HHS Public Access

Author manuscript

Int Rev Neurobiol. Author manuscript; available in PMC 2016 March 23.

Published in final edited form as:

Int Rev Neurobiol. 2014 ; 118: 1–12. doi:10.1016/B978-0-12-801284-0.00001-4.

Neuroimmune Mechanisms of Alcohol and Drug Addiction

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Abstract

Alcohol and other drugs of abuse have significant impacts on the neuroimmune system. Studies have demonstrated that drugs of abuse interact with the neuroimmune system and alter neuroimmune gene expression and signaling, which in turn contribute to various aspects of addiction. As the key component of the CNS immune system, neuroimmune factors mediate neuroinflammation and modulate a wide range of brain function including neuronal activity, endocrine function, and CNS development. These neuromodulatory properties of immune factors, together with their essential role in neuroinflammation, provide a new framework to understand neuroimmune mechanisms mediating brain functional and behavioral changes contributing to addiction. This chapter highlights recent advances in understanding neuroimmune changes associated with exposure to alcohol and other drugs of abuse, including opiates, marijuana, methamphetamine, and cocaine. It provides a brief overview on what we know about neuroimmune signaling and its role in drug action and addiction.

1. INTRODUCTION

Alcohol and other drugs of abuse have profound impacts on a variety of neurobiology systems that are related to reward, stress, habit formation, and decision making, which accounts for the reinforcing and addictive properties of these drugs (Koob & Volkow, 2010). The burgeoning field of neuroimmune research has shown that the neuroimmune system modulates a variety of brain function and behaviors related to alcohol and drug addiction. Neuroimmune signaling acts in concert with neurotransmitter and neuropeptide systems that has far-reaching impact on normal brain function and dysfunction involving neurodegenerative diseases, neuropsychiatric disorders, and addiction (Deverman & Patterson, 2009; Frank, Watkins, & Maier, 2011; Haroon, Raison, & Miller, 2012; Mayfield, Ferguson, & Harris, 2013; Rogers, Mastroeni, Leonard, Joyce, & Grover, 2007; Stertz, Magalhaes, & Kapczinski, 2013). In addition to their primary role in mediating neuroinflammation, neuroimmune factors, such as cytokines and chemokines, are critical for a variety of brain functions. Expressed in neurons and glia, these molecules regulate synaptic function, mediate neuron–glia communication (Boulanger, 2009), interact with

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neuroendocrine and neuropeptide systems, and regulate neurogenesis and CNS development. These findings offer new opportunities and a framework for exploring and understanding the role of the neuroimmune system in addiction.

2. NEUROIMMUNE MODULATION OF SYNAPTIC FUNCTION

Many immune molecules interact with neurotransmitter systems and play essential roles in modulating synaptic function. As a family of G-protein-coupled receptor systems, binding of chemokines to chemokine receptors triggers a cascade of signaling events, which subsequently modulate neurotransmitter release and activities of many receptors and channels. For example, chemokines CCL2 and CXCL-12 regulate the release of several neurotransmitters, including glutamate, GABA, and dopamine (Heinisch & Kirby, 2010; Rostene, Kitabgi, & Parsadaniantz, 2007). The chemokine receptor CCR2 cross-desensitizes GABAa and mu-opioid receptors (Rostene et al., 2007). In addition, activation of CXCR4 by its ligand CXCL-12 triggers the release of glutamate from astrocytes (Cali, Marchaland, Regazzi, & Bezzi, 2008). Studies also demonstrated that proinflammatory cytokines regulate synaptic transmission and plasticity, and contribute to the maintenance of the homeostasis of neuronal networks. For example, TNFα differentially modulates trafficking of AMPA-type glutamate receptors and GABA receptors (Pribiag & Stellwagen, 2013, 2014; Stellwagen & Malenka, 2006). It regulates the synaptic strength by facilitating excitatory synaptic transmission, while decreasing inhibitory synaptic transmission. IL-1β signaling modulates long-term potentiation (Avital et al., 2003; Mori et al., 2014). Type I MHC regulates neural development and activity-dependent synaptic function (Shatz, 2009). In addition, as the key component of the neuroimmune system, microglia dynamically detect the brain environment, even at the resting state, and contribute to postnatal development, neuroplasticity, and circuit function (Kettenmann, Kirchhoff, & Verkhratsky, 2013; Parkhurst et al., 2013; Tremblay et al., 2011; Wake, Moorhouse, Miyamoto, & Nabekura, 2013). It becomes clear that the bidirectional communication between neuron and microglia plays important roles in both normal brain function and neurobiological diseases (Kettenmann et al., 2013; Miyamoto, Wake, Moorhouse, & Nabekura, 2013; Pannell, Szulzewsky, Matyash, Wolf, & Kettenmann, 2014; Schafer, Lehrman, & Stevens, 2013). Thus, the neuroimmune system modulates synaptic functions by presynaptic, postsynaptic, and neural–glial mechanisms. Such actions of the neuroimmune system offer potential neuroimmune mechanisms for brain functional changes associated with alcohol and drug abuse that can alter neuroimmune signaling.

