth factor- β (TGF- β) and glial-derived neurotrophic factor (GDNF), important for the development and function of the BBB. Continuous tight junctions between the BBB endothelial cells as well as metabolic barriers (e.g., enzymes, transport systems) regulate transport across the BBB (e.g., limit the diffusion of molecules across the BBB and control the entry of neurotransmitters into the brain) (Abbott, Rönnbäck, & Hansson, 2006). Disturbances of brain homeostasis as a result of BBB damage are evident in a number of pathological conditions such as stroke, multiple sclerosis, Alzheimer's disease, HIV, and substance use disorders (including methamphetamine dependence). Studies show that although the initial etiologies for BBB disruption are different among these pathologies, characteristic alterations and common intracellular pathways are involved. NF κ B activation and proinflammatory signaling [e.g., via IL-6 and matrix metalloproteinases] often mediate dysfunction of the BBB's structural and functional integrity (Abbott et al., 2006; Persidsky, Ramirez, Haorah, & Kanmogne, 2006). For example, proinflammatory cytokine-mediated release of matrix metalloproteinases (e.g., MMP-9) can increase BBB permeability by activating NF- κ B, regulating microfilament reorganization and reducing the expression of tight junction proteins (or redistributing tight junction proteins from the membrane to the

cytosol) (Aghajanian, Wittchen, Allingham, Garrett, & Burridge, 2008; Bogatcheva & Verin, 2008; Brown et al., 2003; Lu et al., 2009).

4.1.2 Methamphetamine exposure and BBB integrity—Psychostimulant exposure, and in particular methamphetamine abuse, is associated with disruption of the BBB (reviewed in Kousik et al., 2012) as well as with increased expression of proinflammatory factors. Pre-clinical *in vivo* studies and cultured human brain microvascular endothelial cell *in vitro* experiments show that methamphetamine contributes to inflammation-induced BBB dysfunction in a dose- and time-dependent manner by activating NF- κ B, upregulating inflammatory gene expression (TNF- α), increasing the expression and activity of MMP-9, reducing the expression of tight junction proteins [e.g., zonula occludens (ZO)-1, claudin-5, and occludin], increasing the production of ROS (Lee, Hennig, Yao, & Toborek, 2001; Martins et al., 2011; Ramirez et al., 2009). Collectively, these adverse effects on BBB integrity contribute to neurodegeneration and may perpetuate toxic neural-immune interactions. For example, following exposure to high-dose methamphetamine, disruption of the BBB [as measured using immunoglobulin G (IgG) immunoreactivity to identify extravasated IgG in brain] is associated with neurodegeneration and activation of brain microglia and/or infiltration of macrophages. Methamphetamine-induced neurodegeneration is evident in brain regions with notable IgG immunoreactivity (i.e., hippocampus and amygdala) and during hyperthermic conditions (mouse body temperatures $>40.5^{\circ}\text{C}$). It was additionally reported that the hippocampal damage induced by methamphetamine and BBB disruption is likely sufficient to compromise cognitive function (Bowyer & Ali, 2006).

In a follow-up study, Bowyer et al. (2008) investigated BBB integrity to determine whether barrier disruption also plays a role in methamphetamine-induced neurotoxicity in the caudate–putamen—as it did in other brain regions (i.e., amygdala and hippocampus). Mice were administered high-dose methamphetamine and evaluated at 90 min, 4 h, 12 h, 1 and 3 days following drug exposure. The results showed that the BBB was only modestly altered (as indicated by IgG immunoreactivity) in the caudate–putamen at time points and subsequent to observation of neurodegeneration, and similar to previous work, these changes were dependent on hyperthermia (Bowyer et al., 2008; but see discussion of hyperthermia and serotonin involvement; Thomas et al., 2010).

