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Glial and neuroinflammatory targets for treating substance use disorders

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Abstract

Background—The plenary session at the 2016 Behavior, Biology and Chemistry: Translational Research in Addiction Conference focused on glia as potential players in the development, persistence and treatment of substance use disorders. Glia partake in various functions that are important for healthy brain activity. Drugs of abuse alter glial cell activity producing several perturbations in brain function that are thought to contribute to behavioral changes associated with substance use disorders. Consequently, drug-induced changes in glia-driven processes in the brain represent potential targets for pharmacotherapeutics treating substance use disorders.

Methods—Four speakers presented preclinical and clinical research illustrating the effects that glial modulators have on abuse-related behavioral effects of psychostimulants and opioids. This review highlights some of these findings and expands its focus to include other research focused on drug-induced glia abnormalities and glia-focused treatment approaches in substance use disorders.

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Contributors

RKB and JDJ were responsible for conducting the literature review and writing the manuscript. KGH, PMB and SDC reviewed several drafts of the manuscript and provided feedback. All authors have approved the final manuscript.

Conflicts of Interest

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Results—Preclinical findings show that drugs of abuse induce neuroinflammatory signals and disrupt glutamate homeostasis through their interaction with microglia and astrocytes. Preclinical and clinical studies testing the effects of glial modulators show general effectiveness in reducing behaviors associated with substance use disorders.

Conclusions—The contribution of drug-induced glial activity continues to emerge as an intriguing target for substance use disorder treatments. Clinical investigations of glial modulators have yielded promising results on substance use measures and indicate that they are generally safe and well-tolerated. However, results have not been entirely positive and more questions remain for continued exploration in the development and testing of glial-directed treatments for substance use disorders.

Keywords

astrocyte; microglia; innate immune; inflammatory; cytokine; glutamate; cocaine; opioid; morphine; psychostimulant; alcohol

1. Introduction

Drug addiction is a pervasive worldwide problem that is characterized by a physical and psychological dependence on drugs such that compulsion to seek and take drugs is increased, control over drug intake is lost, and withdrawal symptoms (e.g., dysphoria, anxiety, irritability, etc.) emerge when drug use is discontinued. The transition from casual drug use to drug dependence results from neurobiological changes that produce maladaptive brain functioning in the neurocircuitries that regulate motivated behavior (Koob and Volkow, 2010). An important goal of neurobiological research focused on drug dependence is to identify neuropharmacological targets that will aid in the development of medications for drug dependence. Thus, it is essential that neurobiological research provide a better understanding of the molecular, cellular and systemic changes that are impacted by drugs of abuse, and how these drug-induced adaptations contribute to behaviors associated with drug dependence.

Decades of neurobiological research has substantiated the role of dopamine, glutamate and additional neurotransmitters systems in mediating the acute and chronic effects of drugs of abuse. For example, it is well known that many drugs of abuse interact with the mesocorticolimbic dopamine system to produce their acute reinforcing effects (Koob and Volkow, 2010). Chronic administration of abused drugs produces perturbations within this, and other, brain systems (e.g., corticostriatal, extended amygdala, etc.) that ultimately alter emotional regulation and interfere with higher cognitive functions such as impulsive control and self-regulation over drug taking, producing an enduring susceptibility to relapse (Thomas et al., 2008). The focus of a majority of these neurobiological studies has highlighted the ability of drugs of abuse to interact with neuronal sites of action, substantiating the role that neuronal sites of action play in the activation of the mesocorticolimbic dopamine system and development of long-term adaptations in the brain that result from chronic use. Despite improved knowledge of the neuronal actions of drugs of abuse, the availability of effective pharmacotherapies is limited and attempts directed at mesocorticolimbic system dysfunction have been largely unsuccessful.

It has recently come to light that nearly all drugs of abuse also influence non-neuronal glial cells (Beardsley and Hauser, 2014; Crews and Vetreno, 2016; Hutchinson and Watkins, 2014). Glial cells make up the majority of cells in the brain where they play an active role in a variety of brain functions including neurotransmitter release and clearance, synaptic development and maturation, synaptic plasticity, neuronal cell survival, immune responding, and many others (Sofroniew and Vinters, 2010). Glial cells are potently influenced by drugs of abuse and there is emerging evidence that glial cell activity contributes to the behavioral effects of acute and chronic administration of drugs of abuse. These findings raise important questions about the contributions of non-neuronal glial cells in the development and persistence of drug abuse, as well as the clinical implications of glial-directed therapeutic approaches. The Plenary Symposium at the 2016 Behavior, Biology and Chemistry conference provided an opportunity for the speakers to share their latest research findings highlighting the therapeutic potential of glial modulators in the treatment of substance use disorders. Here, we review the literature supporting the notion that glial cells contribute to drug-induced changes in the brain and behaviors, potentially providing an avenue for novel pharmacotherapeutic development.

2. Physiology of Glial Cells in the Brain

Glial cells are extremely abundant throughout the brain and are often categorized based on morphological and physiological characteristics. The primary types of glial cells in the central nervous system include astrocytes, microglia, oligodendrocytes, and ependymal cells. Astrocytes provide numerous structural and metabolic support functions for neurons and regulate the extracellular environment by clearing neurotransmitters, buffering ion concentrations, and releasing signaling molecules (Sofroniew and Vinters, 2010). Microglia are immunocompetent cells that detect pathogens and engage in phagocytosis, lysosomal degradation, and secretion of various pro- and anti-inflammatory substances (Graeber, 2010). Oligodendrocytes are glial cells that wrap around the axons of neurons forming a myelin sheath that insulates the nerve fiber from the extracellular fluid and allows for more efficient propagation of axonal signals (Nave, 2010). Ependymal cells line the spinal cord and brain ventricles where they produce, secrete and circulate cerebrospinal fluid. Collectively, glial cells are an important, and underappreciated, element in nervous system functioning.

Until recently, glial cells were considered to be relatively inactive cells, playing primarily supportive roles for neurons in the brain. It is now abundantly clear that, in addition to their neuronal support function, glial cells actively regulate brain activity through the release and reception of neurochemical signals and homeostatic maintenance of the extracellular environment. They express various neurotransmitter receptors, transporters, and immune signaling complexes that enable them to receive both endogenous and exogenous chemical signals. Glia can also release neurotransmitters, neurotrophic factors, and inflammatory substances that enable them to communicate with neurons and other glial cells. The ability of glial cells to produce various activity states enables them to flexibly regulate the development, maturation, and refinement of neuronal and synaptic functions. Importantly, drugs of abuse modulate the activity of glial cells and alter their interactions with other cells in the brain. While all of the glial cell types have been implicated in drug abuse, the majority

of research has focused on the interaction of drugs of abuse with astrocytes and microglia, and these glial cell types will therefore be the focus of this review.

2.1 Astrocytes

Astrocytes are the most abundant glial cell type in the brain (Volterra and Meldolesi, 2005). They have unique cytoarchitectural and phenotypic characteristics that allows them to sense their surroundings and respond dynamically to changes in their microenvironment. Astrocytes are characterized by the expression of the cytoskeletal protein glial fibrillary acidic protein (GFAP) and changes in the expression of GFAP is often used as an indicator of astrocyte activation (Anderson et al., 2014). Although they can take on various structural morphologies, most astrocytes are star-shaped cells with multiple processes originating from the soma. Large diameter vascular processes extending from astrocytes envelop brain capillaries allowing for the regulation of glucose and water homeostasis through the expression of glucose transporters and aquaporin 4, respectively (Amiry-Moghaddam et al., 2003; Iadecola and Nedergaard, 2007; Kacem et al., 1998; Oberheim et al., 2009). Smaller diameter perisynaptic processes form an integral part of the so-called “tripartite synapse” where astrocytic processes engulf the structural elements of the presynaptic neuronal terminal and postsynaptic neuronal membrane (Araque et al., 1999). Perisynaptic processes aid synaptogenesis and synaptic transmission through the expression of various neurotransmitter receptors and transporters, as well as ion channels, cytokine and neurotrophic receptors.

