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A review on the reciprocal interactions between neuroinflammatory processes and substance use and misuse, with a focus on alcohol misuse

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Abstract

Background: The last decade has witnessed a surge of findings implicating neuroinflammatory processes as pivotal players in substance use disorders. The directionality of effects began with the expectation that neuroinflammation associated with prolonged substance misuse contributes to long-term neuropathological consequences. As the literature grew it became evident, however, that the interactions between neuroinflammatory processes, and alcohol and drug intake are reciprocal; and part of a pernicious cycle in which disease-relevant signaling pathways contribute to escalation of drug intake, which provokes further inflammation-signaling, and thereby exacerbates neuropathological effects of drug misuse.

Objectives: The goal of this review and its associated special issue was to provide an overview and forum for publication of emergent findings relevant to understanding these reciprocal interactions. The review highlights the importance of preclinical and clinical studies in testing and validation of immunotherapeutics as viable targets for curtailing substance use and misuse, with a focus on alcohol misuse.

Methods: a narrative review of the literature on drug and neuroinflammation was conducted, also including articles submitted to the associated special issue.

Results: We argue that (a) demographic variables and genetic background contribute unique sensitivity to drug-related neuroinflammation; (b) co-morbidities between substance use disorders and affect dysfunction may share common inflammation-related signatures that predict efficacy of

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immunotherapeutic drugs; and (c) examination of polydrug interactions with neuroinflammation is a critical area where greater research emphasis is needed.

Conclusions: This review provides an accessible, and example-driven review of the relationship between drug misuse, neuroinflammatory processes, and their resultant neuropathological outcomes.

Keywords

neuroinflammation; substance misuse; immunotherapeutics; review

Introduction

It is now widely recognized that the brain's innate immune system plays a wide and varied role in recovery from tissue damage, infectious disease, and illness-related processes, counteracting impending threats during times of stress, and a myriad of other vital processes that contribute to overall brain health. These responses include activation of microglia and other glial cells and the subsequent release of cytokines, chemokines, and additional molecules that trigger adaptive responses that, first and foremost, promote survival (1). Importantly, these same inflammation-related signaling pathways in the CNS fluctuate across cycles of drug use and hazardous use and have been implicated in both neural plasticity associated with the development of Substance Use Disorders (SUDs) and neuropathological consequences of prolonged drug use (2).

The tapestry of genetic and environmental factors that may culminate in an SUD is composed of many threads that can be disentangled using parametric studies that critically examine the contributing components. The immune system exists perpetually in a state of flux to fit survival to the challenges it encounters, and therefore it is perhaps not surprising that the role of neuroinflammatory processes in SUD requires careful contextualization with biological factors such as age and sex as well as environmental conditions to discern causal relationships (2). The first section of this review will delve into these issues. We particularly focus on sex-related differences in the immune response to drugs, as well as on the differential effects of drug exposure in certain development epochs.

Psychoactive drugs can alter immune function by affecting general homeostatic parameters, for instance by inducing dehydration, alteration in sleep patterns or by reducing appetite. Yet perhaps the most studied mechanism by which psychoactive drugs influence neuroinflammatory processes is via activation of stimulus-specific responses of glial cells. Glial cells have a plethora of surface or transmembrane receptors that react to bacteria or viruses, chronic exposure to psychoactive drugs, or damage associated molecular patterns (DAMPs) secreted by distressed cells, by secreting cytokines and chemokines (3). Among these receptors, Toll-like receptors (TLR) have been involved in coordinating responses to chronic drug exposure (4–6). TLR are proteins, presented in a family spanning TLR1 to TLR13 subtypes, specifically attuned to recognize molecular signatures associated with classes of pathogens and DAMPs. When bound, TLRs initiate immune cell responses that orchestrate a rapid cellular response to aid in clearance of pathogens and dead or dying cells. The second section of this review will touch upon seminal studies, key to demonstrating that

the activation of these receptors after drug exposure activates signaling pathways ultimately resulting in memory, anxiety, and other drug-related impairments, and also promotes drug self-administration. We will also describe the development of molecules that block the activation of TLRs and hence protect from these insidious effects of drug exposure (7).

We will then address (third and fourth sections) genetic mechanisms by which inflammation favors the development of SUDs or of negative motivational states that are intertwined with SUDs. Indeed, accumulating evidence suggests that neuroinflammation may play a key role in the emergence of negative affective states contributing to SUDs, which may manifest with co-morbid depression or anxiety disorders (8). Furthermore, protracted neuroinflammation has been linked to a wide array of neurodegenerative diseases, including Alcohol-Related Brain Damage, Alzheimer's Disease, and Parkinson's Disease, to name a few (9).

