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Review

Neuroinflammation in addiction: A review of neuroimaging studies and potential immunotherapies

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ABSTRACT

Addiction is a worldwide public health problem and this article reviews scientific advances in identifying the role of neuroinflammation in the genesis, maintenance, and treatment of substance use disorders. With an emphasis on neuroimaging techniques, this review examines human studies of addiction using positron emission tomography to identify binding of translocator protein (TSPO), which is upregulated in reactive glial cells and activated microglia during pathological states. High TSPO levels have been shown in methamphetamine use but exhibits variable patterns in cocaine use. Alcohol and nicotine use, however, are associated with lower TSPO levels. We discuss how mechanistic differences at the neurotransmitter and circuit level in the neural effects of these agents and subsequent immune response may explain these observations. Finally, we review the potential of anti-inflammatory drugs, including ibudilast, minocycline, and pioglitazone, to ameliorate the behavioral and cognitive consequences of addiction.

1. Introduction

Neuroinflammation has been attributed to the pathogenesis of a number of central nervous system (CNS) diseases (Block and Hong, 2005; Chen et al., 2016; Tansey et al., 2007), and although classically defined as the accumulation of mobile innate and/or adaptive immune cells in the tissue, there is diversity in what is considered to be inflammation in the brain, including gliosis, microglia activation, and the release of cytokines, chemokines, and pro-inflammatory factors (see "Neuroinflammation in psychiatric disorders: an introductory primer" in this Special Issue for additional background information). Broadly, neuroinflammation is thought to contribute to the neural adaptations following chronic exposure to drugs of abuse (Lacagnina et al., 2017; Liu et al., 2016; Pocock and Kettenmann, 2007), as many drugs render the brain more vulnerable to inflammation and resultant neuropathology. There is considerable interest in the mechanism by which drug use interacts with inflammatory processes, contributing to brain dysfunction, impairing cognitive control, and consequently promoting drug-use behavior. Preclinical studies show that drug exposure increases the release of pro-inflammatory cytokines, and glial cells (microglia and astrocytes) with chemokine and cytokine receptors respond quickly to CNS injury (Pocock and Kettenmann, 2007). Drug-induced dysregulation of neuroimmune signaling may compromise neuronal function, exacerbate neurodegeneration, and increase neurotoxicity, which may contribute to drug-related behavior through the activation of microglia and other glia-mediated synaptic remodeling (Lacagnina et al., 2017; Liu et al., 2016; Pocock and Kettenmann, 2007). Although the neural circuits relevant to substance use disorders may be impaired before inflammation or drug use, drug-induced inflammation may further compromise brain function in individuals with substance use disorders. It is, therefore, important to examine the combination of insults and interactive effects of substance use and neuroinflammation as new

Abbreviations: DA, dopamine; GABA, gamma-aminobutyric acid; IL, interleukin; PET, positron emission tomography; PPAR, peroxisome proliferator-activated receptors; TNF, tumor necrosis factor; TSPO, translocator protein

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therapeutic strategies are considered.

The neuroimmune response to drugs of abuse is characterized, in part, by proliferation and morphological and functional changes of microglia and astrocytes (Ransohoff and Brown, 2012). Microglia are distributed throughout the brain with greatest concentrations found in substantia nigra, basal ganglia, and hippocampus (Lawson et al., 1990). Microglia respond directly to drug-induced CNS injury and are activated by stimulation of chemokine and cytokine receptors or by peripheral signals, potentially resulting from drug-induced damage to the blood brain barrier (Lacagnina et al., 2017; Loftis and Huckans, 2013). Activation of microglia results in a number of downstream processes including cell migration to the site of injury and phagocytosis (Hanisch, 2002; Otten et al., 2000), the production of pro-inflammatory factors, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), and the generation of reactive oxygen and nitrogen species that cause neuronal damage (Beardsley and Hauser, 2014). Astrocytes play a critical role in the uptake of synaptically-released glutamate (Cui et al., 2014), are affected by the activity level of dopamine (DA) neurons (Imaizumi et al., 2008), and can shape DA neuron activity and plasticity (Jucaite et al., 2012). Like microglia, astrocytes produce and secrete pro-inflammatory cytokines in response to tissue injury or other insults (Ransohoff and Brown, 2012), including exposure to substances of abuse (Lawson et al., 1990). Thus, excess neurotransmitters (e.g., DA and glutamate) released by drug use may bind to receptors expressed on glial cells and further amplify inflammatory signaling via additional release of cytokines and chemokines, potentially contributing to positive feedback that promotes inflammation.

