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Review

Neuroimmune signaling in alcohol use disorder

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ABSTRACT

Alcohol use disorder (AUD) is a widespread disease with limited treatment options. Targeting the neuroimmune system is a new avenue for developing or repurposing effective pharmacotherapies. Alcohol modulates innate immune signaling in different cell types in the brain by altering gene expression and the molecular pathways that regulate neuroinflammation. Chronic alcohol abuse may cause an imbalance in neuroimmune function, resulting in prolonged perturbations in brain function. Likewise, manipulating the neuroimmune system may change alcohol-related behaviors. Psychiatric disorders that are comorbid with AUD, such as post-traumatic stress disorder, major depressive disorder, and other substance use disorders, may also have underlying neuroimmune mechanisms; current evidence suggests that convergent immune pathways may be involved in AUD and in these comorbid disorders. In this review, we provide an overview of major neuroimmune cell-types and pathways involved in mediating alcohol behaviors, discuss potential mechanisms of alcohol-induced neuroimmune activation, and present recent clinical evidence for candidate immune-related drugs to treat AUD.

1. Alcohol use disorder

Alcohol use disorder (AUD) is a chronic relapsing disease, contributing to about 88,000 deaths in the United States each year (Stahre et al., 2014). Alcohol abuse produces neuroadaptations in specific brain circuits that are linked with behavioral indices of AUD, including escalating alcohol consumption, tolerance, dependence, and propensity to relapse after a period of abstinence (Becker and Ron, 2014). A central goal of AUD research is to identify the underlying neuroadaptations and molecular targets to discover new or repurposed drug treatments.

Over the past decades, important brain regions and neuronal circuits involved in the development of AUD have been identified (Koob and Volkow, 2016). One example is the mesolimbic reward system, which includes the ventral tegmental area (VTA) and nucleus accumbens (NAc). This system is a key component in the positively reinforcing effects of alcohol (Russo and Nestler, 2013). Alcohol-induced neuroadaptations within this circuit and other brain regions may produce an inability to self-regulate consumption of alcohol. As tolerance and dependence develop, neural systems in the extended amygdala participate in the development of negative affect during withdrawal (Koob and Mason, 2016). Impaired function of the prefrontal cortex (PFC) contributes to craving and preoccupation with alcohol, major drivers of relapse (Goldstein and Volkow, 2011). Several molecular targets specific to neuronal function are also implicated in alcohol action (Jaramillo et al., 2018; Mason, 2017; Mayfield et al., 2016). Despite the progress in our understanding of the neurobiology of AUD, there have been no new pharmacotherapies in more than a decade. The limited number of FDA-approved drugs available for AUD patients are only modestly effective and are under prescribed (Leclercq et al., 2017; Mason, 2017).

Current research supports the neuroimmune system, particularly innate immune responses in the peripheral and central nervous systems, as an important target of alcohol that may contribute to abuse and dependence (Bachtell et al., 2017; Crews et al., 2015; Cui et al., 2014; Mayfield et al., 2013; Robinson et al., 2014). Genetic and behavioral evidence points to a neuroimmune hypothesis of alcohol addiction, which posits that alcohol abuse activates innate immune signaling in the brain and further drives alcohol use (Mayfield and Harris, 2017). Neuroimmune molecules, often expressed and secreted by glia, alter neuronal function to regulate alcohol behaviors (Robinson et al., 2014). Improved understanding of the molecular mechanisms underlying AUD has led to the identification of new immune-related therapeutic targets (Lacagnina et al., 2017). AUD is often comorbid with other psychiatric disorders, such as other substance use disorders (SUDs), post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Changes in neuroimmune signaling also occur in these disorders, suggesting overlapping mechanisms for AUD and other drugs of abuse, PTSD, and MDD.

In this review, we focus on the neuroimmune basis of alcohol action from preclinical and clinical findings. We discuss the key cell types in

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brain, molecular targets, and behavioral consequences of a dysregulated neuroimmune system following exposure to chronic alcohol. We also review the convergent neuroimmune pathways implicated for other drugs of abuse (e.g., opioids and psychostimulants) and other psychiatric disorders comorbid with AUD. Because there are many detailed topics pertinent to this rapidly developing literature, certain aspects are outside the scope of this review or are reviewed elsewhere. Where appropriate, we direct the reader's attention to other relevant reviews.

2. Introduction to neuroimmune signaling

Recent reviews have highlighted the signaling pathways and brain cell types that participate in neuroimmune signaling (Dantzer, 2018; Nisticò et al., 2017; Skaper et al., 2018). Briefly, the innate immune system in the central nervous system (CNS) consists of brain cells adept at recognizing and responding to potential threats in the neuronal microenvironment. Microglia and astrocytes (discussed in detail in later sections) are considered the principal immune mediators in brain, responding to and releasing immune signals, while neurons also express genes and signaling systems that modulate CNS immune responses (Mayfield et al., 2013). A vast array of innate immune signals, such as chemokines and cytokines, danger-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs) activate different families of immune receptors in the brain. Chemokine receptors, cytokine receptors, and pattern recognition receptors (PRR) induce transcription factor signaling and the production of pro- or anti-inflammatory cytokines, chemokines, and other neuromodulators. For example, toll-like receptors (TLRs) are key components of neuroimmune activation. In addition to responding to molecular constituents of microbes, such as the bacterial endotoxin lipopolysaccharide (LPS), TLR4 is stimulated by other endogenous danger signals, including high-mobility group box 1 (HMGB1), a cytokine-like signaling molecule (Crews et al., 2013; Yu et al., 2006). TLR4 activation typically leads to nuclear translocation of the transcription factor, nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB). NF-κB regulates the expression of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 1-beta (IL-1β), and interleukin 6 (IL-6) (Lu et al., 2008). TLR4 regulates specific subsets of genes depending on distinct combinations of adaptor proteins. Several other pathways (e.g., TNF-α, IL-1, TLR2) also modulate NF-κB, while IL-6 and TLR3, for example, activate distinct transcription factors to induce gene expression. Enhanced expression of NADPH oxidase, reactive oxygen species (ROS) production, inducible nitric oxide synthase (iNOS), and Nod-like receptor protein 3 (NLRP3) inflammasome signaling are other consequences of immune activation which feed forward to perpetuate inflammation (Montesinos et al., 2016a). Importantly, the production of anti-inflammatory factors, such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β), is critical to control and resolve immune/inflammatory responses (Crews et al., 2011).

Neuroimmune responses vary according to the nature, severity, and duration of the triggering insult and function to facilitate tissue repair, cellular debris clearance, secretion of neurotrophic factors, and matrix remodeling (Harry and Kraft, 2008). Effects of neuroimmune molecules on neuronal plasticity and overall brain circuit function are now emerging (Blank and Prinz, 2017; Nisticò et al., 2017). In the brain, these molecules are not just involved in immune function, but also play integral roles in normal brain development and behavior through modulation of synaptic activity (Tonelli et al., 2005; Yirmiya and Goshen, 2011). For example, the cytokine IL-1β has many roles throughout brain development, regulating differentiation of oligodendrocyte progenitor cells (Vela et al., 2002) and neurons in the spinal cord (la Mano et al., 2007). In the mature brain, long-term potentiation (LTP) and other mechanisms of learning induce expression of IL-1β, indicating it can function in a non-inflammatory neuromodulatory role (Schneider et al., 1998). The cytokine IL-6 has crucial roles in neurogenesis and overall brain function (Erta et al., 2012). TNF-α regulates activity-dependent synaptic scaling (Stellwagen and Malenka, 2006) and synaptic strength through reorganization of corticostriatal circuits (Lewitus et al., 2014). Pro-inflammatory immune signaling also has neuroexcitatory effects; for example, TNF-α modulates expression of AMPA and NMDA receptors, decreases neuronal $GABA_A$ receptor expression (Olmos and Lladó, 2014), inhibits astrocytic glutamate uptake (Tilleux and Hermans, 2007), and increases astrocytic glutamate release (Habbas et al., 2015). IL-6 suppresses inhibitory transmission by reducing GABA-A and glycine receptor function (Kawasaki et al., 2008). Intranigral injection of the pro-inflammatory cytokine C-C motif chemokine ligand 2 (CCL2) increases striatal dopamine release, and prolonged exposure to CCL2 increases excitability of dopaminergic neurons (Guyon et al., 2009). Thus, different immune molecules in the brain regulate neuronal excitability and plasticity, processes also critical in AUD. A chronic imbalance of neuroimmune signaling may contribute to the development of maladaptive addictive behaviors.

3. Neuroimmune signaling and alcohol behaviors

The first microarray datasets from human postmortem brain tissue from alcoholics reveal an upregulation in immune-related genes compared with age-matched healthy controls (Lewohl et al., 2000; Liu et al., 2006; Mayfield et al., 2002). Subsequent brain transcriptome studies from rodents treated with chronic ethanol show altered expression of genes related to glial or immune function (McBride et al., 2013; Osterndorff-Kahanek et al., 2013, 2015; Saba et al., 2015). In addition to changes in brain gene expression, cytokine and chemokine levels in serum and striatum increase following chronic voluntary ethanol consumption in mice (Pascual et al., 2015). In monkeys, chronic ethanol consumption alters hippocampal levels of the inflammatory cytokine MCP-1 (Beattie et al., 2018). Ethanol exposure alters mRNA levels of pro-inflammatory cytokines (TNF-α, IL-6, and CCL2) in a sex-, brain region-, and time-dependent manner (Baxter-Potter et al., 2017). In general, females may be more sensitive to ethanol-induced neuroimmune responses (Alfonso-Loeches et al., 2013; Bala et al., 2014; Barton et al., 2017; Baxter-Potter et al., 2017; Pascual et al., 2017; Wilhelm et al., 2015). Age is also a factor in susceptibility to alcohol-induced neuroinflammation (Kane et al., 2014). Depending on the brain region, ethanol withdrawal is associated with increased mRNA expression of cytokines and is mediated by release of corticotropin releasing factor and HMGB1 (Knapp et al., 2016; Whitman et al., 2013). In addition, ethanol exposure can potentiate neuroimmune activation caused by systemic administration of other inflammatory agents, such as LPS and the TLR3 agonist polyI:C (Qin and Crews, 2012a; Qin et al., 2008).

Overall, a wealth of biochemical data support that alcohol exposure leads to neuroimmune dysregulation. Thus, many behavioral studies have subsequently investigated the role of neuroimmune molecules in alcohol-related behaviors in rodents. The subsections below provide an overview of preclinical research on some of the candidate neuroimmune targets contributing to these behaviors.

3.1. Toll-like receptors

TLR4 is thought to be a major contributor to ethanol-induced neuroimmune activation (Alfonso-Loeches et al., 2010; Crews et al., 2013; Crews and Vetreno, 2015; Fernandez-Lizarbe et al., 2009; Montesinos et al., 2016b) (Bajo et al., 2016; Lippai et al., 2013; Montesinos et al., 2016b; Rubio-Araiz et al., 2016). This prompted studies of its potential role in promoting alcohol consumption and other relevant behaviors. Although the TLR4 agonist LPS increases voluntary ethanol consumption in male and female mice (Blednov et al., 2011), this was surprisingly not observed in another study using C57BL/6J mice (Lainiola and Linden, 2017). Differences in experimental housing conditions may

Table 1
Preclinical studies investigating the role of TLR signaling in alcohol-related behaviors.

Manipulation	Mechanism	Species (Strain)	Sex	Test	Result	Source
TLR4 inhibition	TLR4 KO	Mice (C57BL/6J background)	Male	2BC	–	Pascual et al., 2011
		Rats (Wistar background)	Both	2BC	–	Harris et al., 2017
			Male	Operant self-administration	–	
				LORR duration	Decrease	
		Mice (C57BL/10ScN background)	Both	2BC, CIE-2BC, DID	–	Blednov et al., 2017
		Mice (Balb/c background)	Male	LORR duration	Decrease	Wu et al., 2011
	(+)-Naloxone	Mice (C57BL/6J)	Male	DID, 2BC, CIE-2BC	–	Harris et al., 2017
		Mice (Balb/c)	Male	LORR duration	Decrease	Wu et al., 2011
	(+)-Naltrexone	Mice (Balb/c, with adolescent EtOH exposure)	Both	CPP	–	Jacobsen et al., 2018a, 2018b
				DID	Decrease	
		Mice (Balb/c)	Male	CPP, 2BC	Decrease	Jacobsen et al., 2018a, 2018b
	Nalmefene	Mice (C57BL/6J)	Female	2BC, DID	Decrease	Montesinos et al., 2017
		Mice (TLR4 KO, C57BL/6J background)	Female	2BC, DID	–	
	T5342126	Mice (C57BL/6J)	Male	2BC, CIE-2BC	Decrease	Bajo et al., 2016
	Tlr4 siRNA	P rats	Male	Binge operant self-administration	Decrease	Liu et al. 2011
	Tlr4 siRNA (CeA, VTA)	P rats	Not stated		–	June et al., 2015
	Tlr4 siRNA (NAc)	Mice (TLR4 floxed, C57BL/6J background)	Male	2BC, CIE-2BC	–	Harris et al., 2017
TLR4 activation	LPS	Mice (C57BL/6J)	Both	2BC	Increase	Blednov et al., 2011
			Male	2BC, DID	–	Lainiola and Linden, 2017
		Mice (B6xNZBF1)	Female	2BC	Increase	Blednov et al., 2011
				CTA	Decrease	
				CPP	–	
		Mice (FVBxB6F1)	Female	2BC	Increase	
		Mice (FVBxNJ)	Female	2BC	–	
		Wistar rats	Male	Operant self-administration	Decrease	Harris et al., 2017
		TLR4 KO rat (Wistar background)	Male	Operant self-administration	–	
TLR2 inhibition	TLR2 KO	Mice (C57BL/6J background)	Male	2BC	Decrease	Blednov et al., 2017
			Both	DID	Decrease	
			Female	2BC	–	
			Both	2BC-EOD		
CD14 inhibition	CD14 KO	Mice (C57BL/6J background)	Both	2BC	Decrease	Blednov et al., 2012, Blednov et al., 2017
			Male	DID	–	
			Female	DID	Decrease	
			Both	CIE-2BC	Decrease	
MyD88 inhibition	MyD88 KO	Mice (Balb/c background)	Male	LORR duration	Decrease	Wu et al., 2011
		Mice (C57BL/6J background)	Both	2BC	–	Blednov et al., 2017
			Male	CIE-2BC, DID	Increase	
			Female	CIE-2BC, DID	–	
IKKβ inhibition	Sulfasalazine, TPCA-1	Mice (C57BL/6J)	Male	2BC, DID	Decrease	Truitt et al., 2016
	Ikbkb siRNA (NAc, CeA)	Mice (C57BL/6J)	Male	2BC	Decrease	
TLR3/TRIF inhibition	Amlexanox (IKKε/TBK1 inhibitor)	Mice (C57BL/6J)	Male	CIE-2BC	Decrease	McCarthy et al., 2017a, 2017b, 2017c