Recent epidemiological work has highlighted how common is the simultaneous use of more than a single substance. Particularly frequent is the simultaneous use of alcohol (the drug we will also refer to as ethanol) and cannabis (usually referred to as simultaneous alcohol and marihuana use), so that the effects of both substances overlap (10, 11). Intriguing research suggests that these drug users experience more drug-related negative consequences than those who use both substances separately (12). The focus on these issues is relatively new, so it is not surprising that there are relatively few basic studies assessing how neuroinflammatory processes are affected by simultaneous use of more than a single substance. This is particularly worrisome since polysubstance use is a common occurrence and can complicate treatment for SUDs. Though the exact mechanisms may differ, brain systems involved in reward and decision-making are implicated in each type of SUD and share some similarity in signaling systems. The immune system is a point of connection across SUDs that needs to be evaluated as a potential synergistic agent in driving SUDs as well as a potential target for intervention. The fifth section of the review will describe recent studies addressing these issues.

The basic studies on behavioral and genetic mechanisms, and on parametric factors, affecting the interaction between psychoactive drugs and the immune system will serve the basis for describing recent developments in inflammation-based pharmacotherapeutics to ameliorate SUDs, including several that have been shown to exert beneficial effects in SUD treatment (see Figure 1 for a schematic of the highlights). Given our emergent knowledge of inflammation as a potential driver of SUDs, more attention has been devoted to systematically examining the immune and neuroimmune mechanisms by which these pharmacological agents exert their effects. Moreover, the very same inflammation pathways contributing to drug use disorders may also contribute to neuropathological outcomes of prolonged drug use. In this way, targeting inflammation-related pathways as a means to curtail hazardous drug use may realize the dual benefit of reducing both SUD and the neuropathological outcomes associated with prolonged hazardous drug use.

Section 1. Parametric studies that critically evaluate the role of age (perinatal, adolescent, adult, or aging-related), sex, and other variables on neuroinflammatory processes provoked by psychoactive drugs.

Clinical epidemiological data indicates that there are sex differences in the prevalence and development of SUDs. While historically SUD incidence rates were higher in men, the sex difference gap has been narrowing (13). The most recent NSDUH survey indicates that while males show higher rates of illicit drug use across most but not all age groups over 12 years old, females show higher levels of use of prescription tranquilizers, painkillers, and stimulants (14). The trajectory of use is also different in women, frequently showing a faster progression to Use Disorders (15), a difference which has also been noted in preclinical models (16).

Likewise, there are sex differences in immune function as well, indicating that the interaction of neuroinflammation with psychoactive drugs may be sex specific (1). Women show higher rates of autoimmune illnesses across the lifespan (17) and lower susceptibility to certain infections than males (18), indicating that differences in innate and adaptive immunity need to be considered when examining immune underpinnings of SUDs. On the other hand, it has been shown that females are resilient to the effects of a pre- or early postnatal challenge with lipopolysaccharide (LPS; a component of cell wall of gram-negative bacteria that activates TLR4 and is used to simulate a bacterial infection) (19, 20). Preclinical work also showed that females exhibited a delayed and more protracted prefrontal cortex cytokine response to poly I:C (polyinosinic-polycytidylic acid, a synthetic double-stranded RNA that activates TLR3 and is used as a viral mimetic), which also altered the timeline of when the mice were most susceptible to immune-associated changes in ethanol consumption (7). Poly I:C administration, 1.0 mg/kg on consecutive days, has been shown to increase ethanol intake in female (Long-Evans rats) only (21).

The neuroimmune response is not static across the lifespan. For instance, induction of cytokine gene expression by LPS is suppressed in adolescent rats as compared to adult counterparts (22), and exposure to alcohol or other substances in adolescence can alter the trajectory of immune development that may impact later adult function. Recent studies have shown that adolescent intermittent alcohol exposure suppresses, in males only, brain cytokine responses to adult ethanol challenge and increased permeability of the blood brain barrier (23–25). Intermittent alcohol exposure is a protocol widely used to model the on-and-off exposure to binge-like doses of alcohol that typically punctuate adolescence, as shown by epidemiological studies (26). This protocol is associated with altered development of key transmitter systems (27) and with heightened alcohol self-administration in adulthood (28).