Methamphetamine exposure, in combination with stress, can synergistically exacerbate BBB damage (i.e., reductions in occludin and claudin-5 immunoreactivity) via inflammatory mechanisms that persist for at least 7 days following methamphetamine (Northrop & Yamamoto, 2012). Collectively, these methamphetamine-induced effects on BBB contribute to immune dysfunction, such as increased leukocyte/monocyte transmigration across the endothelium and into the CNS (Buch et al., 2012; Ramirez et al., 2009, Fig. 7.1) as well as increased invasion of peripheral bacteria and viruses into the brain.

4.1.3 Clinical picture: immune signaling in addictive and related behaviors—In a classic positron emission tomography imaging study, Volkow et al. (2001) demonstrate that protracted abstinence can reverse some methamphetamine-induced brain insults (e.g., reductions in brain dopamine terminals) but suggest that other neurotoxic processes may persist and contribute to neuropsychiatric impairments during and following drug exposure.

Research is beginning to link immune factor signaling with neural and behavioral aspects of addiction, such as impaired cognitive function (Loftis et al., 2011), drug-seeking behaviors, and resilience to relapse (Blednov, Mayfield, Belknap, & Harris, 2012; Blednov, Ponomarev, et al., 2012; Schwarz, Hutchinson, & Bilbo, 2011; Zhang et al., 2012). For example, in a pre-clinical study propentofylline (a phosphodiesterase inhibitor and glial cell modulator) significantly reduced the activation of astrocytes induced by methamphetamine, and treatment with propentofylline suppressed the rewarding effects of methamphetamine, as measured using conditioned place preference testing (Narita et al., 2006). These findings suggest that methamphetamine-induced astrocyte activation and the subsequent release of proinflammatory factors can play a role in the development of the rewarding effects of methamphetamine.

In addition to contributing to the addictive properties of methamphetamine, cytokines and other inflammatory factors can also be potent modulators of mood and cognitive function. This is important because neuropsychiatric impairments can persist following abstinence and are associated with poorer treatment outcomes, such as increased relapse rates, lower treatment retention rates, and reduced daily functioning (e.g., Zorick et al., 2010). Repeated methamphetamine exposure induces alterations in peripheral and central immune factor expression, and in clinical samples of methamphetamine-dependent humans, these peripheral alterations in immune factor expression are associated with cognitive impairments and mood disturbances (Letendre et al., 2005; Loftis et al., 2011). The neuroinflammatory effects of methamphetamine appear to be brain region specific and can lead to differential effects on cognitive function (Chang, Cloak, et al., 2005; Jernigan et al., 2005). Thus, interventions that target immune mechanisms for repairing persistent methamphetamine-induced CNS injury and neuropsychiatric impairments, both vital for successful recovery from methamphetamine dependence, may help reduce relapse rates and improve treatment outcomes in adults recovering from methamphetamine dependence and other substance use disorders (see Section 5.2).

4.1.4 Chronic infection with human immunodeficiency virus and/or hepatitis C virus—Exposure to methamphetamine and other substances of abuse can increase the invasion of peripheral bacteria and viruses, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV), into the brain (e.g., Gavrillin, Mathes, & Podell, 2002). Further, individuals who are infected with one virus have an increased risk of coinfection with the other. Given the high rates of comorbid viral infection with substance use disorders (Fuller, Loftis, Rodriguez, McQuesten, & Hauser, 2009; Loftis, Matthews, & Hauser, 2006), particularly psychostimulant dependence (e.g., Buchacz et al., 2005), the combined effects of substance use disorders and HIV and/or HCV on neural-immune interactions are of scientific and clinical interest (Cadet & Krasnova, 2007). In addition, the effects of chronic viral infection on brain are likely exacerbated by the adverse effects of comorbid methamphetamine dependence on BBB integrity and function (Liang et al., 2008) (Fig. 7.1).

HIV infection of glial cells results in their activation and release of cytokines, ROS, HIV-related proteins, and other neurotoxic mediators (Nath & Geiger, 1998). Reports indicate that HIV-induced neurotoxicity may preferentially affect brain regions rich with dopaminergic transporters (e.g., basal ganglia)—brain areas that also show damage

following methamphetamine abuse (Nath, Maragos, Avison, Schmitt, & Berger, 2001). In fact, methamphetamine use has been linked to worse neuropsychiatric functioning in acute and early HIV infection, a critical period of immune activation (Weber et al., 2013).