2BC, two-bottle choice EtOH drinking; CD14, cluster of differentiation 14; CIE-2BC, 2BC following a chronic intermittent EtOH vapor exposure treatment; CTA, conditioned taste aversion; DID, drinking in the dark; EOD-2BC, every-other-day 2BC; IKKβ, inhibitor of NF-κB kinase subunit beta; KO, knockout; LORR, loss of righting reflex; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response 88; P rat, alcohol-preferring rats; TLR, toll-like receptor; TRIF, TIR-domain-containing adapter-inducing interferon-β;

have contributed to the different results. In rats, LPS transiently decreases operant self-administration of ethanol, but this was possibly due to sickness-like behavior (Harris et al., 2017). Several studies report that genetic deletion of TLR4 does not alter ethanol consumption (Blednov et al., 2017; Harris et al., 2017; Pascual et al., 2011). Inhibition of TLR4 signaling using the mu-opioid inactive stereoisomer (+)-naloxone, which is a selective TLR4 inhibitor (Hutchinson et al., 2008a, 2008b; Wang et al., 2016), also does not alter ethanol consumption in different drinking models (Harris et al., 2017). Moreover, lentiviral-mediated knockdown of *Tlr4* expression in mouse NAc also fails to decrease ethanol consumption in different drinking procedures (Harris et al., 2017). In contrast with these findings, administration of siRNA for *Tlr4* or *Ccl2* into the central amygdala (CeA) or VTA in P rats reduces binge-like drinking (June et al., 2015). The opioid receptor antagonist nalmefene, which also inhibits TLR4 signaling, reduces ethanol-induced inflammation and binge-like drinking in female mice (Montesinos et al., 2017). Moreover, TLR4 blockade by (+)-naltrexone before or after ethanol exposure in adolescent mice reduces binge drinking in adulthood (Jacobsen et al., 2018a). Another recent study showed (+)-naltrexone decreases ethanol preference in mice, particularly during the dark cycle (Jacobsen et al., 2018b). There are some concerns over the use of (+)-naltrexone or (+)-naloxone to inhibit TLR4 signaling, as these compounds fail to inhibit LPS-induced TLR4 activation (Skolnick et al., 2014) and may have off-target/aversive effects, especially at higher doses (Tanda et al., 2016). Another study showed that (+)-naltrexone and (+)-naloxone do not inhibit TLR4-mediated NFκB activation, but rather act as TRIF-IRF3 antagonists (Wang et al., 2016). The experimental TLR4 inhibitor T5342126 decreased ethanol consumption in both dependent and non-dependent mice, but also decreased locomotor activity, saccharin intake, and body temperature, indicating several non-specific effects (Bajo et al., 2016). Based on the current literature, the role of TLR4 in regulating alcohol consumption depends on the animal model, age, sex, drinking test, and genetic or pharmacologic manipulation used (Pascual et al., 2018). Overall, TLR4 alone does not seem to be critical for regulating drinking and likely works in concert with several other neuroimmune factors in

Table 2
Preclinical studies investigating the role of altered chemokine and cytokine signaling in alcohol-related behaviors.

	Mechanism	Species/strain	Sex	Test	Result	Source
Chemokine disruption	CCL2 KO	Mice (C57BL/6J background)	Male	2BC	–	Blednov et al., 2005
			Female	2BC	Decrease	
	Ccl2 silencing (CeA, VTA)	P rats	Not stated	Binge operant self-administration	Decrease	June et al., 2015
	CCL2 infusion (ICV)	Long-Evans rats	Male	Operant self-administration	Increase	Valenta and Gonzales, 2016
				Withdrawal anxiety	–	
	CCL3, CCR2 KO	Mice (C57BL/6J background)	Both	2BC	Decrease	Blednov et al., 2005
	CCL2, CCL3 KO			LORR duration, CTA	Increase	
	CCR5 KO			2BC	–	
	CCR2, CCR5 KO			LORR duration, acute withdrawal	–	
	CCR2 KO			CTA	Increase	
	CCL2, CCL3 KO			Acute withdrawal	–	
	MDK KO			2BC, DID	Increase	Chen et al., 2017a, 2017b
	Mdk silencing (VTA)	Mice (C57BL/6J)	Male	DID	Increase	
Cytokine disruption	IL-1R1 KO	Mice (C57BL/6J background)	Both	2BC, DID, CTA, EtOH clearance	–	Blednov et al., 2015
				LORR duration	Decrease	
				Acute withdrawal severity	Increase	
			Male	2BC	Decrease	Karlsson et al., 2017
				CPP, stress-induced drinking, EtOH motor impairment	–	Blednov et al., 2015, Karlsson et al., 2017
			Female	EtOH motor impairment	Decrease	Blednov et al., 2015
	IL-1R1 and TNF-1R KO (double KO)		Male	2BC, stress-induced drinking	Decrease	Karlsson et al., 2017
				CPP	–	
	IL-1R antagonist	Mice (C57BL/6J)	Male	Acute withdrawal severity	Increase	Blednov et al., 2015
		Mice (Balb/c)	Male	LORR duration	Decrease	Wu et al., 2011
	IL-1R antagonist (BLA)	Mice (C57BL/6J)	Male	DID	Decrease	Marshall et al., 2016
	IL-1R antagonist (CeA)	Mice (C57BL/6J)	Male	DID	–	
	IL-1RN KO	Mice (B6 × 129/SvJ background)	Both	2BC, DID, CTA, acute withdrawal severity	Decrease	Blednov et al., 2012, 2015
				EtOH clearance, LORR duration	Increase	Blednov et al., 2015
				EtOH motor impairment	–	
	IL-6 KO	Mice (C57BL/6J background)	Both	2BC	Decrease	Blednov et al., 2012
				DID	–	
	Il22ra2 shRNA (NAc shell)	P rats	Female	2BC	Decrease	Franklin et al., 2015

BLA, basolateral amygdala; CCL2, C-C motif chemokine ligand 2; CCL3, C-C motif chemokine ligand 3; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; CeA, central nucleus of the amygdala; CPP, conditioned place preference; CTA, conditioned taste aversion; DID, drinking in the dark; EtOH, ethanol; IL-1R1, interleukin 1 receptor type 1; IL-1RN, interleukin 1 receptor antagonist; KO, knockout; LORR, loss of righting reflex; MDK, midkine; NAc shell, nucleus accumbens shell; P rats, alcohol-preferring rats; TNF-1R, tumor necrosis factor receptor 1; 2BC, two-bottle choice EtOH drinking test; VTA, ventral tegmental area.

brain to drive behavior.

Twelve TLRs have been identified in mice, with TLR4 being the most widely studied subtype for alcohol action (Crews et al., 2017). Other TLRs in brain are also implicated in alcohol's neuroimmune effects. For example, TLR2 KO mice exhibit reduced ethanol consumption (Blednov et al., 2017). In addition, TLR2 may mediate ethanol-induced neuroinflammatory responses and anxiety-like behavior associated with ethanol withdrawal (Pascual et al., 2015). Ethanol promotes interactions between TLR2 and TLR4 (Fernandez-Lizarbe et al., 2013), suggesting it could simultaneously target both neuroimmune mediators. Adapter proteins, such as cluster of differentiation 14 (CD14), myeloid differentiation primary response 88 (MyD88), and TIR-domain-containing adapter-inducing interferon-β (TRIF), participate in several TLR pathways and genetic manipulation of these immune molecules regulates alcohol drinking. For example, Male and female CD14 KO mice drink less ethanol; however, male MyD88 KO mice increase binge-like ethanol consumption (Blednov et al., 2017). Pharmacological and brain-specific genetic inhibition of the inhibitor of NF-κB kinase subunit beta (IKKβ), which activates NF-κB signaling as part of the MyD88 pathway, decreases ethanol consumption in mice (Truitt et al., 2016). TLR3-TRIF-dependent signaling is also implicated in ethanol-induced neuroimmune signaling, as chronic ethanol consumption increases *Tlr3* mRNA and components of the TRIF-dependent pathway (mRNA and protein) in the PFC and NAc, compared with decreases in the amygdala 24 h after ethanol removal (McCarthy et al., 2017c). Furthermore, decreased activation of the TLR3-TRIF pathway by the IKKε/TBK1 inhibitor, amlexanox, reduces ethanol consumption (McCarthy et al., 2017c). Some evidence suggests that activation of the TLR3-TRIF pathway by chronic ethanol exposure increases neuroinflammation and neurodegeneration (Qin and Crews, 2012b). Initial findings in preclinical models suggest that TLR2, TLR3, and other mediators appear to be relevant targets for reducing ethanol consumption. Table 1 provides an overview of the pharmacological and genetic preclinical work demonstrating the involvement of TLR signaling in ethanol-related behaviors.

3.2. Cytokines and chemokines

A major component of alcohol-induced neuroimmune activation is increased expression of cytokines, including IL-1β, TNF-α, IL-6, and CCL2 in brain (Lippai et al., 2013). IL-1 receptor (IL-1R) blockade, which attenuates ethanol-induced inflammasome activation and neuroinflammation (Lippai et al., 2013), reduces acute ethanol-induced sedation, protects mice from ethanol-induced motor impairment, and decreases binge-like drinking (Marshall et al., 2016; Yue Wu et al., 2011). Deletion of either IL-1R or the endogenous antagonist IL-1Ra produces opposite effects on ethanol behaviors such as its acute sedative and withdrawal effects (Blednov et al., 2015). IL-1R KO does not alter drinking in two-bottle choice continuous or limited-access drinking tests, but IL-1Ra KO mice show decreased ethanol consumption in both drinking models (Blednov et al., 2012). Double KO mice (IL-1R KO and TNF1R KO) drink significantly less ethanol and exhibit less stress-induced ethanol consumption (Karlsson et al., 2017). Other interleukins also regulate drinking behavior. For example, ethanol consumption is reduced in male and female IL-6 KO mice (Blednov et al., 2012), and *Il22ra2* shRNA in the NAc reduces ethanol consumption in female alcohol-preferring (P) rats (Franklin et al., 2015).

Disruption of chemokine signaling also impacts alcohol behaviors.

Genetic deletion of CCR2, CCL2 (in females), or CCL3 reduces voluntary ethanol consumption and conditioned place preference (CPP) to ethanol in mice (Blednov et al., 2005). Silencing *Ccl2* in the CeA or VTA of rats decreases ethanol consumption (June et al., 2015). In contrast, directly infusing CCL2 into cerebral ventricles of rats led to increased operant ethanol self-administration (Valenta and Gonzales, 2016). Midkine (MDK), a cytokine and neurotrophic factor which regulates CCL2 expression, may function to limit ethanol consumption, as MDK KO mice and mice expressing *Mdk* shRNA in the VTA demonstrate increased drinking (Chen et al., 2017a).

As summarized in Table 2, genetic and pharmacological studies demonstrate that altered expression of cytokines and chemokines regulates alcohol consumption in rodents. Furthermore, the behavioral effects following brain-specific manipulation of these molecules suggest the importance of central immune signaling in drinking behavior.

3.3. Phosphodiesterase inhibitors

Phosphodiesterase (PDE) inhibitors are a class of anti-inflammatory drugs that decrease ethanol drinking (for further review, see (Logrip, 2015; Wen et al., 2018)). Preclinical work examining the effects of PDE inhibitors on ethanol-related behaviors is summarized in Table 3. PDEs regulate several intracellular signaling cascades by reducing cAMP and cGMP levels, which may contribute to excessive ethanol intake (Logrip, 2015). Ibudilast, a non-specific PDE inhibitor, decreases ethanol consumption in rodent models (Bell et al., 2013). There are several isoforms of PDE comprising 11 different families based on structure and functional specificity. PDE-10 inhibition also reduces ethanol self-administration in rats (Logrip et al., 2014). Furthermore, specific PDE-4 inhibitors reduce ethanol consumption. By increasing cAMP levels, PDE-4 inhibitors exhibit a general anti-inflammatory effect in a variety of inflammatory conditions (Zebda and Paller, 2018). Hu et al. (2011) found that treatment with specific PDE-4 inhibitors, rolipram or Ro 20-1724, reduces ethanol intake and preference in mice. Rolipram also decreases ethanol consumption in Fawn-Hooded rats (Wen et al., 2012). Another study testing nine PDE inhibitors with different subtype selectivity shows that only the PDE-4 selective inhibitors reduce ethanol intake and preference (Blednov et al., 2014b). Roflumilast is another PDE-4 inhibitor that decreases ethanol consumption in mice (Liu et al., 2017). Rats genetically bred for high ethanol consumption also show reduced drinking in response to PDE-4 inhibition (Franklin et al., 2015). Apremilast, a PDE-4 inhibitor that is FDA-approved for the treatment of psoriasis and has less emetic activity than other PDE-4 inhibitors, reduces ethanol consumption and preference in male and female mice in different drinking tests (Blednov et al., 2018b). Apremilast also alters the acute behavioral effects of ethanol in mice, causing increased sedation, intoxication, and reduced acute functional tolerance, which may contribute to its ability to decrease drinking (Blednov et al., 2018a). PDE-4 may also regulate negative emotional states induced by ethanol abstinence; for example, rolipram produces anxiolytic- and antidepressant-like effects in acute, repeated, or protracted ethanol abstinence states in rodents (Gong et al., 2017). Jabaris et al. (2015) showed that low doses of PDE-4 inhibitors increase pCREB in the rat brain, ameliorating cognitive deficits and enhancing memory, thus providing evidence for a central mechanism. PDE-4 also modulates ethanol-induced neuroinflammation. Mice chronically fed ethanol demonstrate robust activation of astrocytes, microglia, and inflammatory cytokines, as well as increased PDE4B and decreased brain cAMP. PDE4B KO or WT mice treated with rolipram are resistant to ethanol-induced brain inflammation as well as peripheral inflammation induced by systemic endotoxemia (Avila et al., 2017). Overall, there is strong preclinical evidence for PDE-4 inhibition as a potential mechanism for decreasing ethanol consumption.

