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Chemokines, Cytokines and Substance Use Disorders

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Abstract

Efficacious pharmacotherapies for the treatment of substance use disorders need to be expanded and improved. Non-neuronal cells, particularly astrocytes and microglia, have emerged as therapeutic targets for the development of pharmacotherapies to treat dependence and relapse that accompanies chronic drug use. Cytokines and chemokines are neuroimmune factors expressed in neurons, astrocytes, and microglia that demonstrate promising clinical utility as therapeutic targets for substance use disorders. In this review, we describe a role for cytokines and chemokines in the rewarding and reinforcing effects of alcohol, opioids, and psychostimulants. We also discuss emerging cytokine- and chemokine-based therapeutic strategies that differ from conventional strategies directed toward transporters and receptors within the dopamine, glutamate, GABA, serotonin, and GABA systems.

Keywords

Cytokines; chemokines; alcohol; opioids; cocaine; methamphetamine

1. Introduction

Substance use disorders are a widespread global health problem. In 2018, an estimated 269 million individuals worldwide abused drugs, representing 5.3 percent of the global

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Contributors

Authors Olivia C. Ahearn and Scott M. Rawls developed the idea of writing a review article directed toward the role of cytokines and chemokines in substance use disorders with a focus on ethanol, opioids, cocaine and methamphetamine. Author Olivia C. Ahearn prepared an initial draft of the manuscript. Authors Scott M. Rawls and Mia N. Watson reviewed and edited the manuscript and added additional sections to the manuscript. Author Scott M. Rawls prepared the final draft of the manuscript, which was subsequently circulated to all authors for their comments, critiques and suggestions. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

population (World Drug Report 2020). In the United States, approximately 20.3 million individuals aged 12 or older in 2018 had a substance use disorder attributed to alcohol or illicit drugs (Lipari and Park-Lee, 2019).

The development of a substance use disorder involves dysregulation of neuronal circuits responsible for motivated behavior (Koob and Volkow, 2010). The role of dopamine and glutamate systems in mediating the effects of drugs of abuse is well established, but pharmacotherapies directly targeting these and other classical neurotransmitter systems has been largely unsuccessful in the treatment of substance use disorders, especially for opioids and psychostimulants. Thus, to develop effective pharmacotherapies, it is important to identify new endogenous targets, such as chemokine and cytokine systems, that underlie substance use disorders (Rogers, 2020; Paulus and Stewart, 2020; Bachtell et al., 2017; Cui et al., 2014; Crews et al., 2011).

Cytokines and chemokines are important components of the CNS neuroimmune system and contribute to neuroinflammation, neuronal activity, neuron-glia communication, neuroendocrine interactions, neurogenesis, and CNS development (Bachtell et al., 2017; Bachtell et al., 2015; Boulanger, 2009). Chemokines are chemoattractant cytokines that comprise a family of low molecular weight proteins and play a role in both the immune system and the central nervous system (CNS) (Parsadaniantz et al., 2015; Rostène et al., 2007). They are categorized into four subfamilies based on the position of the cysteine residues within the amino-terminal region: C-, CC- CXC-, and CX_3C-chemokines, and mediate their effects through seven-transmembrane G protein-coupled receptors (GPCRs) designated CR1, CCR1–11, CXCR1–5, or CX_3CR1, respectively (Murphy, 2002; Murphy, 2000). Several chemokines, including CCL2, CCL3, CCL5, CXCL1, CXCL8, CXCL12, and CX3CL1 are secreted in the brain (note that the “L” designation denotes ligand) (Bajetto et al., 2001; Tashiro et al., 1993). The chemokine receptors CCR1, CCR4, CCR5, CCR9, CXCR2, CXCR4, and CX_3CR1 are also expressed in different brain regions, including the hippocampus, cerebral cortex, amygdala, thalamus, and basal ganglia (Gabuzda et al., 1998; Meucci et al., 1998; Bajetto et al., 1999). These GPCRs can signal through $G\alpha_{i/o}$ proteins through which they inhibit adenylate cyclase and decrease protein kinase A activity (Zheng et al., 1999), as well as through Gq proteins through which they can increase intracellular Ca^{2+} levels and protein kinase C via the phospholipase C pathway (Cali and Bezzi, 2010; Khan et al., 2004; Meucci et al., 1998).