One prominent neurotoxin associated with HIV is Tat (released from HIV-infected glia). Tat has been suggested to be pathogenically relevant in HIV-1-induced neuronal injury via diverse mechanisms. For example, coexposure to Tat and methamphetamine causes a synergistic loss of striatal dopamine and binding to the dopamine transporter, suggesting a loss of dopamine terminals (Theodore, Stolberg, Cass, & Maragos, 2006). In addition, methamphetamine and Tat can activate microglia and induce cytokine production. Interestingly, the interaction of Tat and methamphetamine is prevented in MCP-1-deficient mice and this also attenuates methamphetamine + Tat neurotoxicity (Theodore, Cass, & Maragos, 2006). Follow-up studies demonstrate that Tat contributes to increased TNF- α levels that exacerbates dopamine transporter damage from methamphetamine (Theodore, Cass, Nath, et al., 2006). Similarly, methamphetamine use in the presence of HIV produces additive interneuron loss (Chana et al., 2006) and abnormal brain metabolism in frontostriatal pathways (Chang, Ernst, Speck, & Grob, 2005).

The combination of HIV and methamphetamine is also associated with higher rates of neuropsychiatric impairment than either of the independent conditions (Rippeth et al., 2004). However, not all reports have been consistent regarding additive or synergistic effects of HIV and methamphetamine on brain structure and function (e.g., Archibald et al., 2012). The mechanisms of such injury are currently under investigation and inflammation, oxidative damage, and glutamate imbalance appear to contribute to neurotoxicity associated with methamphetamine dependence and comorbid HIV.

A few research groups are investigating CNS mechanisms associated with the neurotoxic effects of HCV and methamphetamine dependence. For example, using neuroimaging techniques, Taylor et al. (2004) found that *N*-acetylaspartate (NAA), a marker of neuronal integrity, was lower in the white matter of patients with HCV and a history of methamphetamine abuse, as compared to participants with HCV and no history of methamphetamine abuse. Importantly, this reduction in NAA was correlated with worse global neuropsychological deficit scores in the individuals with a history of methamphetamine addiction. However, at least one study of methamphetamine users (without HCV or HIV) found that impairments in cognitive function were unrelated to prior drug use histories (including self-reported age at first use, total years of use, route of consumption, or length of abstinence) (Cherner et al., 2010). Thus, more research is needed, as the additive or synergic effects of methamphetamine and viral infection on specific neurotoxicities and neuropsychiatric impairments are yet to be defined.

5. PART 4

5.1. Vaccine development

Anti-addiction or anti-drug vaccines are currently among the most developed immunotherapeutic approaches for substance use disorders [see National Institute on Drug Abuse (NIDA)-sponsored anti-drug vaccine animation at <http://www.drugabuse.gov/news->

events/nida-notes/antidrug-vaccine-animation]. These vaccines are designed to generate and attract antibodies to a substance so that it is too large to pass through the BBB (Cerny & Cerny, 2009; Gentry, Rüedi-Bettschen, & Owens, 2009; Kinsey, Jackson, & Orson, 2009; Li et al., 2011; Orson, Kinsey, Singh, Wu, & Kosten, 2009), thereby blocking its CNS actions and rewarding effects. To date, vaccines have been created against nicotine, morphine/heroin, cocaine, and methamphetamine, and a number of compounds are undergoing clinical trials or are in preclinical development (Goniewicz & Delijewski, 2013; Kosten, Domingo, Orson, & Kinsey, 2014; Shen et al., 2013). Researchers recently completed the first clinical study to establish the safety of a human-mouse chimeric monoclonal antibody (mAb) (i.e., ch-mAb7F9) designed to bind methamphetamine with high affinity and specificity in humans (Stevens et al., 2014). Results from the Phase 1a, double-blind, randomized, placebo-controlled clinical trial are not yet published (<https://ClinicalTrials.gov> Identifier: NCT01603147).