Another ontogenetic epoch in which drug exposure is associated with increased SUD vulnerability is the prenatal window. Prenatal alcohol exposure (PAE) is associated with later increased avidity for alcohol and higher probability of developing an alcohol use disorder (AUD), though it is difficult to tease apart exposure itself from factors that drive the maternal consumption and may carry a genetic component. Preclinical models have

shown, however, that when controlling for maternal history, PAE has long-lasting effects on the immune system; for example by altering the expression of genes in the TLR, Nf-kB, and IL-6 immune signaling pathways (29). PAE affects between 1–10% of pregnancies and results in a host of cognitive and emotional deficits that persist across the lifespan (30). Due to the prevalence of PAE, it is of crucial importance to use preclinical models to dissect the interactions PAE may have with other developmental and neurodegenerative disorders that also have neuroimmune components. For instance, innate immune dysfunction has been implicated in the progression and severity of Alzheimer's Disease (9, 31), and studies such as that presented by Walter and colleagues in this issue (32) are necessary to examine whether a history of PAE may engender an immune vulnerability that can contribute to Alzheimer's Disease progression. It is also possible that alterations in immune response during the prenatal stage primes the subsequent motivational response to drugs. In an intriguing study, Borçoi, et al. (33) found enhanced amphetamine-induced behavioral sensitization and conditioned place preference in mice that had been exposed to poly I:C in utero.

Another aspect of the drug-immune system interaction that requires careful consideration is the implied chronic nature of drug exposure. For example, an acute exposure to ethanol in naïve adult rats resulted in suppressed levels of IL-1β and TNFα and escalated levels of brain IL-6, during the early phase of the ethanol intoxication. This was followed by increased expression of IL-1β and TNFα as blood ethanol concentrations receded (34, 35). The early inhibition of IL-1β and TNFα may relate to acute ethanol stimulating the release of the anti-inflammatory cytokine IL-10, shortly after the induction of ethanol intoxication (36). It has recently been shown that this cascade is dependent on escalated levels of corticosterone (cortisol in humans; CORT) driving the brain IL-6 response (37). However, chronic use of alcohol in humans and in preclinical models results in higher baseline CORT levels and a suppressed CORT response in response to stress challenge (38, 39). Subtle changes in CORT may manifest early in the development of the substance disorder, presenting a potential mechanism by which neuroimmune function in SUDs may be influenced by repeated and chronic drug exposure. Examples of how chronic drug exposure affects immune responses can also be drawn from studies that employed drugs other than ethanol. Rats given chronic cocaine (10 mg/kg i.p, twice a day for 7 days) exhibited elevated levels of corticosterone 2h after cessation of cocaine, an effect that was associated with reduced activity of the immune system after a challenge with concanavalin (40).

The previous studies suggest that as the nature of exposure to drugs becomes chronic, immune and stress responsivity adapts as well. This adaptation, however, is highly dependent on the schedule of drug delivery. A study reported that ethanol kept inducing a significant increase in central IL-6 gene expression when administered daily, whereas a reduction was found when the drug was administered every other day (41). Gano et al., in this issue (42), explores these topics by assessing ethanol drinking in male C57BL/6J mice that were either naïve to ethanol or rendered ethanol-dependent using a vapor inhalation model. The administration of poly I:C resulted in escalated voluntary drinking strongest in dependent mice and enhanced stress-induced ethanol self-administration intake. Humans

exhibit a complex pattern of consumption, which makes habituation/sensitization studies using rodent models especially important.

Contextual variables require examination as well. For example, the context in which cocaine was previously administered can evoke craving and precipitate relapse upon re-exposure to conditioned cues (43). There is an accumulation of data implicating dopamine in these effects, yet it has been shown that the immune response to drugs can be subject to classical conditioning, which may have a role to play as well. Lysle and colleagues have shown that a context associated with heroin exposure acted as a conditioned stimulus to suppress the peripheral pro-inflammatory response to an LPS challenge, and that IL-1β signaling in brain limbic circuitry was instrumental in this effect (44, 45). Similarly, Deak et al. revealed that olfactory and interoceptive cues previously paired with ethanol exposure can enhance the brain IL-6 response to a dose of ethanol that on its own does not elicit cytokine change (46, 47). Moreover, adolescent males acquire this type of learning faster than do adults. In this issue, Mondello and co-authors (48) show that this immune conditioning was associated with classical conditioning of the HPA axis as evinced by enhanced CORT levels in males re-exposed to a scent cue associated with ethanol than their explicitly cue-unpaired counterparts.

Section 2. Mechanistic studies on cellular, molecular, and behavioral mechanisms by which alcohol or other drugs influence neuroinflammatory processes, and how they pertain to substance use disorders.

TLRs rank among the most studied receptors that react to drug exposure, by secreting proteins (e.g., cytokines and chemokines) that affect immune function (3). As an example, mice exposed to methamphetamine twice a day (10 mg/kg/d) for seven days exhibited upregulation of the TLR4 and associated signaling pathway, including the secretion of proinflammatory cytokines (49). Another intriguing study suggested that these effects of methamphetamine can compromise the ability of the immune system to counter infections. Specifically, microglia-like cells treated with methamphetamine exhibited reduced production of cytokine after a challenge with LPS (50).