3.4. Peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptor (PPAR) agonists are anti-inflammatory compounds that have also been studied for their role in reducing ethanol drinking (Blednov et al., 2014a). PPARs are nuclear hormone receptors that function as ligand-activated transcription factors, and PPAR agonists are approved for treating hyperlipidemia and type 2 diabetes (Chigurupati et al., 2015). The isoforms PPARα, PPARγ, and PPARβ/δ are located throughout most peripheral tissues, as well as in brain regions implicated in AUD (Warden et al., 2016). Table 4 summarizes preclinical studies of PPAR-related treatments on ethanol behaviors. The PPARα agonists fenofibrate and tesaglitazar decrease ethanol consumption and other relevant behaviors in rodents (Barson et al., 2009; Blednov et al., 2014a, 2016a, 2016b; Haile and Kosten, 2017; Karahanian et al., 2014) and also alter the expression of brain genes that were previously shown to regulate drinking behavior (Ferguson et al., 2014). Following fenofibrate treatment, mice treated with ethanol show marked increases in blood acetaldehyde (Karahanian et al., 2014), suggesting that PPARα-dependent effects on ethanol consumption are mediated by increased systemic levels of acetaldehyde. PPARγ activation by pioglitazone reduces ethanol drinking in genetically selected P rats, and when combined with naltrexone, an even more potent reduction is observed (Stopponi et al., 2013). These effects are blocked by injection of a selective PPARγ antagonist into a lateral cerebral ventricle, indicating a central mechanism of pioglitazone to decrease drinking (Stopponi et al., 2011). Pioglitazone also reduces ethanol consumption in mice, but only for 6 h after injection (Blednov et al., 2014a). Pioglitazone may further protect against neuronal and cognitive degeneration following binge ethanol exposure (Cippitelli et al., 2017) by rescuing ethanol-induced impairments in reversal and spatial learning and inhibiting expression of pro-inflammatory cytokines and neurodegeneration.

These preclinical studies show that inhibition of several inflammatory targets, through genetic, viral, and pharmacological modulation, decreases ethanol drinking in different animal models of AUD. Overall, the findings suggest that alcohol-induced neuroimmune activation plays a central role in the behavioral actions of alcohol.

4. Cell specificity in neuroimmune activation by alcohol

Glial cells, such as astrocytes and microglia, are exciting new targets in the study of alcohol-induced neuroimmune and behavioral responses. Evidence also points to neuron-specific immune genes as relevant targets. The following subsections address current research on alcohol's effects on the different immunomodulatory cells in brain and the potential consequences of functional dysregulation.

4.1. Microglia

Equipped with highly ramified and motile processes extending from a compact cell body, microglia are constantly surveying their brain microenvironment (Nimmerjahn et al., 2005; Ohsawa and Kohsaka, 2011). Microglia detect foreign pathogens or danger signals in the CNS directly through PPRs (such as TLRs) and, indirectly, through cytokine and chemokine receptors (such as IL-1R or TNFR) (Streit, 2002). When microglia sense these threats, they become “activated”. The classical view of microglia activation consists of a morphological transformation from a ramified phenotype to an amoeboid, phagocytic, macrophage-like cell. This transformation is visualized by increased size of cell bodies, decreased length of processes, and increased immunoreactivity of ionized calcium-binder adapter molecule 1 (IBA1, a calcium binding protein found in microglia and macrophages). Microglia have traditionally been thought to form two distinct activation profiles, M1 and M2, each having opposing effects on inflammation (Tang and Le, 2016). M1 microglia secrete pro-inflammatory molecules (TNF-α, IL-1β, and IL-6) while M2 microglia release anti-inflammatory molecules (TGF-β

Table 3
Preclinical studies examining the effects of PDE inhibition on alcohol-related behaviors.

Manipulation	drug used	Species/strain	Sex	Test	Result	Source
PDE inhibition (non-specific)	Ibudilast	P rats, HAD1 rats	Male	2BC (2 h), CIE-2BC	Decrease	Bell et al., 2013
		C57BL/6J mice (EtOH-dependent)		2BC		
	Propentofylline	C57BL/6J mice			–	Blednov et al., 2014a, 2014b
PDE1 inhibition	Vinpocetine	C57BL/6J mice	Male	2BC	–	
PDE3 inhibition	Olprinone, Milrinone	C57BL/6J mice	Male	2BC	–	
PDE4 inhibition	Rolipram, Ro 20–1724, Mesopram, Piclamilast, CDP840	C57BL/6J mice	Male	2BC	Decrease	Hu et al., 2011, Blednov et al., 2014a, 2014b
	Rolipram	Fawn-Hooded rats	Male	2BC, EtOH-induced anxiety	Decrease	Wen et al., 2012, Gong et al., 2017
	Rolipram, Ro 20-1724	P rats, HAD1 rats	Male	2BC (2 h)	Decrease	Franklin et al., 2015
	Rolipram, Mesopram, Piclamilast, CDP840	C57BL/6J mice	Male	DID	Decrease	Blednov et al., 2014a, 2014b
	Rolipram	C57BL/6J mice	Male	Abstinence-induced anxiety, depressive-like behavior	Decrease	Gong et al., 2017
	Roflumilast	C57BL/6J mice	Male	2BC, DID	Decrease	Liu et al., 2017
	Apremilast	C57BL/6J mice	Both	2BC, 2BC-EOD, AFT	Decrease	Blednov et al., 2018a, 2018b
				CPP, acute EtOH withdrawal, EtOH-induced anxiolysis, extinction of CTA	–	
				CPA, EtOH-induced motor impairment	Increase	
PDE5 inhibition	Zaprinast	C57BL/6J mice	Male	2BC	–	Blednov et al., 2014a, 2014b
PDE10 inhibition	TP-10	Wistar, P, and EtOH-dependent rats	Male	Operant self-administration	Decrease	Logrip et al., 2014
		Wistar rats	Male	CPA	–	

AFT, acute functional tolerance; CPA, conditioned place aversion; CPP, conditioned place preference; CTA, conditioned taste aversion; DID, drinking in the dark; EtOH, ethanol; PDE, phosphodiesterase; 2BC, two-bottle choice EtOH drinking; CIE-2BC, chronic intermittent EtOH vapor followed by 2BC drinking; 2BC-EOD, 2BC every-other-day.

Table 4
Preclinical studies investigating the role of PPARs in alcohol behaviors.

Manipulation	Drug	Species (strain)	Sex	Test	Result	Source
PPARα activation	Gemfibrozil	Sprague-Dawley rats	Male	2BC	Decrease	Barson et al., 2009
	Fenofibrate	UChB rats	Male	2BC	Decrease	Karahanian et al., 2014
		Mice (C57BL/6J)	Male	2BC, DID	Decrease	Blednov et al., 2015, 2016a, 2016b
			Both	2BC-EOD	Decrease	Blednov et al., 2016a, 2016b
			Female	2BC	–	Blednov et al., 2016a, 2016b
		Wistar rats	Not stated	Operant self-administration	Decrease	Haile and Kosten, 2017
PPARα inhibition	MK886	Mice (C57BL/6J)	Both	2BC	–	Blednov et al., 2016a, 2016b
PPARδ activation	GW0742	Mice (C57BL/6J)	Male	2BC, DID	–	Blednov et al., 2015
PPARγ activation	Pioglitazone	Mice (C57BL/6J)	Male	2BC	Decrease	Blednov et al., 2015
				DID	–	Blednov et al., 2015
		msP rats	Male	2BC, operant self-administration	Decrease	Stopponi et al., 2011, Stopponi et al., 2013
				Cue-induced relapse	–	Stopponi et al., 2011
		Wistar rats	Male	Binge alcohol-induced cognitive impairment	Decrease	Cippitelli et al., 2017
PPARγ inhibition	GW9662	msP rats	Male	2BC	–	Stopponi et al., 2011
		Mice (C57BL/6J)	Both	2BC	–	Blednov et al., 2016a, b
PPARγ activation + MOR inhibition	Pioglitazone and naltrexone	msP rats	Male	2BC, stress- or cue-induced relapse	Decrease	Stopponi et al., 2013
PPARα/ PPARγ activation	Tesaglitazar	Mice (C57BL/6J)	Male	2BC, DID	Decrease	Blednov et al., 2015
			Both	2BC	Decrease	Blednov et al., 2016a, b
PPARα/PPARγ/PPARδ activation	Bezafibrate	Mice (C57BL/6J)	Male	2BC, DID	Decrease	Blednov et al., 2015

PPARs, peroxisome proliferator-activated receptors; UChB rats, Wistar rats selected for high voluntary alcohol consumption; msP rats, Marchigian Sardinian alcohol-preferring rats; 2BC, two-bottle-choice EtOH drinking; DID, drinking in the dark.

and IL-10). However, unbiased global analysis techniques, such as whole-genome transcriptome analysis, indicate that microglia activation is more complex than originally considered, and the classical view of M1 and M2 activation states may not accurately account for activity in vivo (Ransohoff, 2016; Wes et al., 2016). Activated microglia undergo changes in gene expression and function that are specific to the ongoing threat (Keren-Shaul et al., 2017). There is significant heterogeneity in this process, even within an individual brain region, with microglia existing in different functional states (De Biase et al., 2017). Such differences may impart specific roles in the healthy CNS and in neuroinflammatory diseases such as AUD.

Ethanol directly activates microglia in vitro to increase expression of mRNAs coding for TNF-α, IL-1β, and iNOS (Fernandez-Lizarbe et al., 2009). Increases in microglial markers (i.e., IBA1 or CD11B) are also observed in mouse brain following binge or chronic ethanol drinking and in human postmortem brain from alcoholics (Alfonso-Loeches et al., 2010; Barton et al., 2017; He and Crews, 2008; Qin and Crews, 2012b; Rubio-Araiz et al., 2016; Walter et al., 2017; Zhao et al., 2013). Immunohistochemistry and transcriptome studies show upregulation of mRNA for TSPO (the 18 kDa translocator protein that is upregulated in activated microglia) in human alcoholic brain (Ponomarev et al., 2012). Methods for live in vivo imaging using PET labeling of TSPO have been developed (Vivash and OBrien, 2016), and reveal activated glia in alcohol-exposed adolescent baboons (Saba et al., 2017). However, PET labeling of TSPO in humans show fewer activated microglia in alcohol-dependent subjects compared with age-matched healthy controls (Hillmer et al., 2017). Cultured monocytes from these alcohol-dependent individuals also indicate blunted pro-inflammatory responses following an LPS challenge. Similarly, alcohol-dependent patients who had undergone recent detoxification show decrease TSPO expression in the hippocampus (Kalk et al., 2017). Hippocampal TSPO is also positively correlated with verbal memory performance in a combined group of healthy control subjects and recently detoxified alcohol-dependent individuals. However, limitations of the TSPO labeling technique (e.g., individual differences in radioligand binding affinity, lack of specificity, and difficulty in quantifying subtle changes in neuroinflammation) hamper interpretation of findings in relation to alcohol dependence (Vivash and OBrien, 2016). Chemically diverse radioligands with variable TSPO binding affinity between individuals and species may also contribute to incongruous results across studies (Sakata et al., 2017). A recent study proposes that decreases in TSPO binding in AUD patients could be due to increased levels of the endogenous TSPO ligand cholesterol, and suggests a relationship between cholesterol levels and TSPO binding in humans, an effect largely driven by inverse correlation in the AUD population (Kim et al., 2018). Discovery of more selective and sensitive biomarkers for brain microglia activation will be an important milestone for studying these cells in different stages of AUD.

Transcriptome profiling of microglia from mouse PFC shows altered expression of coordinately regulated groups of genes after recurring periods of voluntary ethanol consumption (McCarthy et al., 2017b). This study highlights a possible role for TGF-β, and its interaction with sialic acid-binding Ig-like lectin H (Siglec-H), in ethanol-induced immune signaling in the brain. Despite the gene network alterations, IBA1 immunohistochemistry indicates no change in microglia activation 0 or 24 h after ethanol removal (McCarthy et al., 2017c). Hippocampal microglia activation after binge ethanol drinking is also not associated with increased inflammatory markers, suggesting a beneficial or homeostatic role for microglia after ethanol exposure (Marshall et al., 2013; McClain et al., 2011). Although ethanol alters microglia activation, how the functional states vary across brain regions and stages of alcohol dependence remains to be determined.

Ethanol-induced microglial activation is thought to be mediated by multiple immune receptor families, including TLRs (Alfonso-Loeches et al., 2010; Fernandez-Lizarbe et al., 2009). TLR4 KO prevents ethanol-induced changes in IBA1 immunoreactivity and protects against neurotoxicity in mouse cortex (Alfonso-Loeches et al., 2010). In microglial cells, ethanol up-regulates TLR4 and TLR2 and promotes a physical interaction between the two receptors that coincides with inflammatory mediator release (Fernandez-Lizarbe et al., 2013). NF-κB signaling, NADPH oxidase induction, and ROS production are all associated with changes in microglial morphology and neurodegeneration in ethanol-treated mice (Qin and Crews, 2012b).

ATP-activated purinergic P2X receptors (P2XR) in microglia are also implicated in neuroinflammatory responses in preclinical models of

drug addiction (Fernandes et al., 2016). P2X7 receptors are abundantly expressed in microglia and mediate pro-inflammatory IL-1β release through activation of the inflammasome NLRP3 (Bhattacharya, 2018). In murine BV2 microglial cells, ethanol potentiates P2X7-mediated IL-1β release (Asatryan et al., 2017); however, blockade of P2X7 with the antagonist Brilliant Blue G does not alter ethanol intake in a mouse binge-like drinking model (Lainiola and Linden, 2017). Brilliant Blue G, however, may have off-target effects (Bhattacharya et al., 2013) and more specific agents are needed to target P2XRs.