5.2. Neuroimmune-based and other anti-inflammatory treatment strategies

Ibudilast (AV-411 or MN-166) is a nonspecific phosphodiesterase inhibitor which suppresses glial cell activation and causes other anti-inflammatory effects. Prior to its development as a potential substance abuse treatment (e.g., for methamphetamine, alcohol, and opioid dependence), ibudilast had been used clinically for asthma, pulmonary, and cardiovascular diseases. Preclinically, administration of ibudilast following exposure to methamphetamine reduces: (1) the acute, chronic, and sensitization effects of the drug's locomotor activity, (2) stress-induced methamphetamine relapse, and (3) methamphetamine self-administration—suggesting that glial cell activity can modulate methamphetamine's behavioral effects (Beardsley, Shelton, Hendrick, & Johnson, 2010; Snider, Hendrick, & Beardsley, 2013; Snider et al., 2012). To date, a Phase I clinical trial of ibudilast with methamphetamine dependence has been completed. This initial human study was done in order to test the safety of the drug taken in combination with methamphetamine. Results from the Phase I safety interaction trial of ibudilast with methamphetamine are not yet publicly available (<https://ClinicalTrials.gov> Identifier: NCT01217970). Currently, the research is into its second phase, and results from the 12-week Phase II clinical trial are expected to be released in early 2015 (<https://ClinicalTrials.gov> Identifier: NCT01860807).

In addition to the development of therapeutic strategies for preventing and reducing methamphetamine use, interventions that target immune mechanisms for repairing persistent methamphetamine-induced CNS injury and neuropsychiatric impairments may also help reduce relapse rates and improve treatment outcomes in adults recovering from methamphetamine dependence and other substance use disorders. Given that a partial major histocompatibility complex (MHC)/neuroantigen peptide construct [pI-A^b/mMOG-35–55; a.k.a. recombinant T-cell receptor ligand (RTL)] effectively reduces the inflammatory and behavioral effects of experimental models of multiple sclerosis and stroke (Sinha et al., 2007; Subramanian et al., 2009; Vandenbark et al., 2003; Wang et al., 2006), it is possible that partial MHC/neuroantigen constructs could also effectively address the neuropsychiatric effects of chronic methamphetamine addiction. In a preclinical study, RTL-containing MHC coupled to myelin peptide [mouse myelin oligodendrocyte glycoprotein (mMOG)] improves the learning and memory impairments and CNS inflammation induced by repeated

methamphetamine exposure in mouse models of chronic methamphetamine addiction (Loftis, Wilhelm, Vandenbark, & Huckans, 2013).

In addition to vaccine and neuroimmune-based strategies (e.g., ibudilast and partial MHC/neuroantigen peptide constructs), pharmacotherapies that regulate and reduce inflammation and oxidative stress are also under investigation. For example, minocycline (a broad-spectrum tetracycline antibiotic) has anti-inflammatory and antioxidant properties and has demonstrated some efficacy in the treatment of psychiatric disorders and neuropsychiatric symptoms. Preclinically, minocycline improves deficits in novel object recognition (a measure of cognitive function) induced by phencyclidine and methamphetamine treatment in mice (Fujita et al., 2008; Mizoguchi et al., 2008) and reduces the behavioral sensitization induced by methamphetamine and cocaine (Chen, Uz, & Manev, 2009; Zhang et al., 2006). In clinical studies, the results vary, with findings supporting the use of minocycline in schizophrenia, but showing less benefit for nicotine dependence (reviewed in Dean, Data-Franco, Giorlando, & Berk, 2012). Nonsteroidal anti-inflammatory drugs [(e.g., ketoprofen), traditional and selective inhibitors of cyclooxygenase (COX)-2] have also been evaluated for the treatment of psychiatric illness (Berk et al., 2013). For example, in one preclinical study, ketoprofen pretreatment (but not aspirin) dose-dependently attenuated methamphetamine-induced neurotoxicity, as measured by reduction of dopamine transporters and accumulation of microglial cells in the striatum (Asanuma, Tsuji, Miyazaki, Miyoshi, & Ogawa, 2003).