Studies suggest that a single astrocyte residing in cortical gray matter associates with hundreds of dendrites and contacts hundreds of thousands of synapses, perhaps even up to 2,000,000 in humans (Halassa et al., 2007; Oberheim et al., 2009, 2006). Astrocytes are thought to be distributed throughout the brain in microdomains that operate within functional networks that are formed through aqueous channels called gap junctions (Bushong et al., 2004, 2002; Giaume et al., 1991). Gap junctions connect the cytoplasm of astrocytes and allow for direct intercellular communication through the exchange of second messengers, small molecules and ions. The cytoarchitecture of astrocytes and astrocytic networks therefore actively associate with multiple synapses to coordinate neuronal activity. The coordinated release of neurotransmitters, cytokines and neurotrophic factors from astrocytes enables them to broadcast signals to a large area ultimately affecting neuronal activity within multiple networks.

One well characterized function of astrocytes is the clearance of neurotransmitters, such as glutamate, from the synaptic cleft. This function is critical for the termination of synaptic glutamate transmission, maintenance of neuronal excitability, and development of synaptic plasticity. Synaptic clearance of glutamate occurs primarily through the glutamate transporter 1 (GLT-1), a high affinity sodium-dependent transporter expressed exclusively on astrocytes (Chaudhry et al., 1995; Williams et al., 2005). GLT1 is expressed on astrocyte perisynaptic processes that engulf glutamate synapses and engage in glutamate uptake following synaptic release (Yang et al., 2009). Following glutamate uptake, astrocytes convert glutamate to glutamine through the astrocyte-specific enzyme glutamine synthetase (Martinez-Hernandez et al., 1977; Yudkoff et al., 1988). Glutamine is then released out of

astrocytes and transported into neurons where it is converted back into glutamate by the enzyme glutaminase. This process is referred to as the glutamate-glutamine cycle and is the primary mechanism for recycling glutamate that is released into the synapse (McKenna, 2007; Yudkoff et al., 1993).

Astrocytes are also capable of releasing chemical transmitters, such as glutamate, D-serine, adenosine triphosphate, and taurine, in a process called gliotransmission. Glutamate gliotransmission plays an integral role in further shaping synaptic transmission and plasticity by modulating extrasynaptic (i.e., beyond the synapse) glutamate receptors on neurons (Kalivas, 2009). Astrocytic release of glutamate largely occurs through glutamate exchange via the cysteine-glutamate antiporter, although glutamate release is also possible through reverse transport through GLT-1 and calcium-dependent vesicular release (Malarkey and Parpura, 2008; Warr et al., 1999). Once released, glutamate can shape synaptic communication in a variety of ways. First, glutamate release can act at presynaptic metabotropic glutamate receptors (mGluRs) on glutamate terminals. Presynaptic mGluR2/3 are glutamate autoreceptors that couple to inhibitory G proteins. Activation of these receptors through glutamate gliotransmission attenuates synaptic release of glutamate and likely modulates excitatory neurotransmission (Martin et al., 1997; Xi et al., 2002). Second, glial-derived glutamate can also activate group 1 mGluRs, a G_q coupled receptor largely located at postsynaptic glutamate sites where intracellular signaling can facilitate postsynaptic excitatory transmission and thereby increase synaptic plasticity (Doherty et al., 1997). Together, the combined functional capacity of astrocytes to participate in glutamate uptake and glutamate gliotransmisssion enables astrocytes to control glutamate homeostasis and balance synaptic and extrasynaptic glutamate transmission.

Astrocytes can also act as immunocompetent cells under certain physiological conditions (Colombo and Farina, 2016). In this capacity, astrocytes produce both pro- and anti-inflammatory signaling in response to tissue injury or other insults. Astrocytes have the capacity to secrete pro-inflammatory cytokines that signal potential danger to adjacent neurons and other glial cells. The release of anti-inflammatory cytokines and neurotrophic factors, on the other hand, are thought to be beneficial, providing protection against neuronal damage. These two distinct processes are thought to occur in a temporally- and contextually-specific manner that depends on the longevity of the inflammatory insult and the existing resting state of astrocytes and other glial cells within their network (Colombo and Farina, 2016).

2.2 Microglia

The innate immune system of the brain is comprised largely of immunocompetent cells called microglia (Lawson et al., 1990). Microglia are derived from monocytes that infiltrate into the brain and subsequently differentiate into microglia. They are distributed throughout the brain where they engage in immune surveillance of their local microenvironment. Microglia behave similarly to peripheral macrophages by acting as antigen presenting cells, using phagocytic and cytotoxic mechanisms to destroy foreign substances, and engaging in inflammatory signaling (Thomas, 1992). Unlike macrophages, however, microglia are extremely plastic, existing in different morphologies and activity states depending on the

needs and demands of their microenvironment. Quiescent microglia are amoeboid in shape and perform immune surveillance functions by sampling their microenvironment several times a second (Davalos et al., 2005; Nimmerjahn et al., 2005). When danger" signals, such as bacteria, viruses or foreign substances (i.e., xenobiotics) are detected, microglia become ramified by upregulating a variety of surface activation markers and producing and releasing inflammatory substances (e.g., cytokines) (Hanisch and Kettenmann, 2007). Depending on the type and persistence of the signals detected, microglia can enter into different activation states, producing different combinations of proinflammatory signals (Block et al., 2007). One particularly interesting state that is often associated with neurodegenerative and neuropathological disorders has been called "primed" or "sensitized", where microglia are more reactive and produce exaggerated amounts of proinflammatory signals if stimulated again (Frank et al., 2010a, 2010b, Loram et al., 2012, 2011; Perry and Teeling, 2013; Wynne et al., 2009).

Microglia surveillance is accomplished through their expression of a variety of pattern-recognition receptors. These receptors respond to unique pathogen associated molecular patterns (PAMPs), including bacterial carbohydrates, nucleic acids, bacterial peptides, and others, as well as endogenous signals referred to as damage-associated molecular patterns (DAMPs) that signal cellular stress and/or damage (Hanisch and Kettenmann, 2007; Ransohoff and Perry, 2009). The toll-like receptor (TLR) family is perhaps the most well characterized cell surface pattern recognition receptor (Gangloff et al., 2003). Each TLR family member responds uniquely to variety of molecular motifs associated with pathogens such as Gram negative and Gram positive bacteria, short lengths of single and/or double stranded RNA or DNA (Chow et al., 1999; Hemmi et al., 2000; Yoshimura et al., 1999). The receptor for advanced glycation end-products (RAGE) is another pattern recognition receptor that is activated by DAMPs such as S100 proteins and high-mobility group box-1 protein (HMGB1) (Hofmann et al., 1999; Hori et al., 1995). Microglia also contain nucleotide binding and oligomerization domain receptors (NOD-like receptors) that are found within the cytoplasm and recognize peptidoglycan constituents of Gram negative and Gram positive bacteria (Sterka and Marriott, 2006). Given the diverse receptors and activators of these receptors, microglia are equipped to respond to a multitude of immunological insults.

The activation of microglia leads to nuclear translocation of the transcription factor, nuclear factor kappa-beta (NFκB), and transcription of NFκB-related genes including interleukin 1-beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNFα) and others (Blanco et al., 2005; Bowie and O'Neill, 2000; Kobayashi et al., 2006; Nagai et al., 2002; Shimazu et al., 1999). Under physiological conditions, proinflammatory factors coordinate immune defense, debris removal and repair. Proinflammatory central immune signaling also has neuroexcitatory effects through upregulation of surface AMPA and NMDA receptors, increased conductivity of NMDA receptors, and increased spontaneous excitatory neurotransmitter release (Mandolesi et al., 2013; Stellwagen et al., 2005; Viviani et al., 2003).