As mentioned previously, release of pro-inflammatory cytokines produces widespread effects on surrounding neurons and synaptic function. For example, IL-1β release could interact with ethanol's effects on GABAergic signaling in brain regions important for addiction, such as the CeA (Bajo et al., 2014, 2015). In vitro work demonstrates that microglial-derived miRNA let-7 and HMGB1 contribute to ethanol-induced neurotoxicity in a TLR7-dependent manner (Coleman et al., 2017). Microglia are also fundamental to normal CNS processes, such as neurogenesis (Gemma and Bachstetter, 2013), activity-dependent synaptic pruning (Schafer et al., 2012), and excitatory synaptic maturation and function (Miyamoto et al., 2013; Yuwen Wu et al., 2015). For example, microglia control neuronal firing through release of brain-derived neurotrophic factor and other regulators of synaptic plasticity (Ferrini and De Koninck, 2013). They surround the soma of highly active neurons to decrease firing (Li et al., 2012) and also migrate to and displace inhibitory synapses in cortical neurons to increase neuronal expression of neuroprotective molecules (Chen et al., 2014). Thus, changes in microglia activity may impair normal neuronal activity and exacerbate ethanol-induced neurotoxicity through different neuroimmune molecules (Fig. 1).

Anti-inflammatory drugs reduce ethanol-mediated microglia activation (Qin and Crews, 2012a), and studies directly targeting microglia in alcohol behaviors are now in the early stages (Table 5). Pharmacological depletion of microglia (with colony-stimulating factor-1 receptor antagonist, PLX3397) blunts the induction of TNF-α and the enhanced expression of anti-inflammatory genes, IL-4 and IL-10, that occur following acute withdrawal from binge ethanol drinking, indicating that microglia are at least partly necessary for the brain's pro-inflammatory response to ethanol (Walter and Crews, 2017). However, unlike a previous report using minocycline to inhibit activation (Yue Wu et al., 2011), microglia depletion with PLX3397 does not alter ethanol-induced motor impairment (Walter and Crews, 2017). Although the effects of microglial depletion on alcohol drinking behaviors are unknown, using minocycline to inhibit activation decreases ethanol self-administration in mice (Agrawal et al., 2011; Lainiola and Linden, 2017) and attenuates ethanol withdrawal-induced anxiety and relapse drinking following ethanol deprivation in rats (Gajbhiye et al., 2018). Another study found that minocycline does not affect withdrawal-induced anxiety (Harper et al., 2018), perhaps due to differences in length of ethanol exposure and anxiety measurements.

New strategies to directly target and manipulate microglia, such as microglia-specific DREADD (Designer Receptors Exclusively Activated by Designer Drugs) delivery (Grace et al., 2016), Cre-driver mice for microglia-specific genetic manipulation (Burma et al., 2017), and the use of different microglia inhibitor drugs (Leduc-Pessah et al., 2017), will advance understanding of the in vivo effects of microglia within a functioning, intact central immune system and their contribution in modulating alcohol behaviors.

4.2. Astrocytes

Astrocytes are structurally complex with numerous branched processes that allow functional interactions with the blood-brain barrier (BBB), synaptic cleft, and other glia (Vasile et al., 2017). Throughout development and adulthood, astrocytes perform diverse roles in the CNS, including regulating synapse maturation, water balance, ion and neurotransmitter homeostasis, inflammatory responses, and BBB permeability (Sofroniew, 2015; Szu and Binder, 2016; Tong et al., 2014). Fig. 2 shows an overview of functional changes in astrocytes following alcohol-induced neuroinflammation.

Changes in astrocyte markers, such as glial fibrillary acidic protein (GFAP), are found in brains of mouse models and in postmortem brains of humans with different neuropsychiatric diseases or in response to various drugs of abuse (Kim et al., 2017). Changes in GFAP are associated with impaired astrocyte function involving glutamate uptake, neuronal-glial signaling, and release of inflammatory mediators or neurotrophic factors that signal the surrounding parenchyma to resolve or prolong inflammation (Pekny and Pekna, 2014). Inflammatory insults may consequently induce discrete or widespread alterations in astrocyte gene expression, creating a graded continuum through which astrocytes respond to various pathological conditions in the CNS (Zamanian et al., 2012). Like microglia, astrocytes are less homogeneous than previously thought, with subtypes of activated astrocytes showing differential effects (Liddelow et al., 2017). Evidence of brain-region heterogeneity among different populations (Chai et al., 2017; Martín-Fernández et al., 2017; Srinivasan et al., 2016) suggests that this is important for astrocyte reactivity and functional effects. Not all astrocytes express GFAP (Oberheim et al., 2012), and thus new molecular markers associated with the different phenotypes and activated states are needed.

Many studies report altered GFAP expression or morphology in rodent brain following ethanol exposure or in postmortem human brain from alcoholics. GFAP expression increases following ethanol drinking procedures ranging in duration from a 4-day binge (Satriotomo et al., 2000) to 5 months of exposure (Alfonso-Loeches et al., 2010). Changes in GFAP depend on several variables, including the ethanol drinking model, sex, brain region, and time point analyzed (Bull et al., 2014; Evrard et al., 2006; Miguel-Hidalgo, 2005; Qin and Crews, 2012b; Wilhelm et al., 2015). For example, rats self-administering ethanol intermittently for 10 weeks show increased GFAP immunoreactivity in the prelimbic cortex 24 h after the last ethanol exposure, but not after 3 weeks of abstinence (Bull et al., 2015). However, rats consuming ethanol on a continuous basis show decreased GFAP staining in prelimbic cortex after 3 weeks of abstinence (Bull et al., 2015). In the NAc, GFAP immunoreactivity increases after 3 weeks of abstinence following chronic intermittent ethanol self-administration and is positively correlated with motivation to resume self-administration following abstinence (Bull et al., 2014). Sex is also a factor in astrocyte reactivity, as female mice exhibit greater increases in GFAP in response to chronic alcohol treatment compared with males (Alfonso-Loeches et al., 2013). Results from human postmortem alcoholic brain are varied, showing either increased GFAP in PFC (Rubio-Araiz et al., 2016), decreased astrocyte density (Miguel-Hidalgo et al., 2002, 2006), or altered astrocyte morphology (Cullen and Halliday, 1994). Anatomical, molecular, and functional differences in astrocytes between species could partially explain varied findings from studies performed in mouse or human tissue (Oberheim et al., 2009, 2012). For example, hominid cortical astrocytes are larger, more complex, and comprised of more subtypes compared to astrocytes in other mammals (Oberheim et al., 2006). More specific human astrocyte markers that account for functional heterogeneity and distinguish distinct activation states are needed to assess possible changes in astrocyte phenotype in response to alcohol. Overall, these studies show that astrocyte function is dynamically regulated by alcohol exposure.

Another critical function of astrocytes is to regulate synaptic glutamate homeostasis. Astrocytes work to clear extrasynaptic levels of glutamate via different glutamate transporters [i.e., glutamate aspartate transporter (GLAST/EAAT1), glutamate transporter 1 (GLT-1/EAAT2), and cysteine glutamate anti-transporter (xCT)] (Verkhratsky et al., 2015). Glutamine synthetase then converts glutamate to glutamine, which is shuttled back to neurons for reconversion to glutamate for excitatory neurotransmission. The glutamate-glutamine cycle is compromised in neurological disorders (Nakagawa and Kaneko, 2013) and

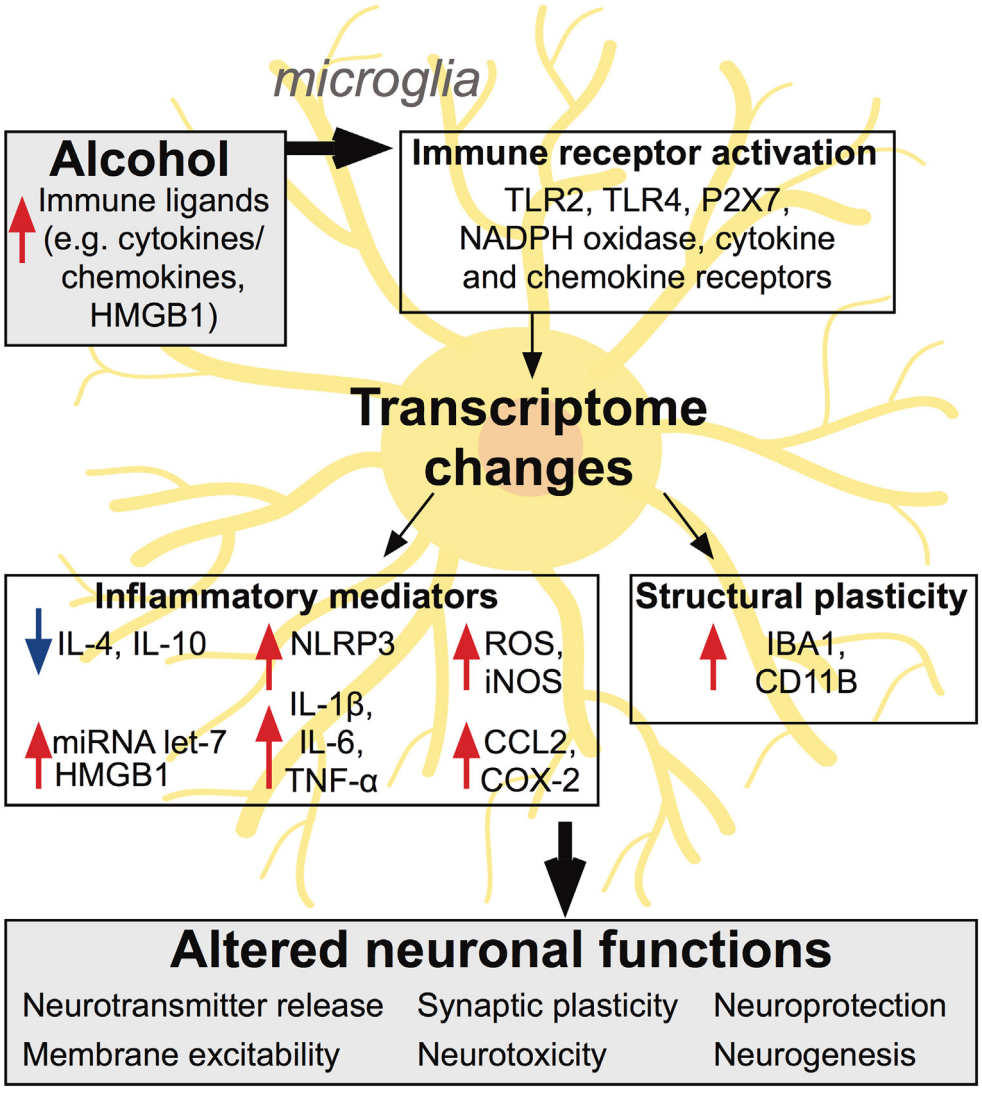

Fig. 1. Microglia-specific consequences of alcohol-induced neuroinflammation. Alcohol exposure generates a proinflammatory environment in brain, resulting in up-regulation of immune ligands such as cytokines and chemokines. This results in activation of immune receptors on microglia, persistent transcriptome changes, structural plasticity, and the production of several inflammatory mediators that can alter neuronal function.

may be a consequence of altered neuroimmune signaling, considering that pro-inflammatory cytokines modulate the expression and function of astrocytic glutamate transporters (Tilleux and Hermans, 2007). Ethanol also regulates glutamate homeostasis. For example, acute ethanol exposure inhibits glutamate uptake (Aschner et al., 2001; Smith and Navratilova, 1999, 2003), and chronic ethanol downregulates the expression of GLT-1 and xCT (Aal-Aaboda et al., 2015; Sari, 2013). Blocking glutamate uptake in astrocytes (using dihydrokainic acid infusion into the lateral ventricle) reduces binge drinking (Smith et al., 2014), and GLAST KO mice show reduced voluntary ethanol consumption and do not exhibit CPP to ethanol (Karlsson et al., 2012). Alcohol-induced changes in adenosine signaling also contribute to

Table 5
Preclinical studies investigating the role of microglia in alcohol-related behaviors.

Manipulation	Drug	Species (strain)	Sex	Test	Result	Source
Inhibit microglia activation	Minocycline (antibiotic)	Mice (C57BL/6J)	Both	2BC	Decrease	Agrawal et al., 2011, Agrawal et al., 2014
			Male	DID	Decrease	Lainiola and Linden, 2017
		Mice (FVB/NJ)	Female	2BC	Decrease	Agrawal et al., 2014
		Mice	Male	LORR duration	Decrease	Wu et al., 2011
		(Balb/c)		EtOH-induced motor impairment	Increase	Wu et al., 2011
		Rats (Wistar)	Male	Withdrawal-induced anxiety, relapse-like drinking	Decrease	Gajbhiye et al., 2018
				Withdrawal-induced anxiety	–	Harper et al., 2018
Microglia depletion	PLX3397	Mice (C57BL/6J)	Male	EtOH-induced motor impairment	–	Walter et al., 2017
P2X7 inhibition	Brillant Blue G	Mice (C57BL/6J)	Male	DID	–	Lainiola and Linden, 2017

DID, drinking in the dark; EtOH, ethanol; LORR, loss of righting reflex; 2BC, two-bottle choice drinking; P2X7, P2X purinoreceptor 7.