Early work by Guerri's group (51) showed that ethanol administration was, much akin to other drugs, associated with activation of TLR4 receptors in glial cells, ultimately leading to IL-1R production. Likewise, it has been shown that morphine (52) and other opioids (53) bind to TLR4. This receptor is also modulated by cocaine (54) and is involved in the motivational effects of this psychostimulant (55). The latter study reported that mice exposed to stress exhibited increased susceptibility to cocaine-induced conditioned place preference and to ethanol self-administration. This phenomenon did not occur in mice lacking the TLR4 gene (55). Another example of alcohol's ability to induce inflammation can be found in the study by Niedzwiedz-Massey et al., found in this special issue, in which male and female mice fed with an alcohol-containing diet for a month exhibited heightened expression of the pro-inflammatory molecules IL-1β, TNF-α, CCL2, and COX2 (56).

Subsequent work (57) by Guerri's group indicated that the loss of function of TLR4 inhibited neuroinflammatory responses by astrocytes. Perhaps more importantly, this study showed that ethanol-induced activation of TLR4 was ultimately associated with caspase-3 activity, a protein that has a key role in the induction of apoptosis. Cell-culture studies or studies in which ethanol is administered by the experimenter are good proof-of-concept studies, with many of these effects also occurring after drug self-administration. A paper led by Dr. Pascual (58) reported that alcohol-induced activation of TLR4 occurs after voluntary ethanol self-administration and that this event is associated with significant long-term health consequences. In this study (58), wild type mice or mice lacking the genes coding for TLR4 were given free choice of 10% alcohol or water for 5 months. The mice were tested after 2 weeks of withdrawal. The wild type, but not their peers lacking the genes coding for TLR4, exhibited altered object memory recognition, anxiety-like behavior and heightened activation of astrocytes and microglia. This seminal study cements the notion that alcohol-induced neuroinflammation is a key mediator in the long-term and insidious memory and anxiety-related consequences of chronic alcohol exposure. It is notable that suppression of TLR4 also protects from the effects instantiated by intermittent alcohol exposure during adolescence (59).

At a more general level, an exciting avenue of research is the development of molecules that can inhibit the drug-induced activation of TLR4s. One of those, the bioactive lipid oleoylethanolamide, seems to act by protecting the intestinal barrier [reviewed in (60)]. In the current special issue Perez-Reytor & Karahanian review the "microbiota-gut-brain axis" concept, wherein they postulate that the intestinal microbiota can release factors that affect neuroinflammatory status of the brain (61). The authors highlight how this communication can take place, for instance by stimulation of the vagus nerve, and remark the value of dietary treatments high in fiber content. According to the authors, such a dietary regime would promote the production of short-chain fatty acids that protect the integrity of the intestine and prevent the neuroinflammatory signaling.

Another important member of the TLR family is the toll-like receptor 3, which identifies double-stranded RNA in endosomes, and subsequently promotes a concerted antiviral action, which includes the secretion of proinflammatory cytokines. In the present special issue, Gano et al. (42) probed the role of that receptor in alcohol drinking in mice that were relatively naïve to alcohol or in counterparts that had been chronically exposed to ethanol via vapor exposure. Unlike the gene deletion used in Guerri's studies, Gano and coworkers (42) used a pharmacological approach, administering the viral mimetic Poly I:C to the mice. The results indicated a modest, albeit significant, effect of Poly I:C in naïve animals. The promoting effect of the viral mimetic on alcohol intake, however, was stronger and long lasting in the mice that had been chronically exposed to ethanol.

Section 3. Genetic studies implicating inflammatory processes in the development or expression of SUDs.

Several studies have analyzed genetic mechanisms implicating inflammatory processes in the expression of SUDs. Most of these focused on AUD and on liver conditions secondary to

alcohol use, such as liver disease induced by alcohol use. These studies provided conclusive evidence for a role of genetic variants in the disease severity or prognosis (62). Likewise, it has been shown that only 10–20% of smokers develop chronic obstructive pulmonary disease, a condition featuring chronic inflammatory response in the lung that are associated with severe changes in lung physiology. Those smokers susceptible to develop chronic obstructive pulmonary disease, however, exhibited genetic variants in several genes, such as IL6R and TNF. Notably, some of those genes (e.g., CHRNA5/3) also provide susceptibility for nicotine use disorders [reviewed in (63)]

Some studies have focused on other inflammatory processes associated with the development of SUDs. A recent study (64) indicated that adult children of a parent diagnosed with AUD, who were currently engaged in hazardous ethanol use, had higher plasma C-reactive protein (CRP) as well as reduced methylation of CRP, when compared to adult children of a parent diagnosed with AUD who were not currently engaged in hazardous drinking. CRP is a well-known biomarker of inflammation, specifically a protein secreted by the liver after cytokine activity, and adult children of a parent diagnosed with AUD are a population at risk for the development of AUD. Thus, the study suggests that activation of inflammation pathways could be one of the mechanisms leading to the development of AUD in this genetically at-risk population.