3. Drugs of Abuse and Glial Cell Activity

Drugs of abuse influence the neuronal circuitries that control important adaptive and beneficial behaviors related to an organism's survival. For example, natural rewards (e.g., palatable food, sex, social interactions, etc.) activate brain circuits that enable learned associations between stimuli paired with rewarding experiences to guide future behavior. Unlike the endogenous neurochemicals that guide naturalistic reward-related learning, drugs of abuse activate neuronal circuitries beyond those seen under naturally occurring reward-related scenarios (Volkow et al., 2009). This can produce aberrant physiological conditions within specific brain microenvironments prompting glial cells to guide maladaptive responding. Glial cells also play an active role in immune surveillance and from an immunological perspective, drugs of abuse may be detected as foreign compounds (that is as xenobiotic) that could potentially harm nervous system tissue. Thus, drugs of abuse may prompt an immunological defensive response upon entry into the brain. Drug-induced dysfunction of glial cells is likely to create instability in neuronal functioning and disrupt plasticity within neural circuits. These effects may be exaggerated under conditions where astrocytes and microglia display preexisting alterations in morphology and function, as seen with genetic variations and following stress exposure. There is an increasing appreciation that activation of drugs of abuse at neuronal sites of action couples with glial cell responding to produce many of the drug-induced adaptations and behavioral consequences of long-term drug use.

3.1 Glial Cells and Susceptibility to Drug Abuse

The factors that influence an individual's vulnerability to developing a substance use disorder has been an extremely well-studied area. While there are many factors to consider, there is some evidence to suggest that susceptibility to substance use disorders may be linked to dysregulation in glial cell function. Genetic studies reveal that drug dependence is highly heritable and gene association studies have uncovered many genes and genetic variants that are associated with drug dependence (Agrawal et al., 2012). A subset of these studies suggest that genes associated with immune function may be among those that contribute to the development of drug dependence. For example, alcoholism has been associated with genetic variations in the 5′ untranslated region and several introns of NFκB, the transcription factor that regulates several immune-related genes in microglia. Single nucleotide polymorphisms (*IL-1β* -511 and -31) in the *IL-1β* gene that lead to enhanced expression of the pro-inflammatory cytokine IL-1β are associated with alcohol and opioid dependence (Liu et al., 2009; Pastor et al., 2005). A single nucleotide polymorphism (*IL-10* -592) in the *IL-10* gene is associated with alcoholism with the polymorphism being associated with decreased expression of the anti-inflammatory cytokine IL-10 (Marcos et al., 2008; Smith and Humphries, 2009). Thus, it appears that genetic variations that lead to enhanced pro-inflammatory and diminished anti-inflammatory signals may be predisposing factors at least for alcoholism.

There is also evidence to suggest that environmental situations that alter the functions of glial cells are linked to drug addiction. Stress is a particularly well-studied environmental factor that has long been associated with drug addiction (Koob, 2008). Nearly all types of

stressors (e.g., restraint, tail/foot shock, social defeat) in animal models have been shown to increase microglial activation markers such as CD11b and Iba1 (Frank et al., 2007; Kreisel et al., 2014; Tynan et al., 2010; Wohleb et al., 2011). CNS immune activation resulting from stress exposure has been linked to a variety of psychiatric disorders and it is plausible that addiction may be another condition observed following stress-induced immune activation (Frank et al., 2016b). In fact, it has been hypothesized that stress exposure primes microglia, rendering them more reactive upon subsequent immune challenges (Crews et al., 2017; Hutchinson and Watkins, 2014). In the next section, we highlight how drugs of abuse can act as an immune challenge by activating the immune system. Therefore, it is conceivable that environmental conditions that activate and/or prime microglia may enhance their reactivity to subsequent drug exposure.

3.2 Mechanisms of Drug-Induced Glial Cell Changes

There are significant unanswered questions about how drugs of abuse activate glial cells. It is conceivable that glial cells respond to the aberrant supraphysiological changes in endogenous neurochemicals that result in various parts of the brain following drug administration. Astrocytes and microglia are equipped with a variety of receptors and transporters that are relevant to the actions of many drugs of abuse. To a large extent, many of the neurotransmitter receptors and transporters expressed by neurons are also expressed by glial cells (Zhang and Barres, 2010). Astrocytes, in particular, express glutamate transporters (GLT-1 and GLAST), GABA transporters and the dopamine transporters (Chaudhry et al., 1995; Hertz, 1979; Minelli et al., 1996, 1995; Russ et al., 1996; Takeda et al., 2002). It has also been shown that astrocytes can express all subtypes of opioid and dopamine receptors subtypes (Bal et al., 1994; Hösli and Hösli, 1986; Ruzicka et al., 1995; Zanassi et al., 1999). It is also plausible that immune responses are generated from direct activation of pattern recognition receptors. Microglia, and to a lesser extent astrocytes, express a large variety of pattern recognition receptors related to immunological signaling (see above). Given the diversity in receptors and transporters on the cell surface of glial cells, a variety of neurochemical and immunological events can be instigated by the administration of drugs of abuse to alter the functioning of glial cells. Highlighted below are several potential mechanisms by which drugs of abuse from various drug classes alter glial cell activity and potentially contribute to drug abuse. We also present the results of pharmacotherapeutics directed at glial cell targets using preclinical models (Table 1).

3.2.1 Opioids—Opioids are known to bind and potently activate all subtypes of opioid receptors (i.e., μ, δ, and κ). Activation of μ opioid receptors expressed on ventral tegmental area neurons is largely associated with the acute reinforcing effects of opioid drugs (Di Chiara and Imperato, 1988; Gysling and Wang, 1983; Matthes et al., 1996; Shoaib et al., 1995). One of the first indications that opioid drugs may alter glial cell activity was the demonstration that chronic morphine increases the astrocyte marker, GFAP, in the ventral tegmental area, an effect inhibited by the opioid receptor antagonist, naltrexone (Beitner-Johnson et al., 1993). There is also evidence to suggest that morphine enhances microglial migration through opioid receptor interactions with purinergic receptors (Horvath and DeLeo, 2009). Lastly, there is evidence that opioid drugs alter immune signaling through the pattern recognition receptor, toll-like receptor 4 (TLR4), by binding to the TLR4 co-receptor

myeloid differentiation factor 2 (Hutchinson et al., 2010; Jacobsen et al., 2014; Liang et al., 2016; Wang et al., 2012). Together, these findings suggest that opioid drugs modify glial cells through several potential mechanisms.

There is increasing evidence that opioid drugs recapitulate the effects of administering prototypical activators of immune signaling, such as LPS. Both acute and chronic administration of morphine, for example, increases the expression of cellular markers associated with immune activation, such as microglial CD11b and astrocytic GFAP (Beitner-Johnson et al., 1993; Hutchinson et al., 2010, 2009; Schwarz et al., 2011). Morphine-induced increases in CD11b and GFAP are prevented by the co-administration of the non-selective phosphodiesterase inhibitor and putative microglial inhibitor, ibudilast (Hutchinson et al., 2009; Schwarz et al., 2011). Administration of opioid drugs also alters intracellular signaling that is associated with upregulation of immune-related genes. For example, morphine-induced phosphorylation of NFκB can lead to increased expression of cytokines such as IL-1β and TNFα, as well as chemokines such as CCL5 and MCP-1 (El-Hage et al., 2006, 2005; Niwa et al., 2007; Sawaya et al., 2009). Furthermore, it is interesting that microglial inhibition with ibudilast prevents many of these morphine-induced changes in immune responding while also increasing the expression of the anti-inflammatory cytokine interleukin 10 (El-Hage et al., 2014; Hutchinson et al., 2009; Schwarz et al., 2011).

Until recently, the functional consequence of the opioid-induced inflammation has been poorly understood. Some of the first evidence for a role of immune activation in opioid reward came from studies demonstrating an increase morphine conditioned place preference following an injection of astrocyte-conditioned medium that contained a complement of proinflammatory cytokines and chemokines into the nucleus accumbens (Narita et al., 2006). More recent findings suggest that opioid interactions with microglia contribute to opioid actions within the brain's reward system to potentially influence the development of substance abuse. Thus, microglia inhibition inhibits morphine-induced dopamine release as measured by microdialysis in the nucleus accumbens and inhibits the development of morphine conditioned place preference (Bland et al., 2009; Hutchinson et al., 2008). There has been recent interest in utilizing the peroxisome proliferator-activated gamma receptor (PPARγ) agonists to reduce immune activation. PPARs belong to the nuclear hormone receptor family and are expressed in neurons, oligodendrocytes, astrocytes and microglia within the central nervous system (Gélinas et al., 2005; Moreno et al., 2004; Sarruf et al., 2009; Woods et al., 2003). PPARγ is expressed primarily in microglia and PPARγ agonists inhibit the expression of proinflammatory cytokines (Kielian and Drew, 2003). Recent studies show that stimulation of PPARγ reduces heroin self-administration and reinstatement of heroin seeking (de Guglielmo et al., 2016, 2015).