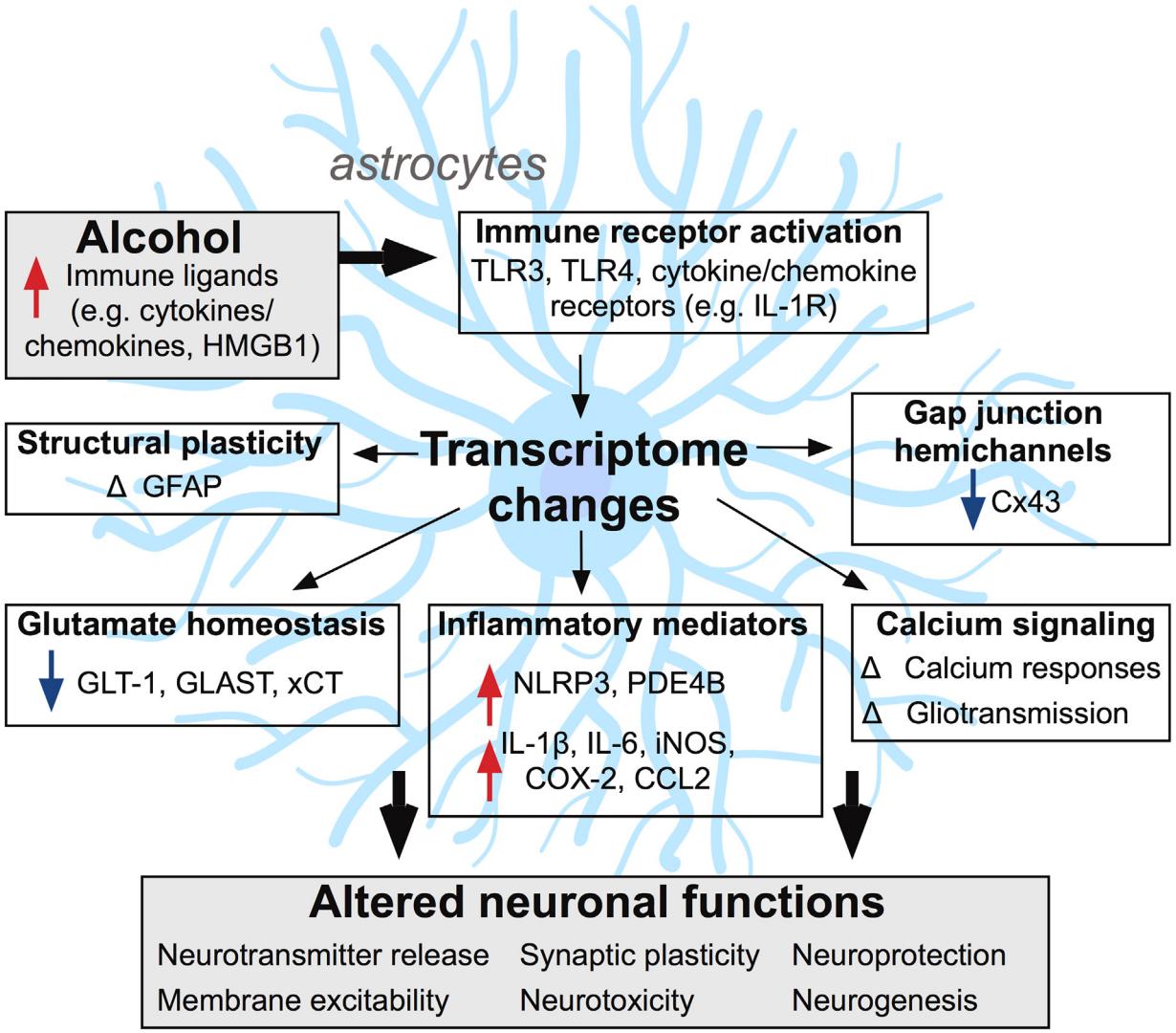

Fig. 2. Astrocyte-specific consequences of alcohol-induced neuroinflammation. Alcohol exposure generates a proinflammatory environment in brain, resulting in up-regulation of immune ligands such as cytokines and chemokines. This results in activation of immune receptors on astrocytes, leading to transcriptome changes which contribute to the modulation of several astrocyte functions, including glutamate homeostasis, calcium signaling, gap junction communication, structural plasticity, and the production of inflammatory mediators, which can alter neuronal function in various ways.

disruptions in glutamate homeostasis in astrocytes (see (Lindberg et al., 2018) for review). Ethanol inhibits type 1 equilibrative nucleoside transporter (ENT1), which leads to elevated extracellular levels of adenosine and reduces GLT-1 expression (Matos et al., 2015). ENT1 KO mice show down-regulated GLT-1, reduced ethanol intoxication, and enhanced ethanol drinking (Choi et al., 2004; Lee et al., 2013). Restoring GLT-1 expression with the anti-inflammatory antibiotic ceftriaxone decreases ethanol self-administration, relapse-like drinking, and ethanol withdrawal severity in rats (Abulseoud et al., 2014; Das et al., 2015; Qrunfleh et al., 2013; Sari et al., 2011, 2016). *N*-acetylcysteine, the antioxidant precursor to glutathione, also enhances GLT-1 and xCT expression and reduces ethanol-reinforced responding, ethanol seeking, and reacquisition of seeking after ethanol abstinence in Long Evans rats (Lebourgeois et al., 2018). Unlike ceftriaxone, *N*-acetylcysteine does not affect cue-primed reinstatement of ethanol seeking in Sprague-Dawley rats, suggesting mechanisms other than modulating glutamate uptake contribute to these behaviors (Weiland et al., 2015). Another drug that increases GLT-1 expression, clavulanic acid, has recently been shown to decrease ethanol drinking in rats (Hakami and Sari, 2017). Administration of anti-inflammatory mesenchymal stem cells (MSC) decreases ethanol consumption and relapse drinking, possibly through upregulation of GLT-1 expression (Ezquer et al., 2018). MSC administration also normalizes ethanol-induced changes in astrocyte reactivity, oxidative stress, and inflammatory marker expression. Thus, astrocyte glutamate homeostasis is important in regulating ethanol drinking, and inflammatory environments can hinder the functionality and expression of proteins required for proper homeostasis. Potential roles for glial glutamate transporters in AUD are reviewed in more detail in (Ayers-Ringler et al., 2016).

Astrocytes also regulate neuronal activity through gliotransmission (i.e., the astrocytic release of neuromodulators) elicited by increases in intracellular Ca^{2+} levels (Martín-Fernández et al., 2017; Oliveira et al., 2015; Theodosis et al., 2008; Yang et al., 2015). In cultured astrocytes, ethanol induces Ca^{2+} transients and gliotransmission, causing release of transmitters such as glutamate, glutamine, and taurine (Kimelberg et al., 1993; Salazar et al., 2008), as well as inflammatory ROS (González et al., 2007). Ethanol also affects downstream neurotransmitter-mediated responses in astrocytes, such as stimulating serotonin-induced inositol metabolism and suppressing muscarinic receptor-mediated Ca^{2+} responses in astrocytes (Catlin et al., 2000; Simonsson et al., 1989). Ethanol thus has several mechanisms through which it alters astrocyte-neuronal signaling. Transcriptome sequencing

of cortical astrocytes isolated from mice following chronic ethanol consumption shows ethanol-induced transcriptome changes in Ca^{2+} signaling, further implicating this mechanism in ethanol responses (Erickson et al., 2018). Gap junction hemi-channels such as connexin 43, which help propagate Ca^{2+} signals in astrocytes, are also differentially expressed by ethanol exposure (Adermark and Lovinger, 2006; Adermark et al., 2004; Miguel-Hidalgo et al., 2014). A few studies have investigated the role of astrocyte Ca^{2+}-related signaling in ethanol-seeking behaviors. Gap junction hemi-channel blockade in the NAc core, which impairs communication between astrocytes, increases ethanol-seeking behavior (Bull et al., 2014). In contrast, activating Ca^{2+} signaling in NAc core astrocytes in rats using DREADDs reduces motivation to self-administer ethanol after 3 weeks of abstinence (Bull et al., 2014). Another study using DREADDs to stimulate astrocytes in the NAc core to inhibit cocaine seeking shows that Ca^{2+} activation induces glial glutamate release (Scofield et al., 2015). These findings indicate that ethanol alters astrocyte Ca^{2+} signaling and intercellular communication, which may regulate addiction-related behaviors via changes in gliotransmission.

Astrocytes express receptors necessary for neuroimmune activation, including cytokine and chemokine receptors and TLRs. TLR3, for example, is enriched in astrocytes and its expression increases in response to LPS (McCarthy et al., 2017a). Ethanol promotes TLR4 and IL-1R signaling in cultured astrocytes, causing increased expression of inflammatory cytokines (IL-1β, TNF-α, IL-6, iNOS, and COX-2) (Alfonso-Loeches et al., 2010; Blanco et al., 2004, 2005). GFAP up-regulation in ethanol-exposed rodents is likely regulated by TLR4 (Alfonso-Loeches et al., 2013) and PDE4B (Avila et al., 2017). Ethanol-induced cytokine release from astrocytes may be mediated by NLRP3 activation (Alfonso-Loeches et al., 2014). Current evidence also points to a role for astrocyte-specific immune signaling in alcohol-dependent behaviors. Astrocytes may contribute to ethanol-induced increases in the cytokine CCL2 in rodents (Kane et al., 2014). Transgenic mice over-expressing CCL2 in astrocytes have slightly reduced alcohol consumption (Bray et al., 2017). These mice also exhibit differences in the effect of ethanol exposure on synaptic protein levels in the hippocampus compared with non-transgenic littermate controls (Gruol et al., 2014). In hippocampal slices, astrocyte-specific increases in CCL2 or the inflammatory cytokine IL-6 confer resistance to the depressive effect of acute ethanol on LTP (Bray et al., 2013; Hernandez et al., 2016). Furthermore, astrocyte-specific CCL2 overexpression alters hippocampal synaptic function associated with ethanol withdrawal (Bray et al., 2018). To summarize, recent work using transgenic mice over-expressing specific inflammatory genes in astrocytes suggests potential roles for astrocytic cytokine release in modulating alcohol effects on synaptic plasticity and behavior. Preclinical studies of astrocyte-specific manipulation and alcohol behaviors are shown in Table 6.

4.3. Neurons

Neurons also express inflammatory mediators and receptors that regulate immune and neuronal function (Oetjen et al., 2017; Veiga-Fernandes and Artis, 2018). For example, TLRs expressed on neuronal precursor cells mediate hippocampal neurogenesis (Rolls et al., 2007), and TLR4 activation in neuronal cultures initiates inflammatory responses in endothelial cells (Leow-Dyke et al., 2012). Inflammatory molecules and receptors localized in neurons also regulate ethanol drinking. For example, ethanol treatment induces neuronal expression of HMGB1, which can then activate glial and neuronal TLRs to stimulate pro-inflammatory cytokine production (Crews et al., 2013). As previously mentioned, conditional deletion of IKKβ in a primarily neuronal population in the NAc or CeA reduces voluntary ethanol intake and preference in mice and corroborates findings using a pharmacological inhibitor of IKKβ (Truitt et al., 2016). Furthermore, silencing neuronal *Tlr4* or *Ccl2* in the CeA and VTA regulates binge drinking in P rats (June et al., 2015). PPAR isotypes are also strongly expressed in neurons of several brain regions relevant to addiction (Warden et al., 2016), providing further evidence that the effects of PPAR agonists on ethanol consumption (Blednov et al., 2014a; Ferguson et al., 2014) may be mediated through neuronal PPARs.

Microglia, astrocytes, and neurons all seem to induce neuroimmune-related changes in the brain that may translate to changes in synaptic activity and alcohol behaviors. Typically, astrocytes and microglia are both “activated” in response to an injury or immune insult. A systemic immune challenge increases cytokines in microglia, which precede astrocyte reactivity (Norden et al., 2016). Studies of neuroinflammatory neurodegenerative disorders suggest that early microglial activation produces an inflammatory microenvironment which subsequently interferes with astrocyte and other glial cell function as pathological conditions progress (Sastre et al., 2006). Release of inflammatory factors from activated microglia stimulates a subtype of astrocytes to secrete neurotoxic factors, which has been proposed as a common mechanism for several human neurodegenerative diseases (Liddelow et al., 2017). Indeed, glial activation acts as a precursor to drug-induced neurotoxicity (Chastain and Sarkar, 2014; Friend and Keefe, 2013); however, the time course of activation for different populations of glia and neurons by alcohol and other drugs of abuse is not known. While it is increasingly apparent that chronic alcohol exposure induces neuroimmune pathology in brain, we must determine the key brain regions, cells, and time points following immune activation to develop targeted neuroimmune pharmacotherapies. Furthermore, while several rodent studies suggest a prominent role of glial dysfunction in alcohol pathology and addictive behaviors, less is known about how alcohol alters neuroimmune cell function in humans. Investigating common mechanisms and potential differences in neuroimmune function between species should be prioritized to better interpret results and predict translatability of preclinical studies.

5. Potential mechanisms of alcohol-induced neuroimmune activation

Alcoholic patients have dysregulated peripheral immune responses, are more susceptible to bacterial or viral infections, and exhibit signs of inflammation in several organs, including lung, liver, and the brain (Cook, 1998). Peripheral innate immune dysregulation is central to the pathogenesis of alcoholic steatohepatitis (ASH) and alcoholic liver disease (ALD), which are both marked by inflammation (Keshavarzian et al., 2009; Mutlu et al., 2009). Alcohol ingestion increases gut permeability to macromolecules, also referred to as “gut leakiness”, allowing translocation of bacterial toxins through the intestines into the bloodstream (Leclercq et al., 2012, 2014b; Parlesak et al., 2000). Increased levels of plasma endotoxins then activate immune responses in peripheral organs. Gut permeability can be increased for up to 2 weeks after cessation of alcohol consumption (Bjarnason et al., 1984). Even in healthy individuals, binge-drinking alcohol increases serum levels of gut-derived bacterial products such as LPS and 16S DNA, activating innate immune signaling and increasing circulating cytokines like TNF-α and IL-6 (Bala et al., 2014; Leclercq et al., 2012). In individuals with an alcohol use disorder, however, endotoxin levels increase > 5-fold compared with healthy controls, leading to increased peripheral inflammatory responses (Parlesak et al., 2000). Excessive drinkers have higher levels of serum LPS and other markers of immune activation that correlate with the quantity of alcohol consumed, and levels of these markers decrease after abstinence (Girard et al., 2017; Liangpunsakul et al., 2017). Acting as a powerful driver of TLR4 signaling, circulating LPS activates hepatic Kupffer cells to produce inflammatory cytokines and chemokines, which contribute to alcohol-induced liver injury (Roh and Seki, 2013). Alcohol also induces miR-155 and HDAC11 expression, which inhibits negative regulators of the TLR4 pathway and increases LPS responsiveness of mouse Kupffer cells (Bala et al., 2017). In addition to the liver, the gut wall or adipose tissue also contribute to systemic inflammation in AUD (de Timary et al., 2017). Similar findings

Table 6
Preclinical studies investigating the role of astrocytes in alcohol-related behaviors.