A genetic association between AUD and immune function has also been provided by traditional genome-wide studies (65). Some of these have presented evidence that neuroinflammatory processes are a common underlying mechanism in the etiology or pathogenesis of SUDs and or psychiatric diseases commonly comorbid with SUDs, such as depression or anxiety (66). Moreover, an overlap in genetic risk factors also seems to exist concerning the role of neuroinflammation between AUDs and neurodegenerative disorders (67). An intriguing study (68) indicated that adult children of a parent diagnosed with an AUD, who we previously indicated as more prone to ethanol-induced inflammation, endorsed more depressive mood than controls. This suggests a complex relationship between the development of SUDs, the expression of associated comorbidities, and inflammatory processes. We will expand on these issues in the next section.

Moreover, as we already anticipated it has been shown that one of the most severe consequences of AUD, namely the development of liver disease, is dependent upon genes associated with inflammation. More in detail, specific polymorphisms in the Cluster of Differentiation 14 (CD14) were associated, in Indian (69) or Greek (70) patients, with greater susceptibility to liver disease induced by alcohol use. CD14 is a pattern-recognition receptor, associated with inflammatory responses via cytokine production. Direct support for a link between cytokine gene variations and proclivity to AUD, independently of alcohol-induced liver disease, has been provided by Marcos, et al. (71). These researchers found that polymorphisms of IL-10 were associated with a diagnosis of AUD but not with greater risk of alcohol-induced liver disease. Similarly, it has been shown that Spanish men with an AUD diagnosis exhibit polymorphism in the interleukin-1 receptor antagonist gene (IL1RN) (72). Future studies should address whether these polymorphisms are associated with a loss-of-function or gain-of-function, pertinent to understand its potential implication in AUD.

It is also worth mentioning studies that, employing microarrays or RNA-seq, have implicated inflammatory processes in the development or expression of SUDs. One of those (73) reported that an LPS challenge induced similar transcriptional changes in the PFC as those induced by chronic exposure to ethanol. Another study assessed global gene expression in the central amygdala, a key area for the maintenance or reinstatement of alcohol drinking, after chronic intermittent ethanol vapor exposure. The procedure resulted in several differentially expressed genes, some of those related to the regulation of innate immune responses.

Section 4. Studies of SUDs and associated co-morbidities that point toward neuroinflammatory processes as a common underlying mechanism.

Several studies have provided support for neuroinflammatory processes as a common underlying mechanism between SUDs and depression, anxiety, or other psychiatric conditions. For instance, Wilhelm, et al. (74) showed, in women, a positive association between self-report measures of depression, anxiety, memory complaints and a peripheral marker of inflammation, the tissue inhibitor of metalloproteinases-1. Likewise, a large (n = 456,748) population-based study conducted in the UK (75) showed that the self-report of depressive-like symptoms was linked to deficient cognitive performance. Some components of the latter (i.e, slower reaction times) were in turn associated with self-reported inflammatory conditions such as rheumatoid arthritis or systemic lupus erythematosus. It is notable that substantial comorbidity has been shown between rheumatoid arthritis and lifetime prevalence of SUDs (76).

At a theoretical level, several associations can be postulated between SUDs and anxiety or depression, and some of those have been supported by research. Ostensibly, those with higher depression or anxiety are more likely to engage in substance use to reduce these negative emotional states (77). Some sub-populations, such as those exhibiting higher levels of negative urgency (the tendency to act impulsively while experiencing aversive stimulation) or lower levels of stress tolerance could be at even higher levels of risk (78, 79). Yet there are other potential links between these conditions. Chronic exposure to psychoactive drugs (49, 50) or chronic exposure to negative emotional states are known to elevate inflammation (80), and this is in turn is a risk factor for the development of the other condition.

The dysregulation of neuroimmune signaling induced by ethanol and other drugs also increases neurotoxicity, which likely contribute to cognitive impairments, further promoting drug use or facilitating other conditions. A study showed, for instance, that chronic alcohol exposure was associated with significant increases in anxiety-related behaviors, an effect associated with increased IL-1β signaling. Treatment with hydrolysates derived from *Theragra chalcogramma* skin inhibited both effects (81). Similarly, Villas Boas, et al. (82) submitted Wistar rats to 15 days of ethanol self-administration. This was associated with enhanced production of IL-6, IL-8 and TNF-α in the amygdala, and IFN-γ, IL-1β, IL-6, and TNF-α in the hypothalamus. As in the previous study, the ethanol-induced upregulation of neuroimmune genes was associated with signs of anxiety in several behavioral tests; yet

these effects subsided by the administration of the antioxidant α-tocopherol (21). Several other studies have shown that drug-induced withdrawal can perpetuate drug use by inducing a state of marked neuroinflammation and that treatments that reduce those states may serve to break this pernicious cycle (83).