The neuromodulatory properties of cytokines and chemokines have been associated with the development of substance use disorders and provide a different framework for understanding functional and behavioral changes contributing to drug addiction (Cui et al., 2014). This review describes recent advances in the role of cytokines and chemokines in alcohol, opioid and psychostimulant use disorders, including a discussion of potential therapeutic strategies targeting these systems.

2. Alcohol

2.1 Background

In 2018, 139.8 million individuals aged 12 or older in the United States were alcohol users, 67.1 million were binge drinkers, and 16.6 million were heavy drinkers the previous month (Lipari and Park-Lee, 2019). Furthermore, an estimated 401,000 adolescents, 3.4 million young adults, and 11.0 million adults had an alcohol use disorder (AUD) (Lipari and Park-Lee, 2019).

2.2 Pathophysiology of Alcohol Liver Disease

Individuals with alcohol use disorder (AUD), particularly those with alcohol liver disease (ALD), frequently experience systemic endotoxemia attributable to increased gut permeability, reactive oxygen species (ROS) generation from ethanol metabolism, and impaired hepatic clearance function (McClain et al., 1997). ROS activate toll-like receptors (TLRs), specifically TLR4, and the associated plasma membrane protein CD14 (Qin et al., 2008). This signal transduction cascade activates various transcription factors, including nuclear Factor kappa-light-chain-enhancer (NF-κB) in liver Kupffer cells, which play a critical role in cytokine gene activation (McClain et al., 1997). Notably, tumor necrosis factor alpha (TNFα) is produced, which enhances the immune response by inducing fever, activating neutrophils and macrophages, and stimulating macrophages to produce cytokines (McClain et al., 1997). These functions can then further increase intestinal permeability, endotoxemia, and ROS generation (McClain et al., 1999).

Additional cytokines that modulate systemic responses to ALD include the: (1) proinflammatory cytokine interleukin-1 (IL-1), which induces fever and stimulates growth and differentiation of immune cells; (2) anti-inflammatory cytokine interleukin 10 (IL-10), which reduces production of proinflammatory cytokines such as TNFα; (3) chemokine interleukin-8 (IL-8), which promotes neutrophil infiltration; (4) hepatic acute-phase cytokine interleukin-6 (IL-6), which stimulates inflammatory mediators and promotes maturation of antibody-secreting cells; and (5) monocyte chemoattractant protein-1 (MCP-1/CCL2), which promotes monocyte infiltration (McClain et al., 1997).

2.3 Cytokine Signaling Dysregulation in ALD

Several studies using animal models and postmortem human alcoholic brains indicate a role for innate immunity in alcohol dependence and addiction. Many differentially expressed genes found in animals chronically treated with alcohol or post-mortem brains from alcoholics contribute to the TLR4 signaling pathway (Blednov et al., 2011). Ethanol-induced microglial activation, production of inflammatory mediators, and apoptosis are prevented in microglia lacking TLR4 *in vitro* and microglia of TLR4-deficient mice (Fernandez-Lizarbe et al., 2009; Alfonso-Loeches et al., 2010). These studies demonstrate an important role for the TLR4 response in ethanol-mediated activation of NF-κB and subsequent transcription of proinflammatory immune genes.

Brain gene expression analyses in mice further identified NF-κB, in addition to many innate immune genes, to be differentially expressed in high and low alcohol consuming rodent lines

(Mulligan et al., 2006). Increased levels of innate immune gene mRNA related to NF-κB were also shown in a study of postmortem human alcoholic brain samples (Liu et al., 2006). Studies on human alcoholics found associations between NF-κB and TNFα polymorphisms and alcohol abuse (Edenberg et al., 2008; Gonzalez et al., 2004; Kebir et al., 2011). Additional polymorphisms of genes encoding proinflammatory cytokines interleukin-1 beta (IL-1β) and IL-1, as well as anti-inflammatory cytokine IL-10, have been associated with a risk for developing alcohol use disorder (Marcos et al., 2008; Saiz et al., 2009; Pastor et al., 2005). These studies suggest that variations in NF-κB gene and innate immune gene expression influence alcoholism susceptibility.