The mechanism by which opioid drugs induce proinflammatory signals in microglia remains unclear, although behavioral evidence suggests that the TLR4 may play a role. For example, TLR4 knockout animals show impaired development of conditioned place preference to morphine and oxycodone. Likewise, the low affinity pharmacological TLR4 inhibitor, (+)-naloxone, not only impairs the development of morphine conditioned place preference and self-administration of remifentanil, but also abolishes the ability of morphine to produce dopamine elevations in the nucleus accumbens (Hutchinson et al., 2012). Other evidence

illustrates the importance of TLR4 in the development of tolerance and withdrawal (Eidson and Murphy, 2013; Watkins et al., 2009). Lastly, chronic antagonism of TLR4 during withdrawal impairs the incubation of heroin craving that occurs after prolonged abstinence (Theberge et al., 2013). These findings suggest the importance of opioid actions at TLR4 for several behavioral effects of opioids. Recent work by Tanda et al. (2016), however, failed to show any effect of the low-affinity TLR4 antagonists, (+)-naloxone and (+)-naltrexone, on intravenous heroin-induced dopamine release raising significant questions about the role of TLR4 in opioid action.

The development of opioid tolerance and dependence has long been associated with opioid-induced alterations in glutamate transmission (Bristow et al., 1997; Fundytus and Coderre, 1994; Trujillo and Akil, 1991). Recent evidence suggests that morphine-induced immune activation through the TLR4 contributes to deficits in glutamate transmission by disrupting glutamate uptake (Eidson et al., 2016). Chronic opioid administration decreases the expression of astrocytic glutamate transporters, GLT-1 and glutamate aspartate transporter, likely impairing the synaptic clearance of glutamate (Ozawa et al., 2001; Shen et al., 2014). While this is likely to have several cascading effects on glutamate transmission, several studies suggest that restoring deficits in GLT-1 prevent many opioid-induced behavioral effects. Administration of the glutamate transporter activator, MS-153, attenuated morphine reward in a place conditioning paradigm, while overexpression of GLT-1 in the nucleus accumbens prevents the development of conditioned place preference for morphine (Fujio et al., 2005; Nakagawa et al., 2005). Administration of the beta-lactam antibiotic, ceftriaxone, upregulates endogenous GLT-1 and has proven effective in attenuating morphine-induced hyperthermia, tolerance, and reinstatement to heroin seeking (Rawls et al., 2010, 2007; Shen et al., 2014). Restoration of opioid-induced GLT-1 deficits with chronic administration of the cysteine pro-drug, N-acetylcysteine, was also effective in reducing heroin seeking (Murray et al., 2012; Reissner et al., 2015; Zhou and Kalivas, 2008). Interesting, both ceftriaxone and N-acetylcysteine display anti-inflammatory properties making it difficult to disentangle their ability to suppress immune activation from their effects on restoring glutamate homeostasis (Csontos et al., 2012; Karalija et al., 2014; Kaur and Prakash, 2017; Lujia et al., 2014; Mahmoud and Ammar, 2011; Purwanto and Prasetyo, 2012; Wei et al., 2012). Regardless, it seems that opioid-induced immune activation and disrupted glutamate homeostasis may be interrelated phenomena that alter neuronal functioning ultimately influencing the behavioral effects of acute and chronic opioid administration.

3.2.2 Alcohol—Alcohol has a wide array of pharmacological actions in the brain that contribute to its diverse behavioral effects. Alcohol administration can alter lipid membrane integrity, enhance $GABA_A$ receptor activity, inhibit NMDA glutamate receptors, and facilitate opioid and serotonin neurotransmission (Gilpin and Koob, 2008). The acute reinforcing effects of alcohol are attributed to the ability of alcohol to increase the activity of the mesocorticolimbic system by disinhibiting dopamine neurons in the ventral tegmental area (Brodie et al., 1990; Weiss et al., 1993). However, the widespread effects of alcohol in the brain and periphery suggest that alcohol can influence glial cells in many ways as well.

Binge alcohol drinking increases circulating levels of cytokines in the blood in both alcoholics and healthy individuals (Bala et al., 2014; Leclercq et al., 2014, 2012).

Heightened cytokines in the periphery are not only associated with peripheral immune-related disorders observed in alcoholics such as leaky gut syndrome and liver disease, but also associated with immune activation in the brain (Ferrier et al., 2006; Leclercq et al., 2014, 2012). Peripheral proinflammatory cytokines can not only stimulate endothelial cells to release cytokines in the brain, but they can also be actively transported across the blood-brain barrier via transporters (Banks and Erickson, 2010; Qin et al., 2007; Watkins et al., 1995). While induction of peripheral immune responding typically subsides within days of the immune challenge, immune signals in the brain can last months (Qin et al., 2007). In fact, chronic alcohol administration potentiates inflammatory signaling in brain microglia to subsequent immune challenges (e.g., LPS) by upregulating the expression of TLR receptors, an effect suggestive of microglial priming (Alfonso-Loeches et al., 2010; Crews et al., 2013; Qin et al., 2008; Zhao et al., 2013). Microglial priming likely results from the combination of peripheral immune signals infiltrating the brain and the ability of brain-penetrant alcohol to activate microglia. Alcohol-induced immune activation is inhibited by the antibiotic and microglial inhibitor, minocycline, as well as anti-oxidant and anti-inflammatory drug, N-acetylcysteine.

Proinflammatory signals induced by alcohol are mediated by TLRs (e.g., TLR2/4) likely expressed on microglia (Alfonso-Loeches et al., 2010; Fernandez-Lizarbe et al., 2013, 2009). It is unclear whether alcohol interacts directly with microglial TLRs, however, there is evidence that alcohol increases neuronal release of HMGB1, an endogenous activator of TLR4 (Crews et al., 2013; Zou and Crews, 2010). Activation of TLR4 increases NFκB DNA binding and transcription of NFκB target genes such as IL1β and TNFα (Alfonso-Loeches et al., 2010; Fernandez-Lizarbe et al., 2013, 2009). Inhibition of HMGB1 and TLR4 activation blocks alcohol-induced immune activation and cytokine release (Zou and Crews, 2014) Chronic alcohol and the resulting continued activation of microglia TLRs are thought to contribute to alcohol-induced neurodegeneration (Crews and Vetreno, 2014).

Evidence supports a functional contribution of alcohol-induced TLR activation in microglia in behavioral models. Administration of putative microglia inhibitors, such as ibudilast and minocycline, reduce alcohol drinking in a 2-h and 24-h two-bottle choice paradigm, a drinking-in-the-dark procedure and a chronic intermittent access procedures using several established high alcohol-consuming rodent lines (Agrawal et al., 2011; Bell et al., 2013; Syapin et al., 2016). Similarly, stimulation PPARγ that is expressed in microglia also reduce alcohol drinking in a 3-h and 24-h two-bottle choice paradigm and a drinking-in-the-dark procedure, potentially through the anti-inflammatory properties of PPARγ agonists (Blednov et al., 2015; Ferguson et al., 2014; Stopponi et al., 2013). Self-administration of alcohol is also associated with increased TLR4 protein expression in the ventral tegmental area of alcohol preferring P rats (June et al., 2015). The C3H/HeJ mouse strain possesses a TLR4 point mutation that can disrupt TLR4 signaling. Interestingly, these mice show very low alcohol preference and consumption using a two-bottle choice paradigm of alcohol drinking (Li et al., 2005). Similarly, knockout mice lacking the *TLR4* or the TLR4 adapter protein, myeloid differentiation primary response gene 88 (*MYD88*), show reduced alcohol-induced sedation and motor impairments compared to control animals (Wu et al., 2012). An equivalent reduction in these behaviors is also observed using the pharmacological low-affinity TLR4 inhibitor, (+)-naloxone. Despite these findings suggesting a prominent role of

TLR4 in alcohol-induced behaviors, a recent report provides evidence that TLR4 is not involved in alcohol consumption. In this report, both pharmacological and genetic manipulations of TLR4 fail to significantly alter excessive alcohol consumption utilizing a two-bottle choice paradigm, drinking-in-the-dark procedure and a chronic intermittent exposure procedure (Harris et al., 2016). These findings suggest that the alcohol-induced immune activation of microglia contribute to alcohol drinking and the subjective effects of alcohol administration, although the role of TLR4 remains unclear.