Section 5. Intersectional studies on poly drug use and potential additive/ synergistic effects on neuroinflammatory processes.

Alcohol and nicotine are frequently used together, and it has been reported that up to 80% of people diagnosed with AUD also use nicotine (84). There has been some hesitancy in the clinical field in treating nicotine use disorder at the same time as alcohol, yet evidence indicates that those who consume alcohol tend to use more nicotine, putting them at increased health risk (85). While rates of tobacco consumption in some countries have been trending downward, they remain high within populations that use alcohol, and are of particular concern for adolescents as electronic cigarette use is increasing rapidly within this age group that is vulnerable to long-term alcohol effects (86).

Preclinical models that examine dual dependency are somewhat rare, and even fewer are focused on neuroimmune targets, though nicotine and alcohol are known to affect neuroimmune signaling. One of the studies published in this special issue advances our knowledge in this regard. Cruz et al. (87) exposed Wistar rats to ethanol self-administration for 70 days, punctuated or not with nicotine exposure or nicotine withdrawal, before conducting measurement of hormonal and inflammatory markers. Ethanol reduced circulating levels of the proinflammatory IL-1β cytokine, whereas circulating leptin levels were not affected by either drug.

It has been shown that nicotine exposure, especially in adolescence (88), can drive increases in drinking behavior (89, 90). Preclinical research on this topic has focused on nicotinic acetylcholine receptors that are activated by nicotine and go on to affect dopamine signaling in brain reward areas such as the VTA and nucleus accumbens (90, 91). However, studies that investigate overlapping immune mechanisms may be warranted as well, given that preclinical studies have indicated that therapeutic effects of naltrexone on drinking were less efficacious when combined with nicotine (92, 93).

Genetic factors that underlie SUD phenotypes can be similar across different SUDs. In one study, ingenuity pathway analysis was used to locate similar immune gene activation across publications reporting on ethanol, nicotine, and opioid use disorders (94). This is not surprising, as opioid use is associated strongly with past nicotine and alcohol use (95). Concurrent use is also not unusual. For instance, a recent study showed that 48% of women who reported using opioids during pregnancy were also using alcohol (96). Yet, models that encompass both drugs are somewhat sparse. A large proportion of the literature investigates opioids as a therapy for AUD with only a secondary consideration for opioid use disorder; for example, one study has shown that using the opioid antagonist naloxone decreased drinking yet increased sensitivity to subsequent opioid exposure (97).

Section 6. Pharmacological studies targeting inflammatory-signaling pathways and their potential use as therapeutics in SUDs.

Given the emergent role of the immune system in the etiology of AUD, using neuroimmune therapy in combination with other approved therapeutics may increase efficacy (2). One such proposed co-pharmacotherapy candidate tool is pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist. PPAR receptors are found peripherally but also within the brain reward systems (98). PPAR agonists counter inflammation by blocking the actions of the Nf-κB pathway and decreasing the ensuant release of pro-inflammatory cytokines (e.g., IL-1β and TNFα)(99, 100). Research has examined Nf-κB as a transcription factor that is induced by ethanol via the activation of TLRs and results in a positive feedback loop that increases the expression of pro-inflammatory cytokines and chemokines, thereby driving neuroinflammation and neurotoxicity in the brain (101, 102). Moreover, it has been shown that polymorphisms in the Nf-κB gene are associated with AUD (103). However, Nf-κB is also induced by the activation of opioid receptors and can in turn upregulate them and or opioid peptides (104), proving to be a potentially ubiquitous driver of inflammation across more drug types than just ethanol. Prior work has shown that PPAR alpha agonists such as fenofibrate can decrease ethanol drinking and seeking behaviors in rats (105). Recently, rat studies have shown that using the PPAR gamma agonist pioglitazone alone can also curb drinking behavior, and further potentiate the ameliorating effects of naltrexone (106).

Another interesting aspect of the recent focus on immunotherapy as an approach to SUD is the realization that a patient's immune history may be varied due to environmental factors across the lifespan as well as cumulative neuroinflammatory damage incurred across drug exposure. This provides an opportunity for identifying potential biomarkers to determine pharmacological treatment approach, taking SUD pharmacotherapy into the realm of personalized medicine. This approach has already gained traction in the depression field, where pro-inflammatory mediators such as IL-6 and IL-1 can be assessed in plasma to determine best approaches to pharmacotherapeutic treatment (107). Just as in the treatment of depression, treatment of SUDs can sometimes be marred by individual variability. For instance, Ibudilast, a phosphodiesterase inhibitor repurposed as an AUD therapeutic that is known to have anti-inflammatory properties (i.e. decreased expression of pro-inflammatory cytokines) (108), has shown efficacy in decreasing drinking via neuroimmune mechanisms (109). Ibudilast ameliorates withdrawal symptoms in patients undergoing heroin use and other SUDs (110), yet its utility is still under investigation. While promising in some patients, Ibudilast is not an effective therapy for all. In the current special issue, the article by Grodin et al. (111) analyzed if response to Ibudilast was dependent on the level of inflammation. Specifically, the authors divided patients diagnosed with AUD, and treated with placebo or Ibudilast, into high and low inflammation groups, as a function of the levels of CRP in plasma. Interestingly the number of drinks per drinking day was similar among high and low groups after placebo treatment. On the other hand, those treated with Ibudilast and exhibiting high levels of CRP had significantly fewer number of drinks per occasion than those similarly treated with Ibudilast but classified in the low CRP group. This