Taken together, these preclinical and initial clinical findings indicate that immunotherapeutic strategies which target specific inflammatory pathways, reduce neurotoxicity, promote neuronal repair, and improve neuropsychiatric function may have potential as treatments for methamphetamine dependence and other substances of abuse.

5.3. Future directions

Genetic variation commonly influences psychiatric responses to drugs and medications, and this variation has implications for substance abuse treatment and the use of personalized therapeutic strategies. Thus, future research on methamphetamine dependence could investigate how drug use patterns as well as different treatment approaches may be influenced by genetic polymorphisms, as in alcohol dependence for example [naltrexone treatment seems more effective in carriers of a specific variant of the μ -opioid receptor gene (i.e., G polymorphism of SNP Rs1799971 in the gene OPRM1)] (Anton et al., 2008). Immunologic genes may be good candidates for affecting vulnerability to substance abuse treatment outcomes (Table 7.2). To date, the single nucleotide polymorphisms (SNPs) shown in Table 7.2 have not been directly studied in the context of methamphetamine addiction, but there is preliminary evidence implicating their possible involvement in neuropsychiatric impairments, particularly depression. A polymorphism near the *IL28B* gene encoding IFN lambda 3 is associated with depressive symptoms, including subjective appetite, energy, and sleep complaints (Lotrich et al., 2010). In addition to *IL28B*, the risk for developing adverse neuropsychiatric symptoms during or following methamphetamine abuse may be influenced by genetic polymorphisms in other cytokine genes, including *IL-6* (*IL6*) (Bull et al., 2009), tumor necrosis factor- α (*TNF*) (Dogra, Chakravarti, Kar, & Chawla, 2011; Thio et al., 2004), and interferon- γ (*IFNG*) (Oxenkrug et al., 2011)—genetic

variations which may have implications for the management and treatment of methamphetamine dependence and other substance use disorders (with or without comorbid viral infection).

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Figure 7.1.

Neuroimmune mechanisms of methamphetamine-induced CNS toxicity. The simplified schematic of brain and periphery illustrates the blood–brain barrier (BBB), immune and neural cells, and pro- and anti-inflammatory factors before (panel on left) and after (panel on right) methamphetamine. Following exposure to methamphetamine disruption of the BBB is observed (reviewed in Kousik, Napier, & Carvey, 2012) as well as activation of brain microglia and astrocytes, infiltration of macrophages/monocytes, alterations in the expression and balance of proinflammatory factors (e.g., IL-1 β), myelin damage, and other

indicators of neurodegeneration. Although not depicted in this figure, methamphetamine-induced neurotoxicity is accompanied not only by changes in immunity but also by alterations in neurotransmitter expression and function (such as excitotoxicity from glutamatergic overactivation) and changes in cellular bioenergetics (including oxidative and nitrosative stress). Collectively, these pathological processes contribute to neurotoxicity (e.g., increased BBB permeability, inflammation, neuronal degeneration, cell death) and neuropsychiatric impairments (e.g., cognitive deficits, mood disorders)—processes that can perpetuate addictive behaviors and hinder recovery efforts.