A number of animal studies have established a link between neuroinflammation and drug exposure (Lacagnina et al., 2017; Loftis and Huckans, 2013), and it is important that work in humans expand on preclinical work to extend the clinical relevance and address the greater complexity of human drug use. The following review will, therefore, focus on findings from human neuroimaging studies of addiction, with an emphasis on positron emission tomography (PET). Although astrocytes are the most abundant type of glial cell in the brain and are affected by substances of abuse (Bull et al., 2015; Cao et al., 2016), there are no techniques to directly quantify astrocyte activation in humans in vivo. Currently, in vivo quantification of glial activation is only available to examine ligand binding of the 18-kDa translocator protein (TSPO), a protein formerly known as the peripheral benzodiazepine receptor and primarily located on the outer membrane of mitochondria. Within the CNS, a variety of cells are capable of expressing TSPO; however, the pattern of expression appears to differ between normal and injured CNS (Cosenza-Nashat et al., 2009). Second generation radiotracers such as [^{18}F]FEDAA1106, [^{11}C]PBR28, [^{11}C]DPA-713, and [^{18}F]DPA-714 now provide better specific binding ratios (Imaizumi et al., 2008) and higher test-retest, intra-individual reproducibility (Jucaite et al., 2012) compared with first generation [^{11}C](*R*)-PK11195. A number of clinical studies show changes in TSPO binding with [^{11}C]PBR28 (Hannestad, 2012), and more studies have begun investigating TSPO levels in addictions, specifically alcohol, nicotine, methamphetamine, and cocaine use disorders. As clinical and preclinical studies have demonstrated a link between immunological cells in blood and activated microglia (Kanegawa et al., 2016), this review will highlight the work conducted using PET as an index for neuroinflammation and also examine relevant work with magnetic resonance imaging linking brain function to peripheral markers of inflammation in substance use disorders. The review includes the limitations of PET imaging as an index of neuroinflammation and concludes with a brief summary of therapeutic strategies that may help target and treat the combination of insults and interactive effects of substance abuse and neuroinflammation.

2. Methamphetamine

Methamphetamine exposure impairs mitochondrial energetic metabolism, which enhances susceptibility to oxidative stress, pro-apoptosis, and neuroinflammation (Shin et al., 2018), including release of inflammatory cytokines and microglial activation (Banerjee et al., 2010; Clark et al., 2013; Goncalves et al., 2008; LaVoie et al., 2004; Loftis et al., 2011; Loftis and Janowsky, 2014; Mahajan et al., 2008; Silverstein et al., 2011; Wisor et al., 2011). Methamphetamine-induced DA and glutamate release also contribute to neuroinflammation. Excess DA autoxidizes to form toxic quinones, and quinone cycling results in oxidative stress, mitochondrial dysfunction, and damage to presynaptic membranes due to the production of superoxide radicals and hydrogen peroxide (Shah et al., 2012). Monoamine oxidase also oxidizes DA to form reactive oxygen species leading to cell damage and death through an increase in hydrogen peroxide, which interacts with metal ions to form toxic hydroxyl radicals (Ransohoff and Brown, 2012). In addition, excess prefrontal glutamate release by methamphetamine activates metabotropic glutamate receptors subtype 5 (mGluR5), which promotes the release of nuclear transcription factors (e.g., nuclear factor kappa light chain enhancer of activated B cells (NF-κB)) through intracellular signaling pathways (AKT/P13K) (Shah et al., 2012). Translocation of the transcription factors to the nucleus promotes the expression of pro-inflammatory cytokines (Ojaniemi et al., 2003; Shah et al., 2012).

Neuroimaging studies provide further evidence for methamphetamine-induced neuroinflammation. Magnetic resonance spectroscopy studies to assess metabolic alterations linked to immune cell activity show reductions in the ratio of creatine plus phosphocreatine (Cr + PCr)/choline-containing compound (Cho) and in the concentration of *N*-acetylaspartate (NAA) in individuals with a history of methamphetamine use (Ernst et al., 2000; Sekine et al., 2002). These markers are also correlated with years of methamphetamine use and severity of psychiatric symptoms (Ernst et al., 2000; Sekine et al., 2002), suggesting that neurotoxicity increases as a function of methamphetamine exposure. Individuals with a history of methamphetamine use (average duration of use: 6.8 years) also exhibit greater microglial activation indexed by [^{11}C](*R*)-PK11195 PET in midbrain, striatum, orbitofrontal and insular cortex (Sekine et al., 2008), and lower levels of microglial activation are associated with greater duration of abstinence (average duration of abstinence: 1.8 years). This study, however, used the time activity curve of healthy controls as an input function, and the effect of differing plasma curves between methamphetamine and controls could lead to inaccurate assessment of regional TSPO binding using compartmental models (see Limitations section).

A recent study shows that increased peripheral IL-6 levels in individuals with a history of methamphetamine use are positively correlated with greater resting-state functional connectivity between the nucleus accumbens, amygdala, and hippocampus but inversely correlated with connectivity between the dorsolateral prefrontal cortex and striatum (Kohno et al., 2018). This is consistent with reports that methamphetamine use is associated with stronger functional connectivity within DA terminal regions, including striatum and limbic structures (Dean et al., 2014; Kohno et al., 2014; Kohno et al., 2016). As peripheral markers of immune activation are associated with impaired cognition (Loftis et al., 2011) and with abnormalities in prefrontal and striatal function (Felger et al., 2016), neuroinflammation may promote mesocorticolimbic and cognitive deficits commonly seen in methamphetamine use disorder. To the extent that DA plays a role in reward processing and executive function, it is possible that neuroinflammation promotes addiction-related brain and behavioral deficits (Dean et al., 2012; London et al., 2015) through altered activity of the mesocorticolimbic DA system. Consistent with this notion, activation of DA D1 and D2 receptors on microglia promotes migration (Farber et al., 2005), and microglial activation precedes the methamphetamine-induced degeneration of DA terminals in the striatum (Thomas et al., 2004; LaVoie et al., 2004). Moreover, individuals with methamphetamine use disorder consistently show low DA D2 receptor availability, which, in turn, is negatively related to mesolimbic functional connectivity (Kohno