Manipulation	Mechanism	Species (strain)	Sex	Test	Result	Source
GLT-1 up-regulation	Ceftriaxone	Mice (ENT1 KO, C57BL/6J background)	Not stated	2BC	Decrease	Lee et al., 2013
		P rats	Male	3BC	Decrease	Sari et al., 2011, Das et al., 2015
			Female	3BC	Decrease	Sari et al., 2016
			Male	Relapse-like drinking	Decrease	Alhaddad et al., 2014, Qrunfleh et al., 2013
		Sprague-Dawley rats	Male	Cue-primed reinstatement	Decrease	Weiland et al., 2015
		P rats, Wistar rats	Male	EtOH withdrawal severity, withdrawal-induced drinking escalation	Decrease	Abulseoud et al., 2014
	N-acetylcysteine	Sprague-Dawley rats	Male	Cue-primed reinstatement	–	Weiland et al., 2015
		Long Evans rats	Male	EtOH reinforced responding, EtOH seeking, reacquisition after abstinence	Decrease	Lebourgeois et al., 2018
	Clavulanic acid	P rats	Male	3BC	Decrease	Hakami and Sari, 2017
	Human mesenchymal stem cells	UChB rats	Female	2BC, relapse-like drinking	Decrease	Ezquer et al., 2018
GLT-1 inhibition	ENT1 KO	Mice (C57BL/6J × 129Xq/SvJ background)	Male	2BC	Increase	Doo-sup Choi et al., 2004
	Dihyrokainic acid (lateral ventricle)	Mice (C57BL/6J)	Male	DID	Decrease	Smith et al., 2014
		Mice (DBA/2J)	Male	CPP	–	
GLAST inhibition	GLAST KO	Mice (C57BL/6J background)	Both	2BC, CPP	Decrease	Karlsson et al., 2012
Gap junction inhibition	18-α-Glycyrrhetinic acid (NAc)	Wistar rats	Male	EtOH seeking	Increase	Bull et al., 2014
	18-α-Glycyrrhetinic acid (PFC)	Wistar rats	Male	2BC	Increase	Miguel-Hidalgo et al., 2009
Calcium activation	hM3Dq DREADD (NAc)	Wistar rats	Male	EtOH seeking	Decrease	Bull et al., 2014
Astrocyte-specific CCL2	CCL2-overexpressing transgenic mice	Mice (C57BL/6J background)	Both	2BC	Decrease	Bray et al., 2017

CCL2, C-C motif chemokine ligand 2; CPP, conditioned place preference; DID, drinking in the dark; DREADD, Designer Receptors Exclusively Activated by Designer Drugs; ENT1, equilibrative nucleoside transporter; EtOH, ethanol; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; KO, knockout; NAc, nucleus accumbens; P rats; alcohol-preferring rats; PFC, prefrontal cortex; 2BC, two-bottle choice; 3BC, three bottle choice.

have been observed in nonhuman primate models of AUD. In primates exposed to chronic ethanol, changes in immune homeostasis in peripheral blood and intestinal mucosa may be partly mediated by ethanol-induced up-regulation in miRNA expression, including miR181a and miR221 in peripheral blood, and miR-155 in colon (Asquith et al., 2014). Transcriptome analysis of peripheral blood from chronic heavy alcohol consuming female macaques identified innate-immune related genes with altered expression (Sureshchandra et al., 2016). Male macaques chronically consuming ethanol showed changes in gene expression related to metabolism and inflammation in different areas of the gut, and 16S rRNA gene sequencing of the gut revealed shifts in relative abundance of putatively beneficial vs. inflammation-associated bacterial populations (Barr et al., 2018). Thus, alcohol-induced peripheral immune dysregulation is a core characteristic of AUD and its associated pathologies.

Increased gut permeability and circulating cytokines are also thought to be responsible for alcohol-induced neuroimmune activation. Increased circulating cytokines in the periphery are associated with immune activation in the brain, which can persist for months after the peripheral immune response has subsided (Ferrier et al., 2006; Leclercq et al., 2012, 2014a). Peripherally-produced cytokines enter the brain via two mechanisms: (1) systemic circulation and (2) neural pathways (Banks, 2015). Pro-inflammatory molecules reach the CNS via BBB-deficient areas in the brain (e.g., circumventricular organs) by entering fenestrated capillaries of the BBB or through cytokine-specific transporters. Specifically, IL-1 s, IL-6, TNF-α, and IFN (interferon)-γ cross the BBB via saturable transport systems (Banks, 2005; Qin et al., 2009). The amount of blood-born cytokines that enter the CNS is comparable to other water-soluble compounds such as morphine (Banks, 2005). Cytokines also stimulate production of other cytokines, nitric oxide, and prostanoids on the abluminal membrane site of the brain (Banks and Erickson, 2010). The BBB expresses TLRs 1–4 and 6, suggesting that PAMPs like LPS may directly alter brain signaling (Nagyoszi et al., 2010). BBB permeability may also be impaired in alcoholics, as suggested by immunohistochemical studies showing reduced expression of proteins, such as collagen-IV and claudin-5, in human postmortem PFC from alcoholics (Rubio-Araiz et al., 2016). Once in the brain, pro-inflammatory molecules are free to propagate immune responses in glial and neuronal cells, as previously discussed.

Recent efforts to understand the role of leaky gut in ASH and ALD highlight the use of potential therapeutics to reduce the gut leakiness and peripheral inflammation associated with alcohol dependence. Endocannabinoids oleoylethanolamine (OEA) and palmitoylethanolamine (PEA), which are PPARα agonists, reverse cytokine-induced permeability of intestinal cells in vitro (Karwad et al., 2017). Likewise, cannabidiol accelerates recovery of cytokine-induced intestinal permeability via cannabinoid receptor 1 (Alhamoruni et al., 2012). Flaxseed oil, which increases endocannabinoid levels, reduces inflammatory cytokine expression in a mouse model of ALD and ameliorates disease symptoms (Zhang et al., 2017). Because plasma markers of inflammation correlate with drug craving in human alcoholics (Leclercq et al., 2012), gut-based therapeutics also have the potential to ameliorate alcohol-dependent behavioral phenotypes. For example, preclinical studies show that targeting the endocannabinoid system or PPARα activation decreases ethanol intake (Blednov et al., 2014a; Sloan et al., 2017). It is not known whether the effects of PPARα activation or other anti-inflammatory therapies on alcohol behaviors are primarily due to peripheral or central immune modulation.

Similarly, it is not known whether peripheral inflammation is required to initiate neuroinflammation in AUD. Alcohol may induce neuroinflammation through direct effects on the brain. Inflammatory responses to ethanol are seen in brain slices (Coleman et al., 2017; Tajuddin et al., 2018; Zou and Crews, 2010, 2014), astrocytes (Alfonso-Loeches et al., 2010), and microglia (Fernandez-Lizarbe et al., 2009, 2013), suggesting that gut permeability and systemic activation of immune responses are not solely responsible for alcohol's neuroinflammatory effects. It's possible that immune responses are also initiated locally in the CNS in response to alcohol-induced neuronal damage (Collins and Neafsey, 2016; Cservenka and Brumback, 2017; de la Monte and Kril, 2014).

In addition to the peripheral and central immune signaling mechanisms of alcohol's neuroinflammatory effects, genetics may also play a role. For example, polymorphisms of NF-κB, IL-1β, and IL-10 are linked to AUD (Edenberg et al., 2008; Marcos et al., 2008; Pastor et al., 2005a) (Liu et al., 2009; Saiz et al., 2009). Alleles that increase expression of pro-inflammatory TNF-α are linked to alcoholism and ALD (Kebir et al., 2011; Pastor et al., 2005b). PPAR variants are also associated with alcohol dependence and withdrawal severity in humans (Blednov et al., 2014a), and variants of P2X7R are linked to alcoholics with comorbid anxiety and mood disorders (Mantere et al., 2012; Soronen et al., 2011). In addition, *PDE4B* may be associated with alcohol consumption (Clarke et al., 2017). The association between immune-related genes and alcohol dependence is reviewed further in (Crews, 2012).

6. Clinical studies of immune modulators for alcohol use disorder

The only drug currently FDA-approved for AUD treatment with potential to target the neuroimmune system is the opioid receptor antagonist naltrexone. Naltrexone is available in both (−) and (+) stereoisomers, both of which have antagonist activity at TLR4 receptors (Hutchinson et al., 2008b). Shortly after identifying naltrexone as a therapeutic agent, its derivative, nalmefene, was tested in two double-blind placebo-controlled laboratory studies (Mason et al., 1994, 1999). Individuals who took nalmefene drank fewer drinks per day, had a greater number of abstinent days, and experienced fewer relapses; in addition, nalmefene does not show the same dose-dependent livertoxicity as naltrexone (Mason et al., 1999). Phase III clinical trials for nalmefene were completed in 2013 (Gual et al., 2013), but it is currently only approved in Europe to reduce heavy drinking. It's unclear whether these opioid antagonists help to reduce drinking through TLR4 blockade, but their effects are usually considered to be due to actions on opioid receptors (Quelch et al., 2017).

More recent studies have investigated the potential for the neuroimmune modulator ibudilast in treating alcohol use disorder. In a double-blind placebo-controlled laboratory study, ibudilast reduces stress and cue-induced cravings for alcohol (Ray et al., 2017). A follow-up analysis revealed that the alcohol craving suppression effects of ibudilast are not generalizable to high-fat/high-sugar food cravings, strengthening its indication as a potential drug addiction treatment (Cummings et al., 2018). Additional clinical trials are in progress to determine its treatment efficacy for reducing alcohol consumption and withdrawal symptoms (see Table 7). In mice, anti-inflammatory PPAR agonists reduce ethanol consumption and preference (Blednov et al., 2014a; Ferguson et al., 2014), and phase II clinical trials with fenofibrate, a selective PPARα agonist, were recently completed (ClinicalTrials.gov identifier: NCT02158273). A phase II clinical trial with pioglitazone began in 2012, but the study was closed due to feasibility concerns (ClinicalTrials.gov identifier: NCT01631630). Several other clinical studies are underway to determine the efficacy of neuroimmune-related compounds in AUD. For example, a study expected to end in 2023 is investigating minocycline's ability to reduce neuroinflammation, alcohol cue reactivity, and alcohol use (ClinicalTrials.gov identifier: NCT03244592). Another study examining the effects of minocycline on alcohol responses, including subjective, motor, and cognitive effects as well as plasma cytokine levels, has an estimated completion date in 2018 (ClinicalTrials.gov identifier: NCT02187211). A phase II clinical trial testing the effects of the PDE-4 inhibitor apremilast on alcohol craving is currently recruiting participants, with an expected completion date in 2019 (ClinicalTrials.gov identifier: NCT03175549). A systematic review of randomized controlled trials using the anti-inflammatory drug *N*-acetylcysteine suggests that it may

Table 7
Neuroimmune modulators in clinical studies of addiction.

Target	Treatment	Drug of abuse	Outcome measures	Result	Source
PDE	Ibudilast	Alcohol	Stress- and cue-induced craving	Decreased	Ray et al., 2017
			Consumption	n/a	In progress; NCT03594435
			Withdrawal symptoms	n/a	in progress; NCT03489850
		Opioids	Withdrawal symptoms	Decreased	Cooper et al., 2016
			Positive subjective effects	Decreased	Metz et al., 2017
			Opioid analgesia	Increased	Cooper et al., 2017
			Positive subjective effects	No effect	Cooper et al., 2017
		Methamphetamine	Positive subjective effects	Decreased	Worley et al., 2016
	Apremilast	Alcohol	Craving	n/a	In progress; NCT03175549
PPAR	Gemfibrozil	Alcohol	Consumption	n/a	In progress; NCT03539432
	Fenofibrate		Consumption, craving	n/a	NCT02158273
	Pioglitazone	Opioids	Positive subjective effects	No effect	Jones et al., 2016
			Withdrawal symptoms	No effect	Schroeder et al., 2018
Microglia activation	Minocycline	Alcohol	Neuroinflammation, cue reactivity, neurocognitive performance, consumption	n/a	In progress; NCT03244592
			Biphasic alcohol effects scale	n/a	In progress; NCT02187211
		Dextroamphetamine	Positive subjective effects	Decreased	Sofuoglu et al., 2011
Astrocytes (GLT-1)	*N*-acetylcysteine	Alcohol	Positive subjective effects	n/a	in progress; NCT03216954
			Consumption	n/a	NCT01214083
		Cocaine	Use, craving	No effect	LaRowe et al., 2013

GLT-1, glutamate transporter 1; PDE, phosphodiesterase; PPAR, peroxisome proliferator-activated receptor; n/a, results not available.

reduce craving in SUDs (Duailibi et al., 2017). Using *N*-acetylcysteine to augment naltrexone therapy to treat alcohol dependence is currently being explored in a randomized controlled trial (ClinicalTrials.gov identifier: NCT01214083). Additional studies on the usefulness of combining neuroimmune therapies with approved drugs for AUD may be warranted, considering the evidence from preclinical studies (Stopponi et al., 2013). Table 7 outlines clinical studies investigating the use of neuroimmune pharmacotherapies for treating AUDs and other substance use disorders.