In addition to alcohol's immune activation effects, it can also modulate the activity of astrocytes. Alcohol administration can significantly alter astrocyte density in the cortical regions. Using GFAP expression to quantify the density of astrocytes, it was observed that oral administration of alcohol increases the density of astrocytes in the cortex (Dalçik et al., 2009; Udomuksorn et al., 2011; Vongvatcharanon et al., 2010). Astrocyte densities were observed to be decreased in the prelimbic cortex of alcohol-naïve rats that were selectively bred for high alcohol preference (Miguel-Hidalgo, 2005; Miguel-Hidalgo et al., 2006). However, these same alcohol-preferring rats show increased astrocyte densities during abstinence from alcohol drinking (Miguel-Hidalgo, 2006). These findings suggest that astrocyte densities may correspond with the developmental trajectories of alcohol dependence, although similar studies in outbred rats have produced more inconsistent findings. Thus, some studies have shown abstinence-induced decreases in cortical astrocytes, increases in nucleus accumbens astrocytes, and others show no change in astrocytes (Bull et al., 2014; Miguel-Hidalgo, 2006; Miguel-Hidalgo et al., 2002). The ramifications of density changes in astrocytes, as measured by GFAP expression, is not yet fully understood, but may reflect the engagement of astrocytes in inflammatory signaling (see above) or represent changes in astrocyte functioning at the perisynaptic sites (Ben Haim et al., 2015).

Alcohol profoundly alters many different neurotransmitter systems, many of which are regulated by perisynaptic astrocyte processes. There is substantial evidence demonstrating that dysfunction in glutamate neurotransmission contributes to the development of alcohol dependence. Chronic alcohol drinking downregulates the expression of two glial glutamate transporters, GLT1 and the cysteine glutamate antiporter, in the nucleus accumbens (Aal-Aaboda et al., 2015; Sari et al., 2013). These alcohol-induced changes result in disrupted glutamate homeostasis as indicated by reduced glutamate uptake and elevated extracellular glutamate following alcohol administration (Dahchour et al., 2000; Dahchour and De Witte, 2003; Melendez et al., 2005a, 2005b). A large body of work suggests that alcohol-induced changes in adenosine signaling contributes to disrupted glutamate homeostasis. Adenosine is a purine nucleoside that is increased extracellularly through alcohol-induced inhibition of the adenosine transporter (type 1 equilibrative nucleoside transporter, ENT1) that is expressed on astrocytes (Nagy et al., 1990). This rise in extracellular adenosine consequentially stimulates both adenosine A_1 and A_{2A} receptors that are also expressed on astrocytes and consequentially reduce GLT1 expression (Matos et al., 2012; Wu et al., 2011). Adenosine also alters synaptic GABA clearance through GABA transporters (i.e., GAT1 and GAT3) located on astrocytes (Minelli et al., 1996, 1995). Thus, alcohol-induced elevations in adenosine have the capacity to enhance the activity of GABA transporters through the activation of adenosine A_{2A} receptors (Cristovao-Ferreira et al., 2013). Together, alcohol can influence the balance of excitatory and inhibitory neurotransmission through

alcohol-induced inhibition of ENT1 that prompts downstream changes in the function of glutamate and GABA transporters that are expressed on astrocytes.

The functional significance of alcohol-induced changes in astrocyte regulation of GABA and glutamate is becoming well established using multiple approaches. Increased motivation to self-administer alcohol was observed by mimicking alcohol-induced disruptions in nucleus accumbens astrocyte function using gap-junction hemichannel blockers that disengage astrocytic networks (Bull et al., 2014). Activation of astrocytes, on the other hand, was sufficient to reduce motivation to self-administer alcohol by using a GFAP promoter to drive the expression of a designer receptor exclusively activated by a designer drug (DREADD) coupled to a G_q protein in astrocytes (Bull et al., 2014). This approach enables the manipulation of intracellular calcium signaling in a temporally and regionally specific manner, and has been shown to normalize drug-induced alterations in extracellular glutamate (Scofield et al., 2015). Mimicking alcohol-induced downregulation of GLT1 in the nucleus accumbens using a broad-spectrum glutamate transport inhibitor increased alcohol drinking in a four-bottle choice paradigm (Kapasova and Szumlinski, 2008). These findings conflict, however, with a more recent study showing that widespread GLT1 inhibition reduced alcohol binge drinking in a drinking-in-the-dark procedure when administered intracerebroventricularly (Smith et al., 2014). Thus, it appears that GLT1 downregulation and increased extracellular glutamate specifically in the nucleus accumbens may be an important consideration in alcohol drinking. Mice having an ENT1 null mutation display many characteristics associated with chronic alcohol consumption including downregulation of GLT1 and increased extracellular glutamate in the nucleus accumbens (Chen et al., 2010; Lee et al., 2013). ENT1 deficient mice also show reduced alcohol intoxication and enhanced alcohol drinking suggesting that alcohol-induced antagonism of ENT1 plays a central role in alcohol-induced disruptions in glutamate homeostasis and alcohol behaviors (Choi et al., 2004). Using an approach similar to that described for opioids, administration of ceftriaxone is sufficient to normalize alcohol-induced downregulation of GLT1 and also reduces alcohol consumption and relapse-like drinking (Alhaddad et al., 2014; Das et al., 2015; Qrunfleh et al., 2013; Rao and Sari, 2014; Sari et al., 2013). These findings suggest that alcohol impairs the ability of astrocytes to regulate glutamate homeostasis and this impairment is critically important in the development of alcohol dependence.

3.2.3 Psychostimulants—Psychostimulant drugs are a class of drugs that have robust reinforcing effects that are largely associated with their ability to elevate catecholamine neurotransmitters, such as dopamine and norepinephrine. Cocaine and various structurally-related amphetamines including d-amphetamine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) are the most commonly used recreational psychostimulant drugs. Psychostimulants produce large increases in extracellular levels of monoamines through the antagonism or reversal of the neuronal monoamine transporters (Ritz et al., 1990). Notably, their actions at the dopamine transporter plays an especially important role in their abuse liability and has been associated with many of the neuroadaptations resulting from chronic use (Chen et al., 2006).

Similar to the findings reviewed above for opioids and alcohol, psychostimulants produce profound alterations in the ability of astrocytes to regulate glutamate homeostasis. These

effects are especially evident following the chronic administration of cocaine and methamphetamine. In particular, chronic administration of both cocaine and methamphetamine has been shown to increase the expression of GFAP in the nucleus accumbens (Armstrong et al., 2004; Bowers and Kalivas, 2003; Narita et al., 2008). Somewhat paradoxically, cocaine self-administration followed by extinction reduces the expression of GFAP in the nucleus accumbens (Scofield et al., 2016). Perhaps more important is the fact that cocaine self-administration and extinction induces astrocyte shrinkage and reduces perisynaptic processes that regulate synaptic transmission (Scofield et al., 2016). These morphological changes correspond well with reductions in GLT1 expression that are observed following chronic psychostimulant administration and withdrawal (Alshehri et al., 2016; Knackstedt et al., 2010). The downregulation of GLT1 resulting from chronic psychostimulant administration likely impairs glutamate uptake such that re-exposure to cues or the psychostimulant itself results in amplified glutamate release and enhanced synaptic glutamate transmission (Scofield and Kalivas, 2014). The amplification of glutamate signals is exacerbated by psychostimulant-induced changes in basal extracellular glutamate tone (Baker et al., 2003; Parsegian and See, 2014). This is an effect thought to be produced by downregulation of the cysteine glutamate antiporter expressed on astrocytes in the nucleus accumbens (Knackstedt et al., 2010).