suggests that efforts should be made to match AUD patients and available treatments and that inflammation markers can help in this process.

Considerable interest has been given, in turn, to minocycline, a tetracycline antibiotic featuring anti-inflammatory activity that appears to reflect inhibition of microglial function, at least in part. It has been shown, for instance, that minocycline reversed motor alterations, pyramidal neuronal loss in the motor cortex loss and microglia proliferation, in rats given ethanol throughout adolescence and adulthood and then submitted to focal ischemia induction (112). Another study (113) found that greater cocaine self-administration after stress exposure was associated with reactive microglia and increased TNF-α mRNA and protein expression in nucleus accumbens core. Intriguingly, minocycline treatment inhibited the promoting effects of restraint stress upon cocaine administration (113).

As we had already indicated, there are suggestions of gut-brain connections, with drug-induced dysregulations of the microbiota being pinpointed as the first station in which inflammation may occur. An intriguing series of studies indicated that the administration of either the antioxidant N-acetylcysteine or the anti-inflammatory aspirin reduced ethanol intake and inhibited relapse drinking, as assessed in an alcohol-preferring strain of rats (83). A subsequent study showed that a similar result could be achieved by treatment with oral administration of Lactobacillus-rhamnosus-GG, a pro-biotic that helps restore the healthy composition of the gut bacteria (114). Regarding drugs other than ethanol, it has been shown (115) that an antibiotic cocktail that knocked down gut bacteria enhanced sensitivity to the rewarding properties of cocaine in mice. Alterations in the microbiota, leading to peripheral or central inflammation, could also derive from nutritional alterations. It is possible that immune co-therapy with more traditional therapeutics may not need to focus on neuroinflammation per se but might instead use a whole-body approach starting with the gut. Trials are currently underway to explore this by performing fecal microbiota transplants that seek to normalize the balance of gut bacteria in individuals with a diagnosis of AUD and cirrhosis, with results indicating that restoring gut balance has anti-inflammatory benefits and reductions in alcohol craving (116).

Table 1 summarizes representative studies of this section. The table describes the different pharmacological strategies proposed, the main goal achieved, and if they were applied at clinical or pre-clinical level.

Discussion and concluding remarks

The over-arching goal of this review and special issue was to provide a brief, accessible, and example-driven framework for understanding the interactions between neuroinflammatory processes and drug use, and their neuropathological consequences. Key findings presented within this review and special issue underscore the importance of demographic variables (age, sex) and other physiological parameters (stress reactivity, microbiome, nutritional factors) as moderators of neuroinflammatory processes, and ultimately, the neuropathological consequences of alcohol and drug use. Inflammatory signaling pathways appear to lie both upstream and downstream of alcohol and drug use, creating a compelling impression that they are uniquely situated to perpetuate drug

use and its adverse health consequences. By promoting coherence between preclinical and clinical research studies, it may be possible to accelerate the development of novel pharmacotherapeutics that can simultaneously curtail problematic drug use and prevent the emergence of its longer-term neuropathological consequences.

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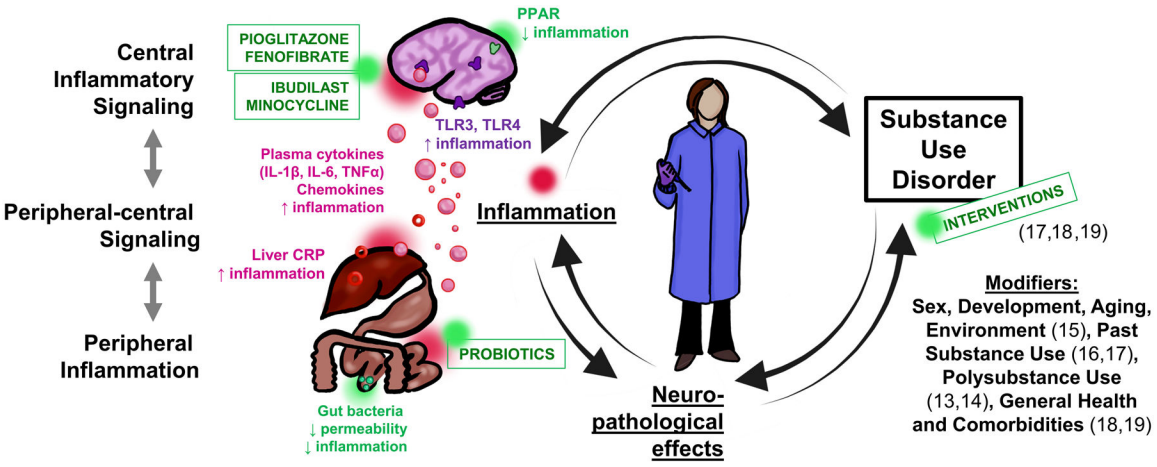