7. Convergent neuroimmune mechanisms for other drugs of abuse

Alcohol is often co-abused with illicit drugs (Soyka, 2015; Witkiewitz and Vowles, 2018) that further alter neuroimmune signaling. Opioids and psychostimulants activate brain microglia and increase levels of astrocyte markers, induce chemokines, increase levels of cytokines (e.g., IL-β and TNF-α), and produce neuronal dysfunction (Beitner-Johnson et al., 1993; El-Hage et al., 2006; Fernandes et al., 2016; Frank et al., 2016; Gonçalves et al., 2017; Hutchinson et al., 2011; Lewitus et al., 2016; Lloyd et al., 2017; Sawaya et al., 2009; Schwarz et al., 2011; Taylor et al., 2016). Furthermore, stressful experiences and adolescent pre-exposure to drug use facilitate these neuroimmune responses (Orso et al., 2017; Schwarz and Bilbo, 2013). Combining substances of abuse may have synergistic effects on neuroimmune activation and cognitive deficits, as was observed in rats administered chronic morphine and alcohol (Adedayo et al., 2018). As with alcohol, the drug exposure procedures, brain regions, and time points analyzed are some of the variables that can impact findings. A comprehensive review of the neuroimmune actions of opioids and psychostimulants can be found in (Lacagnina et al., 2017). Although many mechanistic questions remain, some common themes are emerging that may also enlighten alcohol-neuroimmune research.

Chronic use of methamphetamine is associated with microglial activation in humans as visualized through PET imaging (Sekine et al., 2008), but another PET imaging study using TSPO as a biomarker, shows that cocaine abuse is not associated with microglial activation (Narendran et al., 2014). It's not known if these differences in microglial activation are due to the different drugs of abuse or the use of different biomarkers. Acute LPS exposure in humans enhances methylphenidate-induced dopamine elevations in the dorsal striatum (Petrulli et al., 2017), indicating that systemic immune activation can also amplify the rewarding effects of drugs.

Much research has been devoted to the role of TLR4 and associated signaling cascades in mediating opioid- and stimulant-related behaviors in animal models. Opioids bind to the TLR4 co-receptor, myeloid differentiation factor 2 (Hutchinson et al., 2010; Wang et al., 2012). TLR4 KO animals have impaired drug reward learning, showing attenuated CPP to cocaine, morphine, and oxycodone (Hutchinson et al., 2012) (Kashima and Grueter, 2017). However, TLR4 mutant and KO mice retain opioid-induced analgesic tolerance, hyperalgesia, and physical dependence, indicating TLR4 is not required for these effects (Mattioli et al., 2014). TLR4 inhibition with (+)-naloxone impairs CPP to morphine and cocaine, decreases opioid and cocaine self-administration, and inhibits morphine- and cocaine-induced dopamine increases in the NAc (Hutchinson et al., 2012; Northcutt et al., 2015). However, (Tanda et al., 2016) reports no effect of (+)-naloxone and (+)-naltrexone on intravenous heroin- or cocaine-induced dopamine release. In addition, (+)-naloxone does not reduce methamphetamine craving during withdrawal (Theberge et al., 2013). Similar to findings from alcohol studies, TLR4 may mediate some components of addiction to opioids and psychostimulants but may not be a primary neuroimmune target. Future studies may benefit from newer tools to target TLR4 in brain, such as LPS from *Rhodobacter sphaeroides* (LPS-RS), a potent antagonist of LPS-TLR4 signaling (Brown et al., 2017). When injected into the VTA, LPS-RS decreases maintenance but not acquisition of CPP to morphine and cocaine-primed reinstatement of cocaine seeking (Chen et al., 2017b) (Brown et al., 2017). Also, intra-NAc injection of the weak TLR4 agonist, monophosphoryl lipid A, reduces acute behavioral sensitization to cocaine after prolonged abstinence (Lewitus et al., 2016).

As we discussed for alcohol action, other TLRs and immune receptors are likely important for opioid- and stimulant-induced neuroimmune alterations. For example, morphine-induced microglia activation and pro-inflammatory cytokine expression require TLR2 expression, and TLR2 KO mice show attenuated morphine withdrawal symptoms (Zhang et al., 2011). TLR2 is also implicated in cocaine-induced microglial activation in BV2 cells (Liao et al., 2016). Furthermore, TLR3 deficiency or intra-NAc injection of TLR3 inhibitors significantly attenuates cocaine-induced CPP (Zhu et al., 2018). Recent interest has centered around microglial P2X7R activation as a potential neuroimmune target for addictive behaviors, based on its role in methamphetamine-induced microglia activation (Fernandes et al., 2016) and tolerance to morphine's analgesic effects (Leduc-Pessah et al., 2017).

As discussed for alcohol, several preclinical studies have

demonstrated that dysregulation of astrocyte function, particularly as it relates to glutamate homeostasis, is a common neuroimmune response for other drugs of abuse. For example, chronic opioid or stimulant use decreases astrocytic expression of GLT-1 (Ozawa et al., 2001; Shen et al., 2014) (Althobaiti et al., 2016; Knackstedt et al., 2010). In rats, GLT-1 gene transfer in the NAc shell reduces morphine- and methamphetamine-induced CPP (Fujio et al., 2005), while gene transfer in the locus coeruleus reduces morphine dependence (Ozawa et al., 2004). Ceftriaxone and *N*-acetylcysteine both help restore GLT-1 expression in astrocytes, which may be related to their anti-inflammatory properties (Lasram et al., 2014; Wei et al., 2012). Treatment with these compounds decreases morphine dependence, tolerance (Habibi-Asl et al., 2014), and relapse in preclinical models (Shen et al., 2014). However, ceftriaxone requires intravenous administration and has poor brain penetrability, limiting its potential clinical use. Alternatively, clavulanic acid can be used to increase GLT-1 expression, and it reduces cocaine's reinforcing effects (Kim et al., 2015) and the rewarding properties of opioids in rats (Schroeder et al., 2014). Disruption in astrocyte glutamate uptake appears to be a common neuroimmune response associated with several drugs of abuse, and manipulating GLT-1 expression has the potential to alter drug-induced reward, dependence, tolerance, and relapse.

As discussed with alcohol drinking, administering anti-inflammatory drugs, such as ibudilast, PDE-4 inhibitors, PPAR agonists, and minocycline reduces consumption of other drugs of abuse and drug-seeking in animal models (de Guglielmo et al., 2017; Hutchinson et al., 2008a; Miller et al., 2016; Northcutt et al., 2015; Poland et al., 2016; Zhong et al., 2012). Clinical evidence lends support for the translational potential of some of these compounds to treat symptoms of substance abuse. For example, ibudilast reduces withdrawal symptoms in opioid-dependent humans (Cooper et al., 2016) and reduces the subjective and reinforcing effects of oxycodone in a small sample of non-treatment seeking opioid users (Metz et al., 2017). Another study shows ibudilast enhances opioid-induced analgesia in dependent individuals, but does not alter the subjective drug effects associated with abuse liability (Cooper et al., 2017). However, in non-treatment seeking methamphetamine-dependent individuals, ibudilast reduces the subjective effects (Worley et al., 2016). A phase II clinical trial of ibudilast for outpatients seeking treatment for methamphetamine dependence is underway [ClinicalTrials.gov Identifier: NCT01860807]. Another phase II trial of the effects of ibudilast on neuroinflammation in methamphetamine-dependent users in remission is also in progress [ClinicalTrials.gov Identifier: NCT03341078]. The PPARγ agonist pioglitazone does not affect positive subjective effects of oxycodone in non-dependent prescription opioid users (Jones et al., 2016), and a Phase 1 clinical trial (which was prematurely terminated due to slow enrollment), revealed no evidence that pioglitazone reduces symptoms of withdrawal in opioid dependent patients (Schroeder et al., 2018). *N*-acetylcysteine treatment over an 8-week period does not reduce cocaine use or craving; however, a subset of participants who were abstinent when the trial began did have reduced cocaine cravings and remained abstinent longer (LaRowe et al., 2013). Minocycline reduces the positive subjective effects of the psychostimulant dextroamphetamine (Sofuoglu et al., 2011). Thus, several immune modulators, some of which have also been shown to reduce alcohol consumption or craving, are being actively investigated for their clinical effectiveness in treating opioid and psychostimulant abuse (Table 7). Hence, neuroimmune targeting medications may potentially be used to treat AUD patients who also abuse other substances.

8. Comorbidity of Post-traumatic stress disorder or major depressive disorder with alcohol use disorder and immune signaling

8.1. Post-traumatic stress disorder and alcohol use disorder

Post-traumatic stress disorder (PTSD) is an anxiety-like disorder that may develop after exposure to stressful or traumatic events. The lifetime prevalence of PTSD is approximately 7% in individuals age 18 or older, with rates higher among women (8.6%) than men (4.1%) (Kessler et al., 2005; Pietrzak et al., 2011). PTSD and AUD frequently co-occur (Ralevski et al., 2014). There are strong associations between specific PTSD symptoms and misuse of specific drugs (Dworkin et al., 2018; Head et al., 2016). While avoidance and hyper-arousal symptoms are more strongly associated with substance abuse in general (Head et al., 2016; Saladin et al., 1995), avoidance and re-experiencing trauma are more strongly related to alcohol abuse (Head et al., 2016).

Lifetime trauma, particularly early life adversity, is a major risk factor for development of PTSD and AUD. Systemic inflammation is thought to be a potential overlapping mechanism that mediates increased risk for these diseases (Neupane, 2016; Plantinga et al., 2013; Tursich et al., 2014). Studies of immune activity in PTSD and other psychiatric disorders show disruptions in pro-inflammatory responses among symptomatic individuals, as compared with healthy controls (Baker et al., 2012; Hiles et al., 2012; Modabbernia et al., 2013; Munkholm et al., 2013; Tursich et al., 2014). Similarly, patients with PTSD show increased concentration of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) in peripheral blood compared to healthy controls (Lohr et al., 2015; Passos et al., 2015). Exposure to psychological trauma (e.g., childhood/early life adversity, exposure to violence or assault, combat exposure, accidents, or natural disasters) is positively associated with pro-inflammatory cytokine expression, and the presence of psychiatric symptoms is a significant predictor of increased levels of cytokine expression (Tursich et al., 2014). Moreover, circulating levels of IL-1β and IL-6 positively correlate with PTSD duration and severity, respectively (Lohr et al., 2015). Whole-transcriptome RNA-seq analysis of blood leukocytes from military personnel indicate widespread changes in immune signaling modules (Breen et al., 2015; Guardado et al., 2016). Furthermore, an RNA-seq comparison of marines, before and after deployment, who developed PTSD indicates that dysregulation in innate immune signaling is not only a consequence of trauma exposure, but is significantly associated with the development of PTSD (Breen et al., 2015). In addition, genetic polymorphisms in immune regulators including TNF-α are associated with PTSD (Wang et al., 2017). Preclinical research suggests that stress and alcohol exposure interact to increase plasma endotoxins and enhance microglial activation (Walter et al., 2017). On a clinical level, many of the cytokines increased in PTSD patients also have altered expression in post-mortem brains of human alcoholics. These findings support a role for immune signaling in the pathophysiology of PTSD. However, more studies are required to determine the mechanisms and extent of peripheral vs. neuroimmune dysregulation in patients with PTSD (Olff and van Zuiden, 2017). If overlapping changes in neuroimmune pathways are present in both disorders, then PTSD patients may be at increased risk for developing AUD.

Immune-targeted compounds offer a new approach to treat individuals with PTSD and PTSD/AUD. Treatment with minocycline, which also decreases alcohol consumption in rodents (Agrawal et al., 2011), prevents the physiological and behavioral changes resulting from acute exposure to psychological stress in an animal model of PTSD (Levkovitz et al., 2015). Ketamine, in addition to being an NMDA receptor blocker, has anti-inflammatory effects (via inhibition of transcription factor activator protein-1 and NF-κB), and decreases serum levels of IL-6, TNF-α, iNOS, and C-reactive protein (CRP) (Potter and Brady, 2014). In patients with chronic PTSD, ketamine infusion rapidly reduces PTSD symptom severity and comorbid depressive symptoms

(Feder et al., 2014). These preliminary findings suggest that anti-inflammatory drugs may reduce symptoms of both PTSD and AUD.

8.2. Major depressive disorder and alcohol use disorder

Major depressive disorder (MDD) is another psychiatric illness sharing a high comorbidity with AUD. MDD is characterized by persistent low moods, cognitive impairment, loss of interest or pleasure in activities, and suicide ideation (Kennedy, 2008). In the United States, an estimated 16.1 million adults age 18 or older had at least one major depressive episode in the past year (Han et al., 2017). About 30% of individuals with MDD also report a lifetime of alcohol abuse (Brière et al., 2014; Sullivan et al., 2005). Individuals with AUD have a two- to four-fold increased risk of lifetime depressive disorders and suicide ideation according to general population studies (Krawczyk et al., 2017; Welsh et al., 2017). Depressed individuals with a positive family history of substance abuse are more likely to have attempted suicide and have a family history of suicide than those without this family history (Agrawal et al., 2017; Davis et al., 2008). Current symptoms of depression are also predictive of poorer treatment responses and higher rates of relapse for AUD and other SUDs (Brière et al., 2014; Krawczyk et al., 2017; Nunes and Levin, 2004; Wojnar et al., 2008).

Like individuals with AUD, patients with MDD have higher levels of pro-inflammatory cytokines and circulating leukocytes, leading to the hypothesis that inflammatory/immune processes also mediate the development and progression of depressive illnesses (for review, see (Lotrich, 2015; Miller and Raison, 2016)). Genome-wide association studies suggest immune-related genetic polymorphisms may mediate depression vulnerability, severity of symptoms, and response to antidepressant treatment (Barnes et al., 2017). Meta-analyses of unstimulated measurements of cytokines in patients with MDD show higher concentrations of TNF-α, IL-1β, IL-6, and IFN-γ—many of the same cytokines that are related to PTSD symptomology and AUD progression (García-Marchena et al., 2017; Glaus et al., 2017; Montesinos et al., 2016b). Additional support for a relationship between systemic inflammation and depression comes from cancer patients undergoing cytokine immunotherapy with IFN-α and IL-2, who show increased risk of developing depressive symptoms (Capuron and Dantzer, 2003). Clinical findings link increases in peripheral inflammatory markers with decreases in the functional connectivity of PFC–striatum pathways (Felger et al., 2015). For instance, the inflammatory marker CRP is associated with decreased connectivity between ventral striatum and ventromedial PFC, which in turn correlates with increased depressive symptom severity (i.e. anhedonia) (Felger et al., 2015). Furthermore, symptoms of depression such as fatigue, hyperalgesia, anorexia, and social withdrawal, mirror the adaptive response to acute inflammation known as “sickness behavior” (Dantzer, 2006). Chronic depression may kindle a progressive sensitization of inflammatory pathways, resulting in long-term positive feedback loops between neuroinflammation and resulting cognitive symptoms (Maes et al., 2012; Miller and Raison, 2016).