Psychostimulant behaviors associated with drug dependence can be reduced by restoring the ability of astrocytes to regulate glutamate homeostasis. Activation of calcium signaling in nucleus accumbens astrocytes through the stimulation of a G_q-DREADD restores extracellular glutamate deficits observed during abstinence from cocaine self-administration (Scofield et al., 2015). Stimulation of the G_q-DREADD also inhibits cocaine seeking elicited by a cocaine-associated cue (Scofield et al., 2015). Administration of the glutamate transport activator, MS-153, attenuates cocaine- and methamphetamine-induced reward in a place conditioning paradigm (Nakagawa et al., 2005). Chronic administration of the antibiotic ceftriaxone has been used to effectively inhibit cocaine and methamphetamine seeking (Abulseoud et al., 2012; Knackstedt et al., 2010; Sari et al., 2009). These behavioral effects are thought to result from a normalization of psychostimulant-induced downregulation of GLT1 and the cysteine glutamate antiporter, ultimately restoring glutamate uptake and basal extracellular glutamate in the nucleus accumbens (Abulseoud et al., 2012; Knackstedt et al., 2010; Sari et al., 2009).

Chronic administration of the cysteine prodrug, N-acetylcysteine, also restores cocaine-induced deficits in extracellular glutamate levels and prevents the excessive levels of glutamate observed following cocaine re-exposure (Baker et al., 2003; Madayag et al., 2007; Reissner et al., 2015). These neurochemical changes correspond with a reduction in cocaine seeking. An interesting feature of both ceftriaxone and N-acetylcysteine is that their administration produces relatively lasting reductions in drug seeking when tested in animal models (Madayag et al., 2007; Murray et al., 2012; Reichel et al., 2011). Both ceftriaxone and N-acetylcysteine possess anti-inflammatory effects in addition to reversing psychostimulant-induced changes in GLT1 and restoring glutamate homeostasis (Csontos et al., 2012; Karalija et al., 2014; Kaur and Prakash, 2017; Lujia et al., 2014; Mahmoud and Ammar, 2011; Purwanto and Prasetyo, 2012; Wei et al., 2012). These findings prompt the interesting notion that immune activation and glutamate homeostasis are not mutually

exclusive and may be interrelated phenomena that contribute to the neuropathology of drug abuse.

Several mechanisms have been described regarding how psychostimulants initiate immune activation, although it is not clear whether one or all of these mechanisms contribute to these effects. Psychostimulant-induced imbalances in glutamate homeostasis is a potential mechanism by which endogenous DAMPs are released and activate pattern recognition receptors that are expressed on microglia (Gao and Hong, 2008). HMGB1, for example, has been shown to be increased following methamphetamine administration (Frank et al., 2016a). There is also evidence that cocaine and methamphetamine bind intracellular sigma-1 receptors that typically associate with the endoplasmic reticulum, but can migrate between organelles upon ligand binding (Lever et al., 2016; Nguyen et al., 2005; Sharkey et al., 1988; Yao et al., 2011). In fact, HMGB1 has been shown to increase via sigma-1 receptors in cultured astrocytes treated with methamphetamine (Zhang et al., 2015). Stimulation of sigma-1 receptors is thought to activate microglia, and perhaps astrocytes, to initiate both proinflammatory and anti-inflammatory responses (Gardner et al., 2004; Gekker et al., 2006; Yao et al., 2011; Zhao et al., 2014). Lastly, there is some evidence to suggest that psychostimulants activate TLRs expressed on glial cells (Liao et al., 2016; Northcutt et al., 2015). It is likely that the immune activation is initiated by a combination of these mechanisms over the course of chronic psychostimulant administration.

One of the first illustrations of immune activation in the brain and microglial activation was shown with the administration of methamphetamine (Asanuma et al., 2004; Asanuma and Cadet, 1998; Yamaguchi et al., 1991). Here, high doses of methamphetamine promote NFκB-DNA binding and induce proinflammatory cytokine gene expression. More recent studies have identified that both cocaine and methamphetamine increase proinflammatory cytokines in the nucleus accumbens, hippocampus and prefrontal cortex (Cearley et al., 2011; Gonçalves et al., 2008). Interestingly, cocaine-induced increases in IL1β were inhibited by the low-affinity TLR4 antagonist, (+)-naloxone, suggesting the involvement of the TLR4 receptor (Northcutt et al., 2015). These findings are supported by increases in TNF, IL6 and CCL2 observed in cultured microglia treated with cocaine, an effect associated with activation of TLR2 (Liao et al., 2016).

It is becoming increasingly clear that psychostimulant-induced immune activation powerfully contributes to the behavioral effects of psychostimulant drugs. Thus, the putative microglial inhibitor, minocycline, reduces cocaine-induced dopamine release and conditioned place preference (Northcutt et al., 2015) and the anti-inflammatory glial attenuator and non-selective phosphodiesterase inhibitor, ibudilast, attenuates sensitization to cocaine in male and female rats (Poland et al., 2016). Other microglial inhibitors suppress methamphetamine self-administration, locomotion, sensitization, and relapse (Beardsley et al., 2010; Chen et al., 2012; Snider et al., 2013, 2012). There is little work identifying the effects of PPARγ agonists on psychostimulant effects, although a recent study suggests that PPARγ stimulation reduces cocaine cue reactivity suggesting that it may reduce behaviors associated with relapse (Miller et al., 2016). Pharmacological inhibition of TLR4 impairs the ability of cocaine to elevate dopamine in the nucleus accumbens, disrupts the development of conditioned place preference and reduces the self-administration of cocaine (Northcutt et

al., 2015). Genetic models of disrupted TLR4 function also show reduced cocaine-induced locomotion and impairments in cocaine self-administration (Northcutt et al., 2015; Thomsen and Caine, 2011). Furthermore, there is support for a role of TLR4 in cocaine relapse as cocaine-primed reinstatement is diminished by inhibiting immune signaling initiated by the TLR4 pro-inflammatory pathways (unpublished observations, RKB et al.). Interestingly, inhibition of TLR4 during withdrawal did not reduce the incubation of methamphetamine craving (Theberge et al., 2013). Recent work by Tanda et al. (2016) has also raised concerns about the role of TLR4 in psychostimulant action. These studies reveal that the low-affinity TLR4 antagonists, (+)-naloxone and (+)-naltrexone, fail to alter cocaine-induced extracellular dopamine and higher doses (56 mg/kg, s.c.) of the TLR4 antagonists have generalized suppressive effects on food-reinforced behavior (Tanda et al., 2016). Nonetheless, there is substantial evidence suggesting that immune activation occurs following psychostimulant administration and plays a role in psychostimulant-induced behaviors, although the role of TLR4 in this activation remains inconclusive.

3.3 Clinical Implications of Glial Cell Modulators

Studies demonstrating the significant interaction between drugs of abuse and glia have provided clinical investigators with novel targets in their efforts to develop medications to treat substance use disorders. New and existing medications that affect glial activity have been investigated for their ability to treat various aspect of addiction, from craving to withdrawal (Table 2).

A major target of this area of research has focused on the ability of glial modulators to alter the abuse potential of opioid drugs. Attenuating the abuse potential of opioids has proven to be a significant pharmacological challenge as the physiological targets responsible for their abuse liability (mu opioid receptor) also mediate their medicinal value as analgesics (Feltenstein and See, 2008; Matthes et al., 1996). Accordingly, clinical exploration has been encouraging with glial modulators since these drugs are not acting via traditional neuronal mechanisms of altering the abuse potential of opioids [mu opioid receptor agonism (e.g., buprenorphine, methadone) or antagonism (e.g., naltrexone)]. Glial modulators may prove to be an effective pharmacotherapeutic that can affect abuse potential without altering analgesic value.