et al., 2016). These studies provide compelling evidence that methamphetamine exposure leads to activation of neuroinflammatory pathways in regions where individuals with a history of methamphetamine use consistently show deficits in gray matter volume and brain function (London et al., 2015).

Results from postmortem studies suggest that methamphetamine use enhances oxidative stress. One study assessed 4-hydroxynonenal and malondialdehyde (produced from lipid peroxidation), as markers of oxidative stress in postmortem brain of adults with and without prior methamphetamine exposure. For 4-hydroxynonenal, 50% of those in the methamphetamine group had levels above the upper limits of the control group range, and a dose-response analysis showed that the high-dose methamphetamine group had higher concentrations of 4-hydroxynonenal and malondialdehyde in striatum, cerebral cortex, and cerebellar cortex (Fitzmaurice et al., 2006). Postmortem results of methamphetamine-induced gliosis, however, are conflicting. Two studies examining gliosis assessed with histopathological analysis did not detect methamphetamine-induced gliosis (Moszczynska et al., 2004; Wilson et al., 1996), whereas another study using quantitative analysis of microglia and astrocyte markers found a marked increase of microglial markers in striatum in individuals with a history of methamphetamine use compared to controls (Kitamura et al., 2010). Differences among studies could be attributed to factors including age, genetic heterogeneity, sex, comorbidities, amount and duration of drug exposure, cause of death, and postmortem interval (Gomez-Nicola and Boche, 2015), as well as the qualitative and quantitative analysis methods. Interestingly, a postmortem study of individuals with a history of cocaine use found a marked increase (108%) in the number of activated microglia cells in the midbrain (Little et al., 2009). In the following section, similarities and differences in other markers of immune system signaling between cocaine and methamphetamine use are discussed.

3. Cocaine

Cocaine also increases dopaminergic and glutamatergic signaling; subsequent DA and glutamate stimulation of immune cells likely facilitates an inflammatory response like that induced by methamphetamine. Chronic cocaine use is associated with an increase in IL-6 (Ersche et al., 2014; Fox et al., 2012; Levandowski et al., 2016; Moreira et al., 2016) and also with a reduction in circulating levels of the anti-inflammatory/immunoregulatory factor, IL-10, and an increase in the ratio of pro-inflammatory to anti-inflammatory markers (Moreira et al., 2016). Acute cocaine exposure, however, seems to have an opposite effect and reduces levels of IL-6 (Halpern et al., 2003; Irwin et al., 2007). Whether a reduction in IL-6 is an anti-inflammatory response to acute cocaine use or a pro-inflammatory response is unclear, as regenerative or inflammatory processes of IL-6 are dependent on trans-signaling or classic signaling, respectively (Scheller et al., 2011). Variability between the response to acute exposure or chronic use may explain mixed results in pro- and anti- inflammatory responses and may contribute to differences seen in levels of TSPO.

Postmortem tissue of individuals with a history of cocaine use show a significant increase in activated microglia compared to controls (Little et al., 2009), while there are no significant quantifiable differences in TSPO levels indexed with [^{11}C]PBR28 PET between individuals with prior cocaine use and controls (Narendran et al., 2014). Like IL-6, activation of microglia may also depend on patterns of use, as participants in the PET study were approximately two weeks abstinent from cocaine, while post mortem tissue were collected from individuals with recent use.

Although it is expected that cocaine and methamphetamine would affect microglia in similar ways, differences between cocaine and methamphetamine on DA kinetics have been shown in both human and animals studies, which can manifest in differences in neuroinflammation. In animals, the levels of DA are higher after administration of methamphetamine than after cocaine. Higher levels of intrasynaptic DA and slower clearance of methamphetamine compared to cocaine contributes to the longer behavioral effects, oxidative stress, and damage to the dopaminergic system (Koob, 1998). Amphetamines and methamphetamine have longer half-lives compared to that of cocaine, where the duration of action for cocaine is approximately 1–3 h, while the half-life of amphetamines and methamphetamine are approximately 8–13 h (Harris et al., 2003; Jufer et al., 2000). In non-human primates, [^{11}C]cocaine and [^{11}C]d-methamphetamine show differences in brain distribution, kinetics, and clearance rates. Not only does [^{11}C]d-methamphetamine peak more slowly than [^{11}C]cocaine, but it also clears more slowly than cocaine, and its distribution extends beyond the striatum to cortical brain regions (Fowler et al., 2007). Similarly, in humans, cocaine is concentrated only in the striatum and its uptake and clearance are faster than that of methamphetamine (Fowler et al., 2008).