Table 7.1

Effects of methamphetamine exposure on immunologic outcomes in human and animal models Immune effects measured

	Results	References
Splenocyte immune factor production, following <i>in vivo</i> methamphetamine exposure and <i>in vitro</i> antigen stimulation	Decreased ConA and LPS-induced production of IL-2 and IFN- γ ; normal production of IL-4 and IL-6; increased production of TNF- α	Yu et al. (2002)
Peritoneal macrophage function, following <i>in vivo</i> methamphetamine exposure and <i>in vitro</i> antigen exposure	Reduced macrophage counts and reduced phagocytosis. Following exposure to LPS, reduced cytotoxic activity against melanoma cells; reduced antiviral activity against poly I:C; reduced NO $_2^-$ production; reduced TNF- α , IL-1, and IL-6 production; reduced expression of CD14 receptors	In, Son, Rhee, and Pyo (2004)
Lymphocyte proliferation and NK cell activity, following <i>in vivo</i> methamphetamine exposure and <i>in vitro</i> antigen exposure	In monkeys, following ConA and PHA exposure, increased lymphocyte proliferation and NK cell activity	Saito et al. (2006)
Dendritic cell immune factor production, following <i>in vitro</i> methamphetamine exposure and <i>in vitro</i> stimulation	Within a large gene microarray, altered IL-4/GMCSF induced production of functional classes of genes involved in chemokine and cytokine regulation, signal transduction mechanisms, apoptosis, and cell cycle regulation	Mahajan et al. (2006)
Splenocyte T-cell proliferation and macrophage and dendritic cell function, following <i>in vitro</i> methamphetamine exposure and <i>in vitro</i> antigen exposure	Following OVA exposure, reduced spleen T-cell proliferation; following exposure to <i>Candida albicans</i> and <i>Cryptococcus neoformans</i> , reduced macrophage phagocytosis, and increased fungal replication; within macrophages, collapsed pH gradients and increased accumulation of autophagosomes	Tallosy et al. (2008)
Splenocyte antibody and immune factor production, following <i>in vivo</i> methamphetamine exposure and <i>in vivo</i> antigen sensitization	Following sensitization to OVA, reduced splenocyte production of OVA-specific IgM, IgG1, and IgG2a; reduced IL-4 and IFN- γ production upon <i>ex vivo</i> restimulation with OVA	Wey, Wu, Chang, and Jan (2008)
Dendritic cell immune factor production, following <i>in vitro</i> methamphetamine exposure and <i>in vitro</i> stimulation	Within a large protein array, altered IL-4/GMCSF induced production of a number of functional classes of proteins that modulate apoptosis, protein folding, protein kinase activity, metabolism, and intracellular signal transduction	Reynolds et al. (2009)
Splenocyte T-cell proliferation, and peritoneal macrophage function, following <i>in vivo</i> methamphetamine exposure and <i>in vitro</i> antigen exposure/Disease progression, lung immune factor expression, and antibody production, following <i>in vivo</i> methamphetamine exposure and <i>in vivo</i> antigen exposure	Following exposure to histoplasmosis, reduced splenocyte T-cell proliferation and reduced macrophage function (e.g., reduced phagocytosis), resulting in increased fungal load and infection/ Following exposure to histoplasmosis, increased disease progression (e.g., to death); increased lung expression of TNF- α , IFN- γ , IL-4, IL-10, and TGF- β ; increased IgG2b levels	Martinez, Mihu, Gacser, Santambrogio, and Nosanchuk (2009)
Neuroinflammatory responses to a subsequent peripheral immune stimulus in mice administered a neurotoxic methamphetamine treatment regimen	Methamphetamine exacerbated the LPS-induced increase in central cytokine mRNA. Methamphetamine alone increased microglial Iba1 expression (a marker for microglial activation) and expression was further increased when mice were exposed to both methamphetamine and LPS	Buchanan, Sparkman, and Johnson (2010a, 2010b)
Peripheral blood T-cell proliferation, following <i>in vitro</i> methamphetamine exposure and <i>in vitro</i> T-cell stimulation	Reduced anti-CD3/CD28 induced T-cell proliferation and IL-2 production	Potula et al., (2010)
Peripheral and central immune factor levels, following <i>in vivo</i> methamphetamine exposure in humans and mice during different periods of withdrawal/remission	A number of significant methamphetamine-induced changes in cytokines, chemokines, and adhesion factors were observed. Of particular interest were monocyte chemoattractant protein 1 (MCP-1; a.k.a., CCL2) and intercellular adhesion molecule (ICAM-1; a.k.a. CD54), which were similarly increased in the plasma of methamphetamine exposed mice as well as humans. In human participants, methamphetamine-induced changes in the cytokine and chemokine milieu were accompanied by increased cognitive impairments	Loftis, Choi, Hoffman, and Huckans (2011)
Phenotypic changes in leukocyte subsets (e.g., NK cells, T cells, macrophages) from spleen and lymph node of mice treated with an escalating methamphetamine dose schedule	Methamphetamine exposure was associated with an overall decrease in both proportion and number of splenic NK cells, dendritic cells, and a subset of monocytes/macrophages [i.e.,	Harms, Morsey, Boyer, Fox, and Sarvetnick (2012)