In clinical laboratory studies, abuse potential is typically quantified using self-administration procedures to assess the potential of the drug to serve as a reinforcer, or by using self-report measurements of the positive subjective effects of the drug (Jasinski, 1977; Jones and Comer, 2013). The ability of a medication to reduce the self-administration of an addictive substance or attenuate its positive subjective effects in clinical laboratory studies is typically predictive of its treatment potential outside of the laboratory (Comer et al., 2012, 2010). A glial modulator that has been investigated in this respect is the peroxisome proliferator-activated receptor gamma (PPARγ) agonist, pioglitazone (PIO or Actos). PPARs belong to the nuclear hormone receptor family and are expressed in neurons, oligodendrocytes, astrocytes and microglia within the central nervous system (Gélinas et al., 2005; Moreno et al., 2004; Sarruf et al., 2009; Woods et al., 2003). Interest in PPARγ agonists has grown in many neuroinflammatory disorders due to the expression of PPARγ primarily in microglia

and the ability of PPARγ agonists to inhibit the expression of cytokines by monocytes/macrophages and microglia (Kielian and Drew, 2003). In response to the promising preclinical research (de Guglielmo et al., 2016, 2015), researchers sought to test the ability of PIO to alter the abuse potential of opioids in human subjects. One of these trials maintained non-dependent prescription opioid abusers (n=17 completers) on an ascending daily dose of PIO (0 mg, 15 mg, 45 mg) for 2–3 weeks per dose. In this within-subjects trial, each PIO maintenance period culminated with a laboratory session assessing the subjective, analgesic, physiological and cognitive effects of oral 30 mg oxycodone (OXY). The investigators found that OXY produced dose-dependent increases in positive subjective responses. PIO administration appeared not to alter OXY-induced increases in positive subjective effects as ratings on measures of drug "liking," "high," and "good drug effect" were not significantly altered as a function of PIO maintenance dose (Jones et al., 2016). The authors concluded that PIO may not be useful for reducing the abuse liability of OXY (Jones et al., 2016). Yet among the study's limitations the investigators note that results obtained from a non-dependent sample of opioid users, may not be generalizable to heavier, opioid-dependent users. According to the theory of opioid-induced glial activation and neuroinflammation, chronic opioid (ab)users may have higher tonic levels of glial activity upon which PIO or another glial modulator could act upon (Hutchinson et al., 2007; Mellon and Bayer, 1998; Peterson et al., 1998; Song and Zhao, 2001).

Clinical researchers also followed-up on the promising preclinical findings with ibudilast. In the first clinical assessment, Cooper and colleagues (2016) assessed the ability of ibudilast to alter opioid withdrawal symptoms in participants with opioid use disorder who were maintained on morphine and then abruptly switched to placebo morphine under double-blind conditions. Heroin-dependent volunteers (n=31) were randomized to active (20 or 40 mg, BID) or placebo ibudilast, while concurrently maintained on morphine (30 mg, QID) for 14 days, and subsequently placebo (0 mg, QID) for the last 7 days of the 3-week study. Subjective and clinical ratings of withdrawal symptoms were completed daily using the Subjective Opioid Withdrawal Scale (SOWS) and Clinical Opioid Withdrawal Scale (COWS). All groups exhibited withdrawal during the third week. Analyses pooling the two ibudilast groups demonstrated that they had lower ratings of withdrawal symptoms on SOWS items ('anxious,' 'perspiring,' 'restless,' 'stomach cramps') during the 3rd week, relative to the placebo group.

Metz and colleagues (Metz et al., 2017) extended these findings by testing the effects of ibudilast on the subjective and reinforcing effects of OXY. Non-treatment seeking opioid users (n=11) first underwent inpatient detoxification followed by maintenance on placebo (0 mg ibudilast, BID) and active ibudilast (50 mg, BID). The subjective and reinforcing effects of oral oxycodone (0 mg, 15 mg, and 30 mg/70 kg) were assessed under each maintenance condition. While under active ibudilast maintenance, subjects' ratings of drug "liking" were significantly decreased for the median oxycodone dose (15 mg). The reinforcing efficacy of the 15 mg dose of oxycodone was also significantly lower in the active versus the placebo ibudilast condition, with a statistical trend towards significance being observed for the 30 mg dose. The investigation also found that opioid craving was significantly reduced by ibudilast.

In addition to opioid abuse, ibudilast also has shown potential utility in treating subjects with alcohol use disorder. In a recent trial, the effects of Ibudilast (50 mg, BID) on measures of subjective response to alcohol, drug cue and stress were examined among participants (n=24) with current (i.e., within the past month) mild-to-severe alcohol use disorder (Ray et al., 2017). After 7 days of medication maintenance, participants completed an IV alcohol administration session (up to target breath alcohol contents: 0.02, 0.04, 0.06, and 0.08 g/dl), an alcohol cue session and a stress-exposure session. Active ibudilast maintenance was associated with greater resilience in response to stress- and alcohol-cue exposure and reduced drug craving. Under certain conditions ibudilast was also able to attenuate stimulating and other subjective effects of alcohol.

Ibudilast also has a significant impact on the treatment of drug use disorders involving psychostimulants. Despite numerous clinical trials, no medications have been shown to be consistently efficacious for the abuse of cocaine and amphetamine-type stimulants (Penberthy et al., 2010). For this indication ibudilast has shown promise in clinical laboratory studies. Ibudilast was safe and well tolerated in combination with IV methamphetamine (DeYoung et al., 2016). Worley and colleagues (2016) examined whether ibudilast would reduce subjective effects of methamphetamine among non-treatment seeking, methamphetamine-dependent volunteers (n=11). Using a within-subjects design, the subjective effects of IV methamphetamine (15 mg, 30 mg) were examined using a visual analog scale (VAS), following 7 days of maintenance on placebo, moderate-dose ibudilast (40 mg, BID), and high-dose ibudilast (100 mg, BID). In comparison to placebo, the investigators found that ibudilast reduced methamphetamine-induced effects including: “high,” “like,” “good effect,” “likely to use,” and “stimulated.” Effects of ibudilast were largest for 100 mg on “any effect,” “good effect,” and “high.” A phase 2 efficacy trial of ibudilast 100 mg among outpatients with methamphetamine use disorder will complete enrollment in 2017.

The strength of the association between glial inhibition and reduced abuse potential of psychostimulants is further supported by a clinical investigation with minocycline (Sofuoglu et al., 2011). Among a group of healthy volunteers (n=10), 5 days of minocycline treatment (200 mg/day) was found to attenuate the positive subjective effects of oral dextroamphetamine (20 mg/70 kg). Though these effects are promising, no effect upon drug self-administration was found.

The phosphodiesterase and TNF-α inhibitor, pentoxifylline, was examined as a possible pharmacotherapy for cocaine dependence in a pilot clinical trial of several medications in combination with cognitive behavioral therapy (Ciraulo et al., 2005). Among 16 cocaine-dependent participants maintained for 8 weeks on pentoxifylline (1200 mg/day), the investigators found a trend towards decreased cocaine use and reductions in Addiction Severity Index (ASI) drug composite scores. The glia modulator produced the only positive medication effect observed across five medications tested [paroxetine (antidepressant), pramipexole (dopamine agonist), riluzole (glutamate release inhibitor), venlafaxine (antidepressant)].

Another promising pilot trial with the medication PIO has provided encouraging results for the possibility of using glial modulators as pharmacotherapies for cocaine use disorder (Schmitz et al., unpublished observations). In this double-blind clinical study, participants seeking treatment for cocaine use disorder were randomized to receive either PIO 45 mg (n=15) or placebo (n=15) daily for 12 weeks. Measures of urine toxicology and cocaine craving were recorded at multiple time points throughout the study period. Self-reported cocaine use was significantly lower for the active PIO maintenance group, although the portion of cocaine-negative urine samples was not significantly greater than during placebo treatment. Significant reductions in drug craving were also observed only among participants in the active PIO maintenance group.