While differences in DA kinetics and signaling are factors that may explain differences in patterns of microglial activation in methamphetamine and cocaine use disorder, methodological variability among the studies needs to be noted. Differences in radioligand and analysis methods could contribute to mixed results along with the heterogeneity of genotypes conferring binding affinity. Another important factor is glutamate neurotransmission and both cocaine and methamphetamine use are associated with an increase in glutamate release and down regulation of glutamate transporters (Kalivas, 2007). Inflammatory cytokines similarly increase glucose metabolism (Haroon et al., 2014) and extrasynaptic levels of glutamate by decreasing glutamate transporters (Tilleux and Hermans, 2007) and increasing astrocytic glutamate release (Ida et al., 2008). As excess of glutamate promotes the transcription of inflammatory cytokines and activates microglia (Ojaniemi et al., 2003; Shah et al., 2012), more work is necessary to examine the effects of these stimulants on glutamate signaling and the effects on the neural immune response. In addition, future studies controlling for the heterogeneity in recent exposure to stimulant drugs when investigating activated microglia and markers of inflammation are needed.

4. Alcohol

Alcohol exposure is associated with neurotoxicity, activation of microglia, and release of cytokines and inflammatory mediators; these phenomena are now being recognized as contributing factors to alcohol use disorder pathology (Henriques et al., 2018; Mayfield et al., 2013; Pascual et al., 2017; Vetreno et al., 2014). Much of the work showing elevated pro-inflammatory but reduced anti-inflammatory signaling come from preclinical studies of alcohol administration (Henriques et al., 2018).

Three human PET studies, using [^{11}C]PBR28, show lower TSPO levels in individuals with alcohol dependence (Hillmer et al., 2017; Kalk et al., 2017; Kim et al., 2018) and an inverse relationship between TSPO binding and number of drinks per day and alcohol dependence severity (Hillmer et al., 2017). In contrast, a PET study in non-human primates, using [^{18}F]DPA-714, shows a significant increase in TSPO binding during ethanol exposure, which remains elevated for 7–12 months (Saba et al., 2017). Using PET with [^{11}C]PBR28, a study in rats found no differences in TSPO binding between alcohol dependent and non-dependent rats (Kim et al., 2018). Although one human study recruited well-matched controls in age, sex, and cigarette use (Hillmer et al., 2017), it is possible that other drug use history (e.g., marijuana) and environmental factors could contribute to differences between human and animal studies of alcohol-induced activation of microglia. Alternatively, endogenous TSPO ligands such as cholesterol could be a factor in PBR28 binding as genotypes that affect PBR28 binding also affect the cholesterol-binding domain of TSPO (Kim et al., 2018). Another possible explanation is that chronic alcohol use may attenuate the activation of microglia through gamma-aminobutyric acid (GABA)-

mediated inhibition of cytokines. Activation of microglia increases the expression of GABA receptors, and $GABA_B$ receptor agonists reduce IL-6-mediated activation of microglia (Kuhn et al., 2004; Pocock and Kettenmann, 2007). The neuromodulatory effects of chronic alcohol use on GABA release may also induce anti-inflammatory processes, as acute alcohol exposure can increase IL-10 which results in pre- and post-synaptic regulation of GABA transmission (Suryanarayanan et al., 2016).

Chronic and binge models of alcohol exposure provide evidence for alcohol-induced neurotoxicity, which is mediated by innate immunomodulatory responses, such as activation of glial cells, cytokine production, and the neuronal Toll-like receptor 4 (TLR4) response (Crews et al., 2017). Repeated alcohol-mediated neurotoxic insults may compromise the innate immune response or result in complex compensatory and neuroadaptive processes that limit neuroinflammation. Individual differences such as age and sex, however, are important factors in the neuroimmune response (Pascual et al., 2017; Wilhelm et al., 2017), and more studies are needed to better identify the mechanisms by which alcohol use affects immune signaling.

5. Nicotine

Cigarette smoke is associated with both immunosuppressive and immunostimulatory components (Sopori, 2002; Sopori and Kozak, 1998). It is, however, difficult to dissociate the effects of nicotine from those of constituents in tobacco. Cigarette smoking promotes activation of epithelial and immune cells that release pro-inflammatory factors and promote the recruitment of neutrophils, macrophages, T cells, and dendritic cells (Savage et al., 1991; Sopori, 2002; Sopori and Kozak, 1998). Nicotine, in contrast, is thought to be a significant contributor to the inhibition of the antibody response and the immunosuppressive effects of chronic smoking (Geng et al., 1995; Geng et al., 1996). Animal studies show that smoking can increase reactive oxygen species and decrease levels of antioxidants (Savage et al., 1991; Sopori, 2002; Sopori and Kozak, 1998). Increases in inflammatory markers associated with cigarette smoking are also shown to be dose-dependent and related to smoking intensity and time since smoking cessation (Sopori, 2002).