Other studies found that ethanol treatment increases NF-κB-DNA binding in rat brain *in vivo* and brain slice cultures *in vitro* (Crews et al., 2006; Zou and Crews, 2006). Zou and Crews (2010) reported that chronic ethanol administration increases NF-κB-DNA binding and subsequent proinflammatory gene expression in rat brain slice cultures, including TNFα, IL-1β, and MCP-1. Furthermore, in the same study, NF-κB blockade and TNFα-neutralizing antibody reduced ethanol induction of proinflammatory genes. Thus, ethanol is thought to increase NF-κB-DNA binding and subsequent proinflammatory gene expression, resulting in neurodegeneration and altered neurotransmission (Zou and Crews, 2010).

2.4 Ethanol-induced Neuroinflammation and Cytokine Signaling in the Absence of ALD

Ethanol exposure has been shown to increase liver, serum, and brain cytokine production (TNFα, MCP-1, and IL-1β) and to substantially increase LPS-induced cytokine responses in mice (Qin et al., 2008). Postmortem human alcoholic brains also revealed increased expression of proinflammatory cytokines MCP-1 (He and Crews, 2008) and IL-1β (Crews, 2012). The coordination of these responses may be explained by liver Kupffer and blood monocyte cell cytokine secretion, resulting in cytokine transport across the blood-brain barrier and induction of brain proinflammatory cytokine production (Qin et al., 2008).

Brain proinflammatory cytokines remain elevated after liver and serum cytokines return to baseline levels. This finding is also accompanied by a prolonged reduction in brain anti-inflammatory cytokine IL-10 (Qin et al., 2008). Long-lasting brain induction of proinflammatory cytokines and reduction of IL-10 may contribute to central nervous system pathologies including alcoholic dementia (Qin et al., 2008). This study also found that neurogenesis was decreased in ethanol-LPS treated animals as evident from reduced proliferation of hippocampal neuroprogenitors and reduced differentiation of newly born neurons. Ethanol-induced proinflammatory cytokine cascades may therefore inhibit neurogenesis and influence the development of neurodegenerative diseases (Qin et al., 2008).

Interestingly, alcohol consumption is limited when innate immune gene expression is interrupted (Blednov et al., 2005, 2012). Blednov et al. (2005) demonstrated that deletion of CCR2, MCP-1/CCL2 (females) or CCL3 genes in mice reduced alcohol consumption and preference. These data demonstrate that disruption of cytokine cascades at the ligand or receptor level disrupts the motivational effects of alcohol, which may be explained by a dysregulated chemokine network that facilitates an aversion to alcohol. Moreover, increased

serum cytokine levels and inflammatory endotoxins are positively correlated with alcohol craving and may increase alcohol consumption (Leclercq et al., 2012; Leclercq et al., 2014).

2.5 The Role of Inflammatory Responses in the Liver

Given that the liver is essential in modulating acute inflammation, stress, or trauma and a major producer and scavenger of cytokines, it is not surprising that cytokine dysregulation largely contributes to the systemic manifestations of ALD as well as the liver injury and repair process (McClain et al. 1999; McClain et al., 1997). ALD patients can present systemically with fever, neutrophilia, and anorexia with muscle wasting (McClain et al., 1999). Clinical studies have shown high levels of IL-1, IL-6, IL-8, TNF, and MCP-1 in patients with ALD (McClain et al., 1997). IL-8 may play a role in neutrophilia and neutrophil infiltration of liver tissue in ALD, and MCP-1 may induce monocyte infiltration to ensure a sufficient phagocyte supply to fight infection (Sheron et al., 1993; McClain et al., 1997). Increased TNF may be attributed to the decreased production of the anti-inflammatory cytokine IL-10 by monocytes (McClain et al., 1997). Cytokines induce the liver to produce acute-phase proteins, which is accompanied by a marked decrease in albumin production; disrupted protein metabolism in muscle tissue presents as muscle wasting as component amino acids are required for acute-phase protein synthesis. These metabolic processes reflect a shift to host innate defenses (McClain et al., 1997). Interestingly, these complications are remarkably similar to the biologic actions of TNF, which is suggested to play an etiologic role in liver injury (McClain and Cohen, 1989).