3. NEUROINFLAMMATION

Upon insult by environmental toxins or neuronal damage, microglia release a variety of neuroimmune factors exerting either neuroprotective or neurotoxic effects (Rivest, 2009). At the initial stage of the innate immune response, TNFα and IL1β are the two main cytokines that are produced by microglia. They exert neuroprotective effects by promoting the maturation of oligodendrocytes and increasing the secretion of neurotrophines. However, overactivated microglia releases numerous proinflammatory cytokines, chemokines, and inducible nitric oxide synthase, which synergistically mediate neuroinflammation. To counterbalance neuroinflammation, the brain produces antiinflammatory factors, such as

IL-10 and transforming growth factor-b1, to inhibit inflammatory responses. It is important to note that neuroinflammation may not only be provoked by pathological conditions but also can be trigged by increased neuronal activities, such as those associated with noxious stimuli, psychological stress, and epileptic seizures (Xanthos & Sandkuhler, 2014). In addition, neuroimmune factors mediate neurotoxicity through various other mechanisms. Notably, chemokine receptors CXCR4 and CCR5 are important mediators of HIV-associated neurotoxicity (Kaul, Ma, Medders, Desai, & Lipton, 2007).

4. NEUROIMMUNE MOLECULES IN NEURODEVELOPMENT

Neuroimmune molecules are involved in all stages of neurodevelopment. They are expressed in both the developing and adult brain and play important roles in neuro- and gliogenesis, neuronal migration, axonal path finding, and sculpt neurocircuits (Guyon & Nahon, 2007; Paolicelli et al., 2011; Schafer et al., 2012). Dysregulation of CNS immune molecules at the early stage of brain development causes significant behavioral deficits, which are evident by the increased risk of several neurological disorders (Bilbo & Schwarz, 2012; Canetta & Brown, 2012; Garay & McAllister, 2010). Cytokines and chemokines play diverse roles in embryonic brain development and adult neurogenesis. For example, gp130 family cytokines and TNFα regulate neurogenesis, gliogenesis, and neuronal survival in the embryonic brain (Deverman & Patterson, 2009). Chemokine CXCL-12 is considered an indispensable chemoattractant for neuronal migration and axonal path finding in the developing nervous system (Guyon & Nahon, 2007). Disruption of certain chemokine receptors causes the malformation of granule cell layers of the cerebellum, the dentate gyrus, and cortical interneurons (Lu, Grove, & Miller, 2002). In the adult brain, cytokine TNFα and IL-6 inhibit neurogenesis (Monje, Toda, & Palmer, 2003), whereas the constitutive expression of IL-1β is critical for hippocampal neurogenesis. In addition, the chemokine CXCL-12 and its receptor CXCR4 are expressed in the subventricular zone and regulate migration and proliferation of progenitor cells (Tiveron et al., 2006). Evidence suggests that alcohol exposure disrupts cytokine profile during early neuronal differentiation and influences adult neurogenesis, and alters the neuroimmune gene expression in a brain regional-dependent manner (Camarillo, Kumar, Bake, Sohrabji, & Miranda, 2007; Crews & Nixon, 2009; Kane et al., 2014). In addition, adolescent binge drinking leads to persistent upregulation of innate immune signaling in the prefrontal cortex that correlates with adult neurocognitive dysfunction (Crews & Vetreno, 2011). The essential role of neuroimmune molecules in neurodevelopment and adult neurogenesis provide potential mechanisms to understand the effects of alcohol on CNS development.