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	Results	References
	monocytes expressing high levels of granulocyte antigen 1 (Gr-1 ^{high})	
Astrocyte immune factor production, following <i>in vitro</i> methamphetamine exposure	In human fetal astrocytes, methamphetamine increased IL-6 and IL-8 production (blocked by a metabotropic glutamate receptor-5 inhibitor)	Shah, Silverstein, Singh, and Kumar (2012)

CCR5, C-C chemokine receptor type 5; ConA, concanavalin A; CXCR4, C-X-C chemokine receptor 4; DA, dopamine; GMCSF, granulocyte-macrophage colony stimulating factor; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICAM, intracellular adhesion molecule; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; mRNA, messenger ribonucleic acid; NK, natural killer; OVA, ovalbumin; PHA, phytohemagglutinin-P; STAT1, signal transducer and activator of transcription1; TGF, transforming growth factor; TNF, tumor necrosis factor.

Table 7.2

Candidate polymorphisms with preliminary evidence for possible involvement in adverse neuropsychiatric symptoms relevant to addiction

Gene symbol	Gene name	ID number	Role in neuropsychiatric symptoms	Select references
<i>IDO1</i>	Indoleamine 2,3-dioxygenase 1	rs9657182	Homozygosity for the risk allele (CC) is associated with moderate–severe interferon (IFN)- α -induced depressive symptoms ^a	Smith et al. (2012)
<i>IL28B</i>	Interleukin 28B (interferon, lambda 3)	rs8099917, rs1297860	In adults with HCV, the allele (C) is associated with both better viral clearance and more subjective appetite, energy, and sleep complaints	Ge et al. (2009); Lotrich, Loftis, Ferrell, Rabinovitz, and Hauser (2010)
<i>IL6</i>	Interleukin 6	rs1800795	A functional G > C SNP in the promoter region is associated with differential IL-6 expression and IL-6 plasma concentrations. The C allele is associated with lower plasma IL-6 during immune activation than the G allele. The “low IL-6 synthesizing” genotype (CC) is associated with significantly fewer symptoms of IFN- α therapy induced depression	Bull et al. (2009); Fishman et al. (1998)
<i>IFNG</i>	Interferon-gamma	rs2430561	IFNG (+874)T/A polymorphism. The presence of T alleles represents a genetic risk factor for the development of IFN- α therapy induced depression	Oxenkrug et al. (2011)
<i>TNF</i>	Tumor necrosis factor-alpha	rs1800630, rs1800629	A decreased frequency of the –863CC TNF- α promoter genotype (involved in high production of this proinflammatory cytokine) is present in patients recovered from HCV infection; the G-308A polymorphism of the TNF gene may be independently associated with hypertension, leptin levels, and hypercholesterol emia, leading to metabolic syndrome	Gupta et al. (2012); Lio et al. (2003)

^a IFN- γ and IFN- α transcriptionally induce IDO, the rate-limiting enzyme of the kynurenine pathway of tryptophan metabolism.

It is hypothesized that IFN-induced upregulation of IDO contributes to depression, in part, by shifting tryptophan metabolism from the formation of serotonin to the production of neuroactive/toxic kynurenines (Loftis & Turner, 2010).