The discovery of immune imbalances in depressive illness led to the “macrophage hypothesis of depression” (Neupane, 2016; Smith, 1991). As the resident macrophage of the CNS, microglia are major contributors to heightened pro-inflammatory states in MDD and SUDs. Postmortem analysis of brain tissue from subjects with depression and those who committed suicide show increased microglia activation in cortical areas related to depression (Steiner et al., 2008). In rodent models of depression, microglia isolated from stressed mice release higher levels of IL-1β and IL-6 following ex vivo exposure to LPS, suggesting stress/depression prime microglia for enhanced pro-inflammatory responses (Frank et al., 2007; Wohleb, 2016). Furthermore, transgenic mice lacking CX3CR1, a key microglia fractalkine receptor, have stunted neurodevelopment, deficient PFC-hippocampus connectivity, and impaired social interactions (Parkhurst et al., 2013; Zhan et al., 2014).

Postmortem human studies also indicate decreased numbers of astrocytes in cortical regions in subjects with depression (Peng et al., 2015; Rajkowska and Stockmeier, 2013), while preclinical studies have demonstrated an important role for cortical astrocyte function in mediating depressive-related phenotypes and anti-depressant functions. In rats, pharmacological ablation of PFC astrocytes is sufficient to drive depressive-like behaviors (Banasr and Duman, 2008), and intra-PFC blockade of astrocyte glutamate uptake induces anhedonia (John et al., 2012). Deficiencies in PFC astrocytic ATP release have been linked to depressive-like behaviors in adult mice (Cao et al., 2013). In addition, gap junction blockade in PFC astrocytes induces anxiety and anhedonia in rats (Sun et al., 2012). PFC astrocytes also show Ca^{2+} signaling in response to treatment with fluoxetine and citalopram, suggesting that these antidepressants may partly exert their effects via stimulation of astrocyte activity (Schipke et al., 2011). Several studies suggest that normal astrocyte function may be crucial for antidepressant treatment efficacy (Allaman et al., 2011; Etiévant et al., 2015; Sarrouilhe et al., 2018). Astrocyte activity and pro-inflammatory responses, particularly in the PFC, may thus contribute to behavioral symptoms of depression.

A proof-of concept study for a role for neuroimmune signaling in depression examined infliximab (a TNF-α inhibitor) in patients with treatment-resistant depression (Raison et al., 2013). Twelve weeks after the initiation of therapy, infliximab reduces depressive symptoms by at least half among patients with baseline CRP levels > 5 mg/L, but not among those with lower baseline levels (Raison et al., 2013). Another trial showed that adjunctive treatment with celecoxib, an anti-inflammatory drug that selectively inhibits COX2, is more effective in reducing depressive symptoms than sertraline alone in patients with MDD (Abbasi et al., 2012). A reduction of serum IL-6 levels also correlates with a reduction in the depression score, suggesting that cytokine levels correlate with depression severity and possibly treatment efficacy (Abbasi et al., 2012). Meta-analysis of clinical trials using anti-cytokine treatments indicate that these treatments persistently improved symptoms of depression (Kappelmann et al., 2016). Moreover, the PDE inhibitor ibudilast attenuates the stimulant and mood-altering effects of alcohol in patients with greater symptoms of depression, which may have relevance for treating MDD/AUD comorbid populations (Ray et al., 2017). Finally, ketamine has attracted interest for its role as a rapidly acting anti-depressant (Lang et al., 2018). In mouse models of ethanol withdrawal, ketamine is particularly effective in reversing depressive-like behavior in abstinent animals (Holleran et al., 2016). Currently, ketamine is being investigated in a human clinical trial to determine its efficacy in lowering relapse rates and severity of depressive symptoms (McAndrew et al., 2017).

Immune and neuroimmune mechanisms may drive the comorbidity found for AUD with PTSD or MDD. As shown in Fig. 3, these commonly comorbid psychiatric diseases share several core risk factors that have the potential to drive neuroinflammation. Inflammatory activation in brain can alter the behaviors and symptoms related to these disorders, including alcohol consumption, mood disturbances and PTSD symptoms, which may feed-forward to enhance specific neuroimmune-sensitive risk factors, thus creating a persistent cycle of inflammation. As suggested above, anti-inflammatory drugs may offer viable treatment options in patients with comorbid psychiatric diseases with common neuroimmune mechanisms.

9. Future directions and conclusions

Perturbations in neuroimmune pathways are now recognized as a central component of AUD neurobiology. Alcohol activates neuroimmune signaling in brain, creating an inflammatory environment characterized by glial pathology, induction of chemokine and cytokine expression, and neuronal dysfunction. Anti-inflammatory compounds target alcohol behaviors, indicating a link between immune actions and behavioral changes leading to addiction. While neuroimmune-related research has uncovered a wealth of molecular targets, key questions

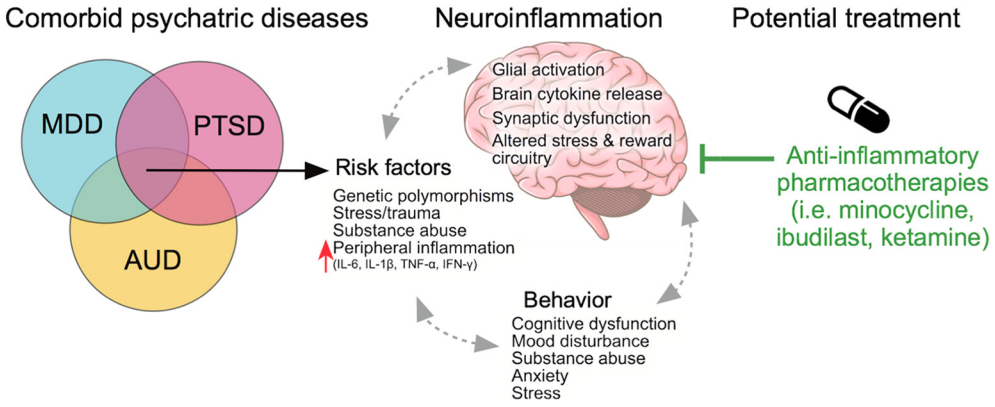

Fig. 3. Potential neuroimmune-mediated mechanisms that underlie associations between psychiatric diseases including alcohol use disorder (AUD), major depressive disorder (MDD), and post-traumatic stress disorder (PTSD). AUD, MDD, and PTSD are frequently comorbid. Environmental and biological factors that can influence and lead to neuroinflammation are associated with all three disorders. Sustained neuroimmune imbalance can lead to physiological consequences that drive behavioral phenotypes associated with psychiatric disease. Altered behavior may enhance further risk for neuroinflammation, resulting in a persistent cycle that leaves patients vulnerable to additional psychiatric disorders. Pharmacotherapies that target neuroinflammation are possible treatment options for comorbid psychiatric diseases with common neuroimmune elements.

remain concerning the primary neuroimmune molecules and downstream targets, cell-type specific signaling in brain, identifying suitable biomarkers for human studies, and appropriate methods for manipulating these CNS pathways in patients to treat AUD and other psychiatric disorders.

A pervasive theory has been that TLR4 is a principal mediator of alcohol's neuroimmune effects and the development of excessive drinking (Crews et al., 2017). However, several negative findings regarding its direct role in alcohol consumption necessitate the exploration of other immune receptors and molecules. Additional TLRs, including TLR2, TLR3, and TLR7, should be considered for their contribution in modulating alcohol-induced inflammation and behavioral effects. P2XRs are also demonstrating potential roles in neuroimmune activation by alcohol and other drugs of abuse. P2X7-targeted ligands for use in PET imaging (Fantoni et al., 2017; Territo et al., 2017) are currently being developed and validated and may prove useful as biomarkers of neuroinflammation in AUD. Many of the pharmacotherapies discussed here, such as PDE inhibitors, PPAR agonists, and glial modulators, show promise in regulating alcohol-related behavior and neuroinflammation, yet the precise mechanisms behind their efficacy remain unclear. A key question for future studies is whether these treatments target the brain, the peripheral immune system, or a combination of both to exert their behavioral effects. Studies utilizing global KO mice demonstrate numerous cytokines and chemokines can regulate alcohol drinking, but since neuroimmune molecules are normally expressed in a variety of tissues and cell types, pinpointing the behaviorally relevant functional context is difficult. Microglia and astrocyte dysregulation are hallmarks of chronic alcohol exposure, but their individual and collective contributions to neuroimmune-mediated behaviors are relatively unknown. Furthermore, most studies targeting astrocytes or microglia do not account for glial heterogeneity within and across brain regions or pathological states. Single cell sequencing approaches to identify more specific molecular indicators of addiction-associated microglia and astrocytes may be useful to address this issue (Keren-Shaul et al., 2017). Future research will also need to examine unique stages, time courses, and neuronal consequences of glial activation during the development and progression of AUD. These questions are in the early stages of investigation and are key to dissecting neuroimmune signaling in alcohol-related behaviors and developing targeted treatments. Newer tools, including cell-type specific depletion drugs (Walter and Crews, 2017), brain-region specific viral manipulations (Scofield et al., 2015), cell-specific transgenic mice (Bray et al., 2017), and Cre driver lines (Lewitus et al., 2016) are beginning to enable the research advances required to yield new neuroimmune-based treatments for AUD.

Several findings suggest females may be more vulnerable to neuroimmune signaling following alcohol exposure (Alfonso-Loeches et al., 2013; Bala et al., 2014; Barton et al., 2017; Baxter-Potter et al., 2017; Pascual et al., 2017; Wilhelm et al., 2015). In turn, the ability of neuroimmune-related drugs to reduce drinking may also depend on sex (Blednov et al., 2016a). Although more recent behavioral studies of neuroimmune signaling have tested both male and female mice (Bray et al., 2017; Burma et al., 2017; Harris et al., 2017) (Blednov et al., 2016a), the majority of studies examined only males. Including females in future studies will provide key insights into the potential sex-specific mechanisms of neuroimmune dysregulation in AUD.

Human analyses will be essential to confirm biomarkers of alcohol-induced neuroinflammation and assess translatability of mechanistic findings from preclinical studies. Cell-type specific transcriptome analysis of post-mortem human alcoholic brain is an important future direction, and will be more feasible with advances in cell isolation methods (Habib et al., 2017; Krishnaswami et al., 2016; Simpson et al., 2018) and computational techniques (Kelley et al., 2018). Functional studies on alcohol-exposed human glia should also be prioritized. New in vitro models present an opportunity for examining alcohol's functional effects on human microglia (Mizee et al., 2017) and astrocytes (Canals et al., 2018; Kitamura et al., 2018). Accordingly, tracking alcohol-induced neuroimmune activation in human subjects would be ideal, but methods are not yet adequate to achieve this goal. Studies with non-human primates can help link rodent findings to relevant human biomarkers, possibly through identification of peripheral predictors of CNS inflammation. Continual development of PET labeling methods for TSPO, P2X7, and other inflammatory markers in live human brain are also likely to provide important insight. A recently completed study examined the effects of alcohol on immune biomarkers, neurobiological measures, and cognitive function in healthy adults (ClinicalTrials.gov identifier: NCT03370783), and these findings will hopefully guide future research to develop useful biomarkers of inflammation in humans to diagnose and monitor treatment efficacy.

Several anti-inflammatory compounds, including minocycline, amlexanox, ibudilast, and ampremilast show promising results in rodent models and testing is now underway in humans. Translating potential pharmacotherapies in animal models to humans requires careful consideration of several details, including dosage. The highest approved fenofibrate dose used in the human clinical trial was lower than the dose found to reduce drinking in mice, which may impact its success. However, the effective dose of apremilast that decreased ethanol consumption and preference in mice is roughly equivalent to the dose being tested in humans (Blednov et al., 2018b), indicating its translational potential for AUD could be higher. Also, potential drug side effects that could drive immune signaling should be considered, especially given the immune dysregulation that already exists in patients with AUD. Liver toxicity, for example, is a potential side effect of fenofibrate (Bhardwaj and Chalasani, 2007), which could be exacerbated with concurrent use of alcohol or other medications. In this regard, apremilast offers another potential advantage in that it is considered very

safe for use in humans with relatively few side effects compared with other PDE inhibitors (Blednov et al., 2018b; Langley and Beecker, 2017). Another consideration is the mechanism for drug action in animal models – is modulation of drinking behavior due to a peripheral or central immune mechanism? Are large doses required for a candidate drug to reach the brain, and if so, can effective doses be achieved in humans?

The common neuroimmune link among MDD, PTSD, and AUD suggests that neuroimmune pharmacotherapies may be particularly useful for individuals with co-occurring neuropsychiatric disorders. More research is needed to identify the genetic determinants underlying drug-induced immune activation in comorbid patients, especially in light of the polymorphisms found in P2X7Rs in treatment outcomes for mood disorders in patients with comorbid AUD (Soronen et al., 2011). In addition, AUD shares etiologies with other SUDs, often involving dysfunction of the same brain circuits and neurotransmitter systems (Koob and Volkow, 2016). Overlapping mechanisms of glial activation and neuroimmune regulation of behavior may identify shared targets for different substances of abuse. Drugs of abuse may also produce additive effects on neuroimmune activation (Alshehri et al., 2017; Althobaiti et al., 2016), and treatment efficacy may depend on the particular substances abused (Sari et al., 2016). This raises important considerations given that a majority of individuals who die from drug abuse worldwide are polydrug abusers (Preedy, 2016). Better preclinical models and more clinical investigation of comorbid psychiatric and substance use disorders will be essential to elucidate proper treatment strategies.

Exploration into the neuroimmune mechanisms of AUD has revealed new molecular targets and potential drug candidates for advancing treatment strategies. Now researchers must delve deeper into the genetic components of cell-type signaling pathways in different brain regions, in a unified effort to define targetable neuroimmune molecules and biomarkers in animal drinking models with potential efficacy in the human laboratory. Integrated approaches across disciplines will be critical to gain the understanding necessary to advance work in animal models to the clinical level.

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