2.6 Cytokine-based Therapeutic Approaches for ALD

Despite extensive and life-threatening complications associated with ALD, there are no FDA-approved therapies. Recommendations include smoking cessation and weight loss for obese patients as these risk factors are associated with oxidative stress and may contribute to cytokine production and ALD progression (McClain et al., 2004). Nutritional support is advised for patients suffering from malnutrition, which may decrease gut permeability and bacterial translocation and improve hepatic function (McClain et al., 2004).

Several therapeutics approaches modulating cytokine signaling pathways have been studied (McClain et al., 2004). Specific strategies include: (1) cytokine neutralization with antibodies or soluble receptors; (2) cell-bound receptor neutralization with antibodies; (3) inhibition of cytokine synthesis; (4) administration of anti-inflammatory cytokines (*e.g.* IL-10); and (5) removal or neutralization of proinflammatory cytokine-producing cells (McClain et al., 2004). In fact, the majority of interventions and therapeutics designed to treat ALD target cytokine metabolism (McClain et al., 1999).

Corticosteroids that inhibit proinflammatory cytokine production represent first-line drug therapy for ALD patients (McClain et al., 2004). Animal model data suggest that targeting Kupffer cell function, glut flora, or TNFα all improve outcomes of alcohol-related liver injury (McClain et al., 1997). Pilot studies in ALD patients suggested that a TNFα-soluble receptor and an anti-TNFα antibody were safe and tolerable, but human studies using infliximab (anti-TNFα antibody) and prednisone, as well as etanercept (TNFα-neutralizing molecule), have not demonstrated therapeutic efficacy and were discontinued due to

increased infections (Naveau et al., 2004; Boetticher et al., 2008). The greatest limitations to existing therapeutics are infection and impaired liver regeneration as basal TNFα levels may be essential in the latter process (McClain et al., 2004). Cytokine synthesis inhibitors such as pentoxifylline, a broad phosphodiesterase inhibitor, generated promising results in patients with severe alcoholic hepatitis (AH), particularly in decreasing the risk of developing hepatorenal syndrome (Akriviadis et al., 2000; Arteel et al., 2003; De et al., 2009).

Future directions for anti-cytokine therapy will require effective strategies to reduce cytokine production while preserving therapeutic efficacy and improving safety. As previously mentioned, TNF and IL-6 are critical for liver regeneration, thus complete inhibition of these cytokines in a patient with ALD could inhibit recovery (McClain et al., 1997). While attenuation of Kupffer cell NF-κB activation with proteasome inhibitors may be a therapeutic strategy for liver injury, complete hepatocyte NF-κB inhibition may sensitize the cell to TNFα cytotoxicity (McClain et al., 1999). Furthermore, anti-cytokine therapeutics may benefit one organ system while harm another (McClain et al., 1999).

In summary, there is compelling evidence for the role of dysregulated cytokine metabolism in the systemic manifestations of ALD in both experimental animal models and patients. While anti-cytokine therapy in ALD appears promising, future clinical trials should consider numerous factors, including cytokine toxicity, drug dosing, and targeted drug delivery.

3. Opioids

3.1 Background

Opiates and opioids, which encompass synthetic opioid analgesics, play an essential role in modulating pain and antinociception (Scott, 1969; Al-Hasani and Bruchas, 2011). Approximately 10.3 million individuals aged 12 or older in the United States misused opioids in 2018 (9.9 million prescription pain reliever misusers and 808,000 heroin users), which corresponds to 3.7 percent of the population (Lipari and Park-Lee, 2019). Moreover, an estimated 2.0 million individuals aged 12 or older had an opioid use disorder, representing 0.7 percent of the population (Lipari and Park-Lee, 2019).

3.2 Opioids and Opioid Receptors

Opioid receptors are seven-transmembrane G-protein coupled receptors (GPCRs) that exist in μ-, κ-, and δ-opioid receptor (MOP, KOP, DOP) isoforms (Rogers, 2020). Opioids prescribed for pain management most often act on the MOP and exert an inhibitory effect on neuronal activity to modulate pain behavior and antinociception (Al-Hasani and Bruchas, 2011). Opioids induce analgesia by inhibiting neurons in ascending pain pathways while activating inhibitory neurons in descending pathways (Mansour et al., 1995). Receptors for opioids are expressed on multiple CNS cell types including neurons, astrocytes, and oligodendrocytes. In the context of the immune system, endogenous opioids are produced at sites of inflammation by inflammatory cells and commonly exhibit immunosuppressive activity (Rogers, 2020).