Whether from nicotine or cigarette smoke, neuroimaging studies provide evidence for neuroadaptations in individuals who smoke cigarettes. Smokers, compared to non-smokers, show gray-matter abnormalities throughout the brain (Franklin et al., 2014; Morales et al., 2014; Morales et al., 2012), differences in functional connectivity in prefrontal executive control regions (Fedota and Stein, 2015; Lerman et al., 2014), and an upregulation of nicotinic acetylcholine receptors (Brody et al., 2013; Sabbagh et al., 2002). A recent PET study using [^{11}C]DAA-1106 found less TSPO binding in smokers compared to non-smokers (Brody et al., 2017). As activation of nicotinic acetylcholine receptors result in immunosupressive properties (Guan et al., 2015; Kalra et al., 2004; Wang et al., 2003), the results may highlight an anti-inflammatory effect of cigarette smoking. Evidence points to nicotinic acetylcholine alpha 7 receptor subunits in mediating nicotine-induced suppression of neuroinflammation (Wang et al., 2003) through the inhibition of microglial activation and subsequent pro-inflammatory cytokine release (Guan et al., 2015). As individuals who smoke have lower levels of TSPO, which are inversely correlated with the number of cigarettes smoked per day (Brody et al., 2017), the data are in line with the literature suggesting neuroprotective properties of nicotine and the idea that the anti-inflammatory responses of nicotine may be responsible for the decreased incidence in neurological diseases seen in individuals who smoke cigarettes (Birtwistle and Hall, 1996; James and Nordberg, 1995; Newhouse et al., 1997).

6. Cannabinoids

Despite considerable interest in the neural effects of cannabis (also known as marijuana), there have been no published PET studies of microglial activation in individuals who use cannabis. There are several reports, however, on the neuroprotective properties of cannabinoids, components of the cannabis plant. Acute exposure to cannabinoids [e.g., delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN)] can lower cellular immune responses, inhibit production of inflammatory cytokines and chemokines, reduce excitotoxicity, and decrease neuronal cell damage (Jean-Gilles et al., 2010; McCoy, 2016; Schwaeble and Constantinescu, 2010; Tanasescu and Constantinescu, 2010). Repeated exposure to cannabinoids also has immunomodulatory effects. One study found that individuals with HIV who use cannabis have lower levels of peripheral blood $CD16^+$ monocytes, an index of immune activation, than individuals with HIV who do not use cannabis (Rizzo et al., 2018). Cannabinoid receptor agonists reduce beta-amyloid-induced activation of microglia in Alzheimer's disease models and reduce the onset and severity of autoimmune characteristics of multiple sclerosis in animal models, along with reductions of inflammation (Pacher and Kunos, 2013; Zhang et al., 2009; Martín-Moreno et al., 2012). Resting microglia lack cannabinoid 2 (CB2) receptors; however, there is a significant increase in CB2 receptor expression on microglia on diseased tissues or in culture (Stella, 2009), suggesting that the anti-inflammatory effects of cannabinoids may be mediated by CB2 receptors. The effect of cannabinoids in lowering excitotoxicity and inhibiting the release of pro-inflammatory mediators has important implications in pathological inflammatory conditions, especially substance addiction where co-use is common.

While most evidence supports an anti-inflammatory effect of cannabis, there are reports consistent with pro-inflammatory effects. Individuals with cannabis use disorder show increases in plasma pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α) compared to individuals with no history of cannabis use (Bayazit et al., 2017). Neuroinflammatory responses to cannabis may depend on age at initiation of use. Adult female Sprague-Dawley rats treated with THC in adolescence (postnatal days 35–45) exhibit a persistent neuroinflammatory state within the prefrontal cortex, including up-regulation of CB2 receptors on microglia cells, increased expression of TNF-α and other pro-inflammatory factors, and a reduction in IL-10 levels. Interestingly, this neuroinflammatory phenotype is attenuated by the anti-inflammatory drug, ibudilast when administered during THC treatment (Zamberletti et al., 2015).

The effect of cannabis on inflammatory mediators has important implications in pathological inflammatory conditions, especially addiction, where co-use is common. As evidence supports both pro- and anti-inflammatory responses to cannabis, it is critical for future studies to disentangle the independent effect of cannabis and the interactive effect with other drugs of abuse on immune signaling.

7. Implications for treatment

Methamphetamine, cocaine and, under some circumstances, alcohol evoke a neuro-inflammatory response. Thus, interventions aimed at reducing inflammation may serve as a useful adjunct to behavioral treatments for substance use disorders. Several potential anti-inflammatory pharmacotherapies that have been or are currently being tested in human clinical trials are summarized in Table 1.

Ibudilast (3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine), an anti-inflammatory non-selective phosphodiesterase inhibitor, has neuroprotective and immunomodulatory properties and has shown therapeutic benefit for neuroinflammatory conditions (Burnouf and Pruniaux, 2002), including addictions (Ray et al., 2014). The compound suppresses the production of nitric oxide, reactive oxygen species, IL-1β, IL-6, and TNF-α and enhances the production of anti-inflammatory markers, including nerve growth factor, glia-derived neurotrophic factor, and neurotrophin-4 in activated microglia (Mizuno et al., 2004; Suzumura et al., 1999). Similarly, ibudilast attenuates alcohol drinking in animal models (Bell et al., 2015) and humans (Ray et al., 2017) and reduces methamphetamine-induced locomotor activity and stress-

Table 1
Clinical trials of potential anti-inflammatory treatments for substance use disorder.