Figure 1:

The special issue in which this review is enclosed examines bidirectional interactions between neuroinflammation and Substance Use Disorders (SUDs). The studies herein highlight the role of environmental factors and subject characteristics such as sex, polysubstance use, or ontogenetic epoch, in determining the outcomes of these interactions, and point toward immune therapy as an excellent candidate for personalized treatment of SUDs. Parametric preclinical studies such as Cruz et al. (87) and Walter et al. (32) highlight how the central and peripheral markers of inflammation that are associated with SUDs may be influenced by polysubstance use and substance history (i.e. prenatal alcohol exposure), respectively. Mondello and co-authors (48) highlight the role of environmental factors by examining the classical conditioning of corticosterone by ethanol-associated cues and their effects on inflammation. Gano et al.'s article (42) uses a chronic ethanol exposure model to show that immune activation exacerbates voluntary ethanol consumption in an animal of AUD, whereas Niedzwiedz-Massey and co-authors (56) utilize a novel model of binge drinking to demonstrate that PPARgamma agonist pioglitazone can block the inflammatory effects of ethanol. Together, findings such as these expand our understanding of the mechanisms by which the immune system contributes to SUDs and expands our arsenal for novel therapeutics. For example, in Grodin and co-authors' article, it is shown that inflammation as indexed by baseline C-reactive protein levels predicts whether patients receiving treatment for AUD are responsive to Ibudilast pharmacotherapy (111). Understanding the contributions of whole-body inflammation also allows for interesting new approaches such as that suggested by Pérez-Reytor and Karahanian in treating peripheral inflammation in the gut to curb immune-driven AUD (61).

Table 1:

Summary of representative studies from Section 6.

Reference	Proposed treatment	Subjects/participants	Main outcome
Stopponi S et al. (106)	Pioglitazone (PPARg agonist)	Marchigian Sardinian rats	Pioglitazone reduced alcohol drinking, more so when combined with naltrexone
Karahanian et al. (105)	Fenofibrate (PPAR aplha agonist)	UChB drinker male rats	Fenofibrate reduced ethanol consumption and increased ethanol-induced blood acetaldehyde levels after alcohol deprivation.
Cooper et al. (110)	Ibudilast (phosphodiesterase inhibitor exhibiting anti-inflammatory properties)	Non-treatment-seeking volunteers with a diagnosis of heroin use disorder	Volunteers given ibudilast reported lower withdrawal symptoms during detoxification
Grodin et al. (111)	Ibudilast	Patients diagnosed with Alcohol use disorder	Fewer drinks per occasion in ibudilast-treated participants that had exhibited high plasma C-reactive protein
Oliveira et al. (112)	Minocycline (antibiotic featuring anti-inflammatory activity via inhibition of microglia)	Female Wistar rats	Reversion of motor impairments, microglial activation and neural death in ischemic rats given chronic ethanol exposure.
Avalos et al. (113)	Minocycline	Male Wistar rats	Minocycline inhibited the promoting effects of stress on extracellular glutamate and cocaine self-administration.
Israel et al. (83)	N-acetylcysteine (antioxidant), aspirin (anti-inflammatory) or both drugs co-administered	Male Wistar rats	Either treatment reduced alcohol drinking, more so when combined; aspirin reversed alterations in cortical glutamate transporter GLT-1
Ezquer et al. (114)	Lactobacillus rhamnosus Gorbach-Goldin (LGG)	Male Wistar rats	LGG treatment inhibited ethanol intake by 66–80%, and by 90% when combined with N-acetylcysteine+ aspirin.
Kiraly et al. (115)	Cocktail of antibiotics inducing a reduction of gut bacteria	Male Mice	Enhanced sensitivity to cocaine-induced reward and behavioral sensitization
Bajaj et al. (116)	Fecal microbiota transplant from a donor enriched in Lachnospiraceae and Ruminococcaceae	Patients with AUD-related cirrhosis	Greater microbial diversity and reduced alcohol craving, as a function of the treatment.