3.3 Cellular Pharmacology

Opioid receptors are primarily coupled to Gi/o signaling, and activation of opioid receptors elicits subsequent dissociation of the Gα and Gβγ subunits that lead to inhibition of adenylate cyclase and reduction of cyclic adenosine monophosphate (cAMP) levels (Pathan and Williams, 2009). These G-protein complexes further activate potassium channels and inhibit calcium channels, thereby hyperpolarizing cells and reducing neuronal excitability (Pathan and Williams, 2012). Additional downstream signals include induction of the mitogen-activated protein kinases and NF-κB signaling pathway via up-stream signaling of protein kinase A, phosphoinositide 3-kinase, or phospholipase C (Al-Hasani and Bruchas, 2011; Rogers, 2020). Following activation of downstream signaling pathways is homologous desensitization, in which the opioid receptor is phosphorylated by G protein-coupled receptor kinases (GRKs), β-arrestin is recruited to promote receptor internalization, and the desensitized receptor is degraded or re-sensitized (Rogers, 2020).

3.4 Heterologous Desensitization

GPCR desensitization may also take place by heterologous desensitization, whereby an activated GPCR desensitizes an unrelated, non-ligated receptor (Rogers, 2020). As opioid and chemokine receptors are both GPCRs, evidence demonstrating their cross-desensitization has been shown in the immune, central, and peripheral nervous systems and shown to be cell- and receptor subtype-specific (Szabo et al., 2002; Zhang et al., 2003; Chen et al., 2004; Zhang et al., 2004; Zhang et al., 2005; Chen et al. 2007; Benamar et al., 2008; Heinisch et al., 2011). Opioid and chemokine receptors have been detected on the same neurons, substantiating the potential for their interactions in the nervous system (Heinisch et al., 2011; Chen et al., 2004).

3.4.1. Opioid-induced cross-desensitization of chemokine receptors—Grimm et al. (1998) first reported opioid-induced heterologous desensitization of chemokine receptors by demonstrating that met-enkephalin, an endogenous opioid derived from proenkephalin that preferentially binds DOPs, and morphine administration inhibited the activity of CXCR1, CXCR2, CCR1, CCR5, or CCR2. Studies have shown that MOP activation induces heterologous desensitization of CCR5, but not CXCR4 (Finley et al., 2008; Szabo et al, 2003; Szabo et al., 2002). Interestingly, KOP and NOP are the only known opioid receptors to mediate cross-desensitization of CXCR4 (Rogers, 2020; Finley et al., 2008). In contrast, CXCR4 receptor activation causes desensitization of MOP and DOP receptor signaling (Chen et al., 2007; Heinisch et al., 2011). These findings identify chemokine-opioid receptor cross-talk and suggest that opioid-induced heterologous desensitization of chemokine receptors contribute to the immunosuppressive effects of opioids (Szabo et al., 2002).

3.4.2. Chemokine-induced cross-desensitization of opioid receptors—Elevated proinflammatory cytokines at sites of chronic inflammation play a role in increased pain sensitivity (Rogers, 2020). Studies have thus explored chemokine-induced heterologous desensitization of opioid receptors. Szabo et al. (2002) found that chemokine receptors CCR2, CCR5, CCR7, and CXCR4, but not CXCR1 or CXCR2, induced cross-desensitization of MOPs and DOPs. Activation of CCR1, CCR2, and CXCR1 was later

shown to desensitize MOPs in neuronal and non-neuronal cells (Zhang et al., 2004). Szabo et al. (2002) found that periaqueductal gray (PAG) pretreatment with CCR5 or CXCR4 agonists inhibited the ability of MOP to elicit an analgesic response to opioid administration as measured by the cold water tail-flick (CWTF) assay (Szabo et al., 2002). CCL5 was reported to induce hyperalgesia in the CWTF test, and its effects were blocked by an antibody to the chemokine (Benamar et al., 2008). Lee et al. (2013) reported decreased pain responses in CCR5 knockout mice to chemical or inflammatory stimuli. Furthermore, Chen et al. (2007) found that activation of CCR1, CCR5, and CXCR4 in the PAG desensitized MOP and DOP, and that CX3CR1 activation in the brain desensitized MOP, DOP, and KOP. Taken together, these studies show that activation of proinflammatory chemokine receptors downregulates opioid receptor activity and enhances the perception of pain at inflammatory sites.