Several clinical trials have also assessed N-acetylcysteine as a potential pharmacotherapeutic in treating substance use disorder. An initial study assessed cocaine craving and its rewarding properties following intravenous cocaine administration using an inpatient (n=4 cocaine dependent males), laboratory-based, crossover study design comparing two doses of N-acetylcysteine and baclofen (Amen et al., 2011). Compared with baclofen, both low (400 mg, TID) and high (800 mg, TID) doses of N-acetylcysteine reduced cocaine craving following an intravenous cocaine injection, but did not alter the reinforcing properties of cocaine. In a follow-up placebo controlled study in treatment-seeking cocaine-dependent adults (n=111), N-acetylcysteine was tested for its efficacy in promoting cocaine abstinence (LaRowe et al., 2013). All participants received cognitive-behavioral therapy over an 8-week treatment period and were randomized to receive either 600 or 1200 mg (BID) N-acetylcysteine or placebo during the treatment phase. Treatment with N-acetylcysteine did not reduce cocaine use or craving, although it was observed that participants administered 1200 mg (BID) who were abstinent from cocaine at the beginning of the trial remained abstinent longer and had reduced cocaine cravings.

Another clinical trial assessed the effects N-acetylcysteine (vs placebo) in combination with cognitive-behavioral therapy on post-traumatic stress disorder symptomology and substance abuse (i.e., alcohol use disorder or cocaine use disorder) among 35 dual-diagnosed veterans (Back et al., 2016). The investigators found that active N-acetylcysteine maintenance (2,400 mg/day for eight weeks) significantly reduced drug craving and depression, although no medication effects on drug-taking behavior were found. Similar reductions in craving were observed in a double-blind, controlled crossover study of methamphetamine-dependent volunteers (N=23 completers). In this within-subjects design participants were randomized to begin four weeks of maintenance on active N-acetylcysteine (600 mg/day for one week, 1200 mg/day three weeks) or placebo. Mean drug craving scores across the four weeks were significantly lower during active N-acetylcysteine maintenance (Mousavi et al., 2015). Additional trials for nicotine and cannabis dependence have also yielded promising findings (Grant et al., 2014; Gray et al., 2012). Thus, there appears to be some promise in targeting glial-mediated glutamate dysregulation, although there is mixed support for the glial glutamate modulator N-acetylcysteine as a viable pharmacotherapeutic for psychostimulants. The ability to alter glutamate dysregulation/glial activity in selective brain regions in preclinical studies may be the cause of the discrepant findings, highlighting the challenges in translating preclinical findings to effective clinical pharmacotherapeutics.

Thus, despite preclinical findings suggesting that glial-mediated glutamate dysregulation is a unifying feature of various substance use disorders, there is mixed support for the glial glutamate modulator N-acetylcysteine as a viable pharmacotherapeutic.

4. Conclusions

The contribution of drug-induced glial activity to sustained drug abuse and dependence is not yet fully understood, but the evidence for their association continues to grow. The molecular and pharmacological discovery of their interaction has led to preclinical behavioral studies demonstrating that the manipulation of glia modulates the effects of many drugs of abuse. Results from some clinical investigations modulating this interaction have been promising, although not all have been positive. Yet, given the few studies involving this approach, there remains significant opportunity for continued exploration in the development and testing of glial-targeted medication and treatment for substance use disorders.

Although some current pharmacotherapies that directly or indirectly alter the neuronal targets of addictive drug are effective to a degree, targeting glial may prove to be an additional approach to treat intractable cases. Of particular pertinence may be the neuroadaptive and behavioral changes that are associated with repeated exposure to commonly abused drugs. With more research, an enhanced understanding of the relationship between glia and the pathophysiology of substance abuse will lead to improved development and testing of medications to evaluate the efficacy of glial modulators as addiction therapies.

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Highlights

- Drugs of abuse alter the functioning of astrocytes and microglia.
- Drug-induced changes in glial function contribute to lasting behavioral changes.
- Glia-directed pharmacotherapies show promising preclinical and clinical efficacy.

Table 1

Effects of Glial Modulators in Preclinical Behavioral Studies

Drug of abuse	Behavior	Intervention	Effect	Citation
Opioids	Conditioned Place Preference	Microglial inhibitor	↓	Hutchinson et al., 2008
		TLR4 antagonist	↓	Hutchinson et al., 2012
		GLT-1 upregulation/activation	↓	Fujio et al., 2005; Nakagawa et al., 2005
	Self-administration	TLR4 antagonist	↓	Hutchinson et al., 2012
		PPARγ agonist	↓	de Guglielmo et al., 2015
	Drug Seeking	Microglial inhibitor	↓	Arezoomandan and Haghparast, 2016
		TLR4 antagonist	↓	Theberge et al., 2013
		PPARγ agonist	↓	de Guglielmo et al., 2016, 2015
		GLT-1 upregulation/activation	↓	Shen et al., 2014
		Cystine-glutamate exchange activator	↓	Zhou and Kalivas, 2008
Alcohol	Drinking/Self-administration	Microglial inhibitor	↓	Agrawal et al., 2011; Bell et al., 2013; Syapin et al., 2016
		TLR4 antagonist	NC	Harris et al., 2016
		PPARγ agonist	↓	Blednov et al., 2015; Ferguson et al., 2014; Stopponi et al., 2013
		GLT-1 upregulation/activation	↓	Alhaddad et al., 2014; Das et al., 2015; Sari et al., 2016, 2011
		Astrocytic G_q DREADD activation	↓	Bull et al., 2014
	Drug Seeking	Microglial inhibitor	↓	Bell et al., 2013
		GLT-1 upregulation/activation	↓	Qrunfleh et al., 2013; Rao and Sari, 2014; Weiland et al., 2015
Psychostimulants	Conditioned Place Preference	Microglial inhibitor	↓	Northcutt et al., 2015; Poland et al., 2016
		TLR4 antagonist	↓	Northcutt et al., 2015
		GLT-1 upregulation/activation	NC	Abulseoud et al., 2012
	Self-administration	Microglial inhibitor	↓	Snider et al., 2013
		TLR4 antagonist	↓	Northcutt et al., 2015; Tanda et al., 2016
		GLT-1 upregulation/activation	↓	Ward et al., 2011
		Cystine-glutamate exchange activator	NC	Murray et al., 2012
	Drug Seeking	Microglial inhibitor	↓	Beardsley et al., 2010
		TLR4 antagonist	NC	Theberge et al., 2013
		PPARγ agonist	↓	Miller et al., 2016
		Astrocytic G_q DREADD activation	↓	Scofield et al., 2015
		GLT-1 upregulation/activation	↓	Abulseoud et al., 2012; Knackstedt et al., 2010; Sari et al., 2009
		Cystine-glutamate exchange activator	↓	Baker et al., 2003; Madayag et al., 2007; Murray et al., 2012; Reichel et al., 2011; Reissner et al., 2015

↓ - Significant decrease; NC - No significant change detected

Table 2

Effects of Glial Modulators in Clinical Studies

Drug of Abuse	Indication	Intervention	Outcome Measure	Effect	Sample Size	Citation
Opioids	Withdrawal	Microglial inhibitor	SOWS COWS	↓	31	Cooper et al., 2016
	Abuse Potential	PPARγ agonist (Cytokine inhibitor)	Positive Subjective Effects	NC	17	Jones et al., 2016
		Microglial inhibitor	Positive Subjective Effects	↓	11	Metz et al., 2017
			Drug Self-Admin	↓		
			Drug Craving	↓		
Alcohol	Abuse Potential	Microglial inhibitor	Stress and Cue-Induced Craving	↓	24	Ray et al., 2017
			Positive Subjective Effects	NC		
Psychostimulants	Abuse Potential	Microglial inhibitor	Positive Subjective Effects	↓	11	Worley et al., 2016
			Positive Subjective Effects	↓	10	Sofuoglu et al., 2011
		Cystine-glutamate exchange activator	Positive Subjective Effects	NC	4	Amen et al., 2011
			Drug Use	NC		
			Craving	↓		
		Cytokine inhibitor	Drug Use	↓	16	Ciraulo et al., 2005
		Cystine-glutamate exchange activator	Craving, Cue Reactivity	↓	15	LaRowe et al., 2007
			Drug Use	NC	111	LaRowe et al., 2013
			Craving	NC		
			Craving	↓	35	Back et al., 2016
			Craving	↓	23	Mousavi et al., 2015
		PPARγ agonist (Cytokine inhibitor)	Craving	↓	15	Schmitz et al., 2017

↓ - Significant decrease; NC - No significant change detected