Clinical trial	Study design	SUD[a]	Participants	Dose/duration	Outcome measures
Ibudilast					
NCT03341078 Not yet recruiting	Phase II: Double-blind, randomized, placebo controlled, parallel assignment	MA	Use disorder N = 65	20 mg bid (2 wks) 50 mg bid (4 wks)	Neuroinflammation (PET); Monetary Incentive Delay Task and functional connectivity (fMRI); Cognitive function, Craving and MA use
NCT02025998 Completed	Phase I: Double-blind, randomized, placebo controlled, cross-over	Alcohol	Dependence/abuse N = 24	50 mg bid (1 wk)	Alcohol effects; Alcohol urge; Cue & stress-induced craving; Differential emotion
NCT03489850 Not yet recruiting	Phase II: Double-blind, randomized, placebo controlled, parallel assignment	Alcohol	In treatment/seeking N = 50	20 mg (2 d) 50 mg bid (12 d)	Alcohol-related negative reinforcement; Cue-reactivity (fMRI); Withdrawal-related dysphoria
NCT01860807 Not yet recruiting	Phase II: Double-blind, randomized, placebo controlled, cross-over	MA	Treatment seeking N = 140	50 mg bid (12 wks)	MA use; Treatment retention
NCT01860807 Completed	Phase I: Double-blind, randomized, placebo controlled, crossover	MA	Dependence N = 11	20 mg (1 wk) 50 mg bid (1 wk)	Safety and tolerability with MA; Craving and drug effects; Discounting tasks
Minocycline					
NCT03244592 Not yet recruiting	Phase I & II: Double-blind, randomized, placebo controlled, parallel assignment	Alcohol	Dependence/abuse N = 32	200 mg (4 wks)	Neuroinflammation (PET); Cue-induced craving; Alcohol use; Cognitive function
NCT02541500	Phase III: Open label, single group assignment	Opioid Stimulant	Dependence N = 40	200 mg (4 mos)	Stimulant use; Treatment retention; HIV-risk (sex and drug behaviors); Neuropsychological function
NCT02359006 Completed	Double-blind, randomized, placebo controlled, crossover	Opioid	Current methadone maintenance N = 55	200 mg (15 d)	Pain sensitivity; Withdrawal symptoms; Cognitive performance
NCT02187211 Recruiting	Phase I: Double-blind, randomized, placebo controlled, cross-over	Alcohol	Heavy social drinkers N = 60	200 or 400 mg (10 d)	Effects of alcohol
Pioglitazone					
NCT01395784 Completed	Phase II: Non-randomized	Opioid	Prescription abuse N = 32	15 then 45 mg (9 wks)	Subjective drug effects (VAS) Analgesic Response (Cold pressor test)
NCT01517165 Completed	Phase I: Randomized, Parallel Assignment	Opioid	In treatment with buprenorphine N = 24	mg not specified (13 wks)	Abstinence without severe withdrawal; Proportions of negative urine toxicology and need for adjuct medication
NCT01395797 Completed	Phase I & II: Randomized, Parallel Assignment	Opioid Nicotine	Dependence to heroin or nicotine N = 82	0, 15 mg or 45 mg (2 wks)	Persistence of responding (Drug Break Point) Subjective drug effects (VAS)
NCT01631630 Completed	Phase II: Randomized, Parallel Assignment	Alcohol	Use disorder N = 16	45 mg (2 wks)	Alcohol urge; Anxiety, Depression scales; Craving
NCT02774343 Completed	Phase I & II: Randomized, Parallel Assignment	Cocaine	Cocaine dependent N = 30	30 then 45 mg (12 wks)	White-matter Integrity (DTI); Obsessive Compulsive Drug Use Scale; Cue reactivity; cocaine use and craving
NCT03060772 Recruiting	Phase II: Randomized, Parallel Assignment	Alcohol	Use disorder N = 36	30 mg (4 wks)	Phagocytic Index; NADPH oxidase; Alveolar macrophage oxidative stress; GSH/GSSG; Cys/CySS redox potential

[a] Studies of opioid use disorder are included in the table, although the role of neuroinflammation in opioid addiction was not a focus of this review. Recent, comprehensive reviews on glia and opioids are available (Bachtell et al., 2017; Kadhim et al., 2018). Abbreviations: DTI, diffusion tension imaging; MA, methamphetamine; SUD, substance use disorder; VAS, visual analogue scale.

induced methamphetamine reinstatement (Beardsley et al., 2010). In a recent human study, ibudilast reduced methamphetamine use and craving for methamphetamine (Worley et al., 2016).

Minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline) is a second-generation antibiotic that is a semi-synthetic tetracycline analogue and is approved by the US Food and Drug Administration (FDA) for the treatment of some sexually transmitted diseases, rheumatoid arthritis, and acne (Garrido-Mesa et al., 2013). Similar to ibudilast, minocycline shows potential as a neuroprotective and anti-inflammatory agent, independent of its antibiotic properties (Garrido-Mesa et al., 2013). Minocycline inhibits microglial p38 mitogen-activated protein kinase and pro-inflammatory cytokine production, but it has no known phosphodiesterase activity (Garrido-Mesa et al., 2013). In animal models, minocycline extinguishes morphine- and methamphetamine-induced conditioned place preference and blocks drug-induced reinstatement (Arezoomandan and Haghparast, 2016; Attarzadeh-Yazdi et al., 2014; Fujita et al., 2012). Furthermore, minocycline reduces methamphetamine self-administration (Snider et al., 2013) and methamphetamine-induced release of DA (Fujita et al., 2012; Hashimoto et al., 2013; Zhang et al., 2006), suggesting that minocycline can attenuate the reward effects of methamphetamine and reduce relapse. Minocycline also holds promise in attenuating the effects of cocaine and alcohol, where minocycline treatment prevents the development of cocaine sensitization (Chen et al., 2009) and reduces ethanol intake in male and female mice using a free choice voluntary drinking model (Agrawal et al., 2011). In humans, minocycline reduces the subjective effects of amphetamine in healthy controls (Sofuoglu et al., 2011) and attenuates cigarette craving in individuals with nicotine dependence (Sofuoglu et al., 2009).

Peroxisome proliferator-activated receptor (PPAR) agonists are also under investigation as pharmacotherapeutic strategies for substance use disorders. PPARs function as transcription factors that regulate the expression of genes that are involved in lipid and glucose metabolism and inflammation (Daynes and Jones, 2002). There are two subtypes of PPARs that have been studied in substance use, PPAR-α and PPAR-γ (Le Foll et al., 2013). PPAR-γ activation has anti-inflammatory effects that involve inhibiting the expression of cytokines (IL-1β, IL-6, and TNF-α), the production of inducible nitric oxide, and the expression of matrix metalloproteinase 9 and macrophage scavenger receptor 1 on monocytes, macrophages, and epithelial cells (Daynes and Jones, 2002; Delerive et al., 2001; Kielian and Drew, 2003; Willson et al., 2000). As PPAR-γ are highly expressed in brain regions associated with the

development and maintenance of addictive behaviors, such as the nucleus accumbens, dorsal striatum, ventral tegmental area, and hippocampus, many studies have examined how PPAR-γ agonists affect drug-seeking behavior.

Repeated administration of methamphetamine in mice is associated with an increase in PPAR-γ activity and protein levels in the nucleus accumbens (Maeda et al., 2007). Pioglitazone and ciglitazone, PPAR-γ agonists (thiazolidinediones), both reduce behavioral sensitization to methamphetamine during the withdrawal period (Maeda et al., 2007). In human cocaine use disorder, a 12-week treatment of pioglitazone reduced craving for cocaine and increased white-matter integrity in the corpus callosum and thalamic radiation (Schmitz et al., 2017). Similarly, a three-week treatment of pioglitazone reduced cigarette craving in heavy smokers; however, pioglitazone was not effective in reducing the reinforcing effects of cigarettes or in reducing smoking-cue reactivity (Jones et al., 2017). There are currently no published reports on the effect of PPAR-γ agonists in humans with alcohol use disorder; however, one study has shown a link between PPAR genotypes (single nucleotide polymorphisms in PPAR-α and PPAR-γ) with alcohol withdrawal and alcohol dependence (Blednov et al., 2015). In preclinical studies, PPAR-γ agonist treatment is effective in reducing alcohol use, where activation of PPAR-γ with pioglitazone and rosiglitazone selectively reduce alcohol drinking in rats—an effect blocked by pretreatment with GW9662, a selective PPAR-γ antagonist (Stopponi et al., 2013; Stopponi et al., 2011). Preclinical data suggest that pioglitazone and other PPAR-γ agonists are promising candidates in attenuating drug-seeking behavior and craving, but more research in humans with substance use disorders is required to evaluate the effects of PPAR agonists in individuals with substance use disorders.

PET measures of glial activation could be used to clarify whether the mechanism by which these pharmacotherapies affect addictive behaviors is mediated by their anti-inflammatory effects. To our knowledge, however, there are no published studies that examine the effect of these agents on microglial activation in addiction. Reports of any animal or human PET studies of anti-inflammatory drugs are sparse. Minocycline decreases binding of [^{11}C](*R*)-PK11195 in zymosan-treated female rats (Converse et al., 2011), but PET has not been used to test either ibudilast or thiazolidinediones effects on microglial activation. Clearly, there is a critical need for clinical trials that leverage PET neuroimaging to measure the effect of anti-inflammatory agents on microglial activation in addiction.