5. NEUROIMMUNE FACTORS MODULATE NEUROENDOCRINE FUNCTION

The involvement of neuroimmune molecules in the regulation of neuroendocrine function is demonstrated in animal models and by human conditions of stress and depression. Increased levels of cytokines are associated with depression and sickness behavior (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Irwin & Miller, 2007). The underlying molecular and cellular mechanisms of these conditions are believed to be primarily due to the dysregulation of the HPA axis, as well as serotonergic and dopaminergic systems, by neuroimmune factors. A variety of cytokines have potent effects on the HPA axis by

regulating the release of neuropeptides and neurohormones, including corticotrophin release factor, ACTH, or cortisol (Hueston & Deak, 2014). Conversely, glucocorticoids induced by chronic stress have a significant impact on the neuroimmune system by regulating expressions of cytokines in the hippocampus, the prefrontal cortex, and the hypothalamus (Munhoz et al., 2006; Sorrells, Caso, Munhoz, & Sapolsky, 2009). In addition, several chemokines are expressed in the paraventricular nucleus of the hypothalamus and regulate the stress-related neuroendocrine responses, such as the release of arginine vasopressin (Callewaere et al., 2006; Callewaere, Banisadr, Rostene, & Parsadaniantz, 2007). One hallmark of alcohol and drug abuse and addiction is the dysregulated HPA axis. The ability of neuroimmune molecules in regulating the HPA axis suggests that neuroimmune molecules may play an integrative role in the close link between stress responses and addiction.

6. NEUROIMMUNE MECHANISM AND ADDICTION

Studies using animal models and postmortem human alcoholic brains suggest that alcohol exposure has a significant impact on the neuroimmune system. Expressions of several immune-related genes are altered in human alcoholic brains and are differentially correlated with the high and low alcohol consuming rodent lines (Flatscher-Bader et al., 2005; Liu et al., 2006; Mulligan et al., 2006). In addition, polymorphisms of genes encoding IL-1β and IL-1, as well as the gene for an antiinflammatory cytokine IL-10, are associated with the susceptibility to alcoholism (Marcos, Pastor, Gonzalez-Sarmiento, & Laso, 2008; Pastor, Laso, Romero, & Gonzalez-Sarmiento, 2005). Furthermore, a study using a mouse binge drinking model revealed a long-lasting increase of the chemokine CCL2 and the cytokine TNFα but a decrease of the anti-inflammatory cytokine IL-10 in the mouse brain (Qin et al., 2008). Together, these studies provide molecular and cellular evidence that ethanol alters the neuroimmune system in the brain. Recent *in vivo* animal studies provide further evidence that neuroimmune modulation contributes to alcohol dependence. Interruption of certain neuroimmune gene expression (Blednov et al., 2005, 2012) or targeted disruption of TLR4 in the central amygdala (Liu et al., 2011) reduced alcohol consumption. In addition, pharmacological suppressions of various neuroimmune signaling pathways reduce alcohol intake in different animal models (Bell et al., 2013; Mayfield et al., 2013). However, it remains largely unclear how neuroimmune alteration may contribute to alcohol dependence. Recent studies begin to shed light on this question. For example, binge and chronic alcohol exposure induce neuroimmune activation through TLRs and HMGB1 (Alfonso-Loeches, Pascual-Lucas, Blanco, Sanchez-Vera, & Guerri, 2010; Crews, Qin, Sheedy, Vetreno, & Zou, 2013); TLR4 and CD14 play an important role in the acute ethanol effects on GABAergic transmission in the central amygdala (Bajo et al., 2014), and cytokines facilitate alcohol withdrawal-induced anxiety via the CRF signaling in the central amygdala (Knapp et al., 2011; Whitman, Knapp, Werner, Crews, & Breese, 2013). In addition, human studies of alcoholics show positive correlations between alcohol craving and serum levels of cytokines and inflammatory endotoxins suggesting that activation of innate immune signaling may increase alcohol craving and consumption (Leclercq et al., 2012; Leclercq, De Saeger, Delzenne, de Timary, & Starkel, 2014). This is consistent with the animal studies

discussed above where injection of lipopolysaccharide increased alcohol consumption and deletion of immune-related genes decreased consumption.

Similar to alcohol, opiate drugs interact with the central immune system and glial activation can enhance the rewarding properties of opiates such as morphine (Bland, Hutchinson, Maier, Watkins, & Johnson, 2009). Glia activation results in the release of proinflammatory cytokines and chemokines, which can affect glia-neuronal signaling, modulate neuronal activity (i.e., dopamine release) and behavioral outcomes resulting from opioid exposure. A key proinflammatory cytokine, IL-1β, has been shown to be unregulated following morphine exposure (Raghavendra, Tanga, & DeLeo, 2004) and single nucleotide polymorphisms involved in increased IL-1β production have been associated with risk for opioid dependence in humans (Liu, Hutchinson, White, Somogyi, & Coller, 2009). Toll-like receptors that play an important role in induction of innate immunity have been shown to be important for modulating glia-neuronal signaling and in the reinforcing properties of opiates (Terashvili et al., 2008). Overall, a vast array of research has clearly demonstrated opioid exposure results in a complex pattern, and cascade of neuroimmune changes and interactions with neuronal signaling that modulates opioid-induced reward, dependence, withdrawal, and analgesia.

Cocaine's effects on central immune signaling involve indirect activation of glia-specific mediators and receptors involved in glutamate homeostasis. These changes have been linked to cocaine's rewarding effects (Chiamulera et al., 2001), withdrawal and long-term cocaine-induced incubation of drug reinstatement behavior (Lu et al., 2009). In addition, brain region-specific administration of the chemokine, CXCL-12, and activation of the CXCR4 receptor have been shown to modulate the behavioral effects of cocaine (Trecki & Unterwald, 2009).

Central immune signaling has also been shown to modulate the effects methamphetamine. Pharmacological agents that reduce glial activation, such as ibudilast, have been shown to attenuate methamphetamine-induced relapse (Beardsley, Shelton, Hendrick, & Johnson, 2010). CNS exposure to methamphetamine results in activation of microglial, which has been linked to neurodegeneration through proinflammatory processes (Ehrlich et al., 1998; Gadient & Otten, 1997; McGuire et al., 2001). Evidence from animal models has shown microglia involvement in neurotoxicity associated with methamphetamine exposure, which results in damage to striatal dopaminergic terminals and, overall, a reduction in striatal dopamine (Thomas & Kuhn, 2005). Positron emission tomography imaging data have revealed significant increase in microglial cells in the brains of methamphetamine addicted individuals, further linking methamphetamine exposure to microglia activation and neurotoxicity (Sekine et al., 2008).

7. SUMMARY

Alcohol and other drugs of abuse have significant impacts on the neuroimmune system. Neuroimmune activation may contribute to addiction via a variety of mechanisms. The neuromodulatory properties of immune factors on neuronal activity, endocrine function, and CNS development provide a new framework to understand the role of neuroimmune

mechanisms mediating brain functional and behavioral changes contributing to addiction. Importantly, neuroimmune signaling pathways could provide novel drug targets for the treatment of addiction (Coller & Hutchinson, 2012; Mayfield et al., 2013). The chapters included in this volume highlight recent advances in understanding neuroimmune changes associated with the drugs of abuse, including on alcohol, opioids, methamphetamine, marijuana, and cocaine. In addition to providing a critical review on neuroimmune contributions to changes in brain function and behavior associated with addiction, important reviews and perspectives are provided on the alterations of neuroimmune system in FASD, comorbidity of HIV and addictive substances, and neuroimmune therapies for the treatment of addiction. Thus, this volume provides updated and timely information and characterization of neuroimmune mechanisms, at the molecular, cellular, and system, and how the mechanism impacts on behavior contributing to alcohol and drug addiction.

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