7.1. Limitations

Although the improvements of second generation radiotracers have promoted more studies to investigate TSPO binding as an index for activated microglia in a number of psychiatric disorders, the method is not without limitations. TSPO is upregulated on activated microglia and greater TSPO binding is thought to represent a biomarker of neuroinflammation. Studies have shown that [^{11}C]PBR28 provides accurate estimates of TSPO densities and high levels of specific binding; such that, > 95% of brain uptake represented specific binding to TSPO in rhesus monkeys (Imaizumi et al., 2008). This fraction, however, is lower in humans and genotype dependent (Owen et al., 2014), which may account for mixed results across species. The multicellular expression of TSPO, however, would suggest that TSPO binding with PET imaging may not solely reflect the activation of microglial cells and may represent a broader inflammatory process (Lavisse et al., 2012). In addition, TSPO immunoreactivity is present in various CNS cell types, including microglia, astrocytes, and vascular endothelial cells (Notter et al., 2018). The partial volume effect from endothelial cells can be accounted for by including an additional blood to endothelial compartment in the standard two-tissue compartmental model, which results in stronger correlations between binding and mRNA TSPO expression than the standard two-compartment model (Rizzo et al., 2014). A recent paper examining TSPO binding in schizophrenia suggests that TSPO binding may reflect an anti-inflammatory response that limits acute inflammation, whereas a downregulation may represent a chronic low-grade inflammatory state (Notter et al., 2018). In light of the findings from the alcohol and nicotine studies, this notion would be consistent with the animal literature that drugs of abuse contribute to neuroinflammation. Although contrary to the increase in TSPO binding in individuals with a history methamphetamine use (Sekine et al., 2008), the increase in TSPO binding in methamphetamine use disorder has not been re-examined with second generation radiotracers. In addition, this study used the time-activity curve of healthy controls as a reference-tissue input function rather than using an arterial input function, which makes the assumption that groups are similar in uptake and specific binding. Future studies of methamphetamine use disorder and second generation TSPO tracers that use an arterial input function or if applicable, a cerebellar reference region, as recently used in Alzheimer's disease (Lyoo et al., 2015), are needed. Although PET imaging allows for an in vivo quantitative assessment of TSPO in humans, the use of in vivo imaging techniques depends upon careful validation with preclinical studies, well-controlled postmortem evaluations, and other measurements to assess rigor, specificity, and sensitivity. Further, altered TSPO binding is not equivalent to altered microglia activation exclusively; complementary measures of inflammation are recommended (Notter et al., 2018).

8. Conclusions

Pathological neural activity induced by drugs of abuse contribute to an immune response, however the interactions and interplay between drug-induced neurotransmitter release and multiple receptor subtypes on microglia remains unclear. As excess glutamate promotes the transcription of inflammatory cytokines and activates microglia (Ojaniemi et al., 2003; Shah et al., 2012), drugs promoting glutamatergic neurotransmission may enhance excitotoxicity and further induce neuroinflammatory processes. Neuroprotective effects of some drugs suggest neural adaptive mechanisms to limit neuroinflammation through upregulation of receptors and the inhibition of microglia activation. Neuroimmune responses through IL-6 and TNF-α inhibition is associated with activation of nicotinic acetylcholine or GABA receptors. This is consistent with human PET investigations of neuroinflammation, where alcohol and nicotine use disorders are associated with lower levels of TSPO than controls, with opposite effects for methamphetamine use disorder.

It is important to consider the effects of polydrug use and the possible amplification or attenuation of the neurotoxic cascade. Nicotine and marijuana use are ubiquitous in substance use disorders and both drugs need to be controlled for in future studies. This is especially true with the mixed results seen in studies of stimulant use. Although the differential effects of methamphetamine and cocaine on TSPO binding are unexpected and could be attributed to differences in DA kinetics and toxicity, radiotracer affinities, methodological analysis techniques or genotype imbalances, carefully controlled studies of polysubstance use are warranted. Studies of addiction have not well-characterized or controlled for marijuana use or other polydrug use in the context of neuroinflammation, and establishing this link would help better clarify the long term impact of drugs of abuse on the immune response.

8.1. Future directions and treatments to reduce inflammation

Use of anti-inflammatory drugs is a promising avenue for the treatment of substance use disorders (Table 1); however, it is yet to be determined whether ibudilast, minocycline, or pioglitazone attenuate human drug use behavior through a reduction in neuroinflammation. Non-pharmacologic forms of treatment may also attenuate drug-induced neurotoxicity, and one study shows that 12 weeks of aerobic exercise significantly reduces serum methane dicarboxylic aldehyde (oxidative stress marker), and improves cognitive processing speed in

individuals with a history of methamphetamine dependence (Zhang et al., 2018). Another study in adults with methamphetamine dependence shows an increase in DA D2 receptor availability after an eight-week exercise program (Robertson et al., 2016). Whether these effects are independent of reversing drug-induced toxicity, these data suggest that exercise can contribute to healing drug-induced neural deficits. More work using neuroimaging is necessary to understand the mechanism by which anti-inflammatory drugs or aerobic exercise can affect and improve neural immune signaling pathways, thereby ameliorating drug-induced adaptations and adverse behavioral consequences of drug abuse.

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