3.5 Chemokine-based Therapeutic Approaches

Opioids are some of the most efficacious analgesics but pose a risk for dependence by activating dopamine reward pathways that produce euphoria (Al-Hasani and Bruchas, 2011). The U.S. opioid epidemic continues to be a major medical problem: in 2017, 47,600 drug overdose deaths involved opioids (Scholl et al., 2019). Among individuals 12 or older in 2018 who misused prescription pain relievers, 63.6% reported the main reason for their misuse was to alleviate physical pain (Lipari and Park-Lee, 2018). These concerns have driven research to pursue adjunctive and non-opioid strategies for alleviating pain in an effort to reduce the risk of opioid use disorder.

In chronic neuropathic pain, which typically involves inflammation, the analgesic efficacy of opioids is reduced (Martínez-Navarro et al., 2018). The previously mentioned chemokine-opioid studies provide a potential explanation for the reduced effectiveness of opioids against neuropathic pain: chemokines released during inflammation induce cross-desensitization of opioid receptors, resulting in downregulation of opioid signaling cascades and reducing opioid efficacy. Thus, therapeutic strategies directed toward reducing chemokine signaling may be capable of enhancing the analgesic efficacy of opioids while simultaneously reducing risks of opioid dependence and other adverse opioid effects such as constipation, respiratory depression, and tolerance.

Recent preclinical studies have indeed explored whether or not co-administration of chemokine receptor antagonists (CRAs) with morphine increases opioid analgesic potency in a preclinical model of inflammatory pain (Inan et al., 2018; Inan et al., 2019, Eisenstein, 2020). Inan et al. (2018) generated dose-response curves for morphine, a CCR5 antagonist (maraviroc), and a CXCR4 antagonist (AMD3100 [Plerixafor]), and found that co-administration of either CRA with morphine resulted in enhancement of the analgesic effect on incisional pain in rats. An additional study by Inan et al. (2019) reported that co-administration of the same two CRAs with either oxycodone or meperidine, commonly prescribed analgesics, also enhanced the analgesic potency of these opioids on incisional pain in rats. Eisenstein et al. (2020) found enhanced morphine potency when CRAs were administered with a submaximal dose of morphine in three different pain assays. Taken together, these studies demonstrate enhanced analgesia when sub-therapeutic doses of

opioids are combined with CRAs. These results suggest that the same analgesic effects of opioids may be obtained in lower doses when co-administered with CRAs, with a plausible mechanisms being inhibition of chemokine-mediated cross-desensitization of opioid receptors.

Studies investigating a role for cytokine and chemokine systems in the addictive effects of opioids remain limited. However, emerging evidence suggests that the rewarding effects of morphine are influenced by inflammatory responses in the mesolimbic system. For example, inhibition of glial cell activity in the nucleus accumbens reduces morphine conditioned place preference (CPP), a learned behavior when a subject prefers an environment previously associated with a reward (Zhang et al., 2012). Regarding the involvement of specific chemokine systems, a role for the CXCL12/CXCR4 system is suggested by evidence showing that rats conditioned with morphine display elevated levels of CXCL12 mRNA and protein levels in the VTA (Liu et al., 2018). Moreover, the inhibition of CXCL12 in the VTA with a neutralizing antibody inhibits the development of morphine CPP in rats and also reduces the maintenance of CPP in rats with an established morphine preference (Liu et al., 2018). Cytokines, particularly the anti-inflammatory cytokine IL-10, may also influence the addictive effects of opioids. The delivery of plasmid DNA encoding IL-10 into the nucleus accumbens of rats reduces the self-administration of remifentanil, a potent, short-acting synthetic opioid, but does not affect sucrose self-administration, suggesting reinforcer-specific effects of IL-10 (Lacagnina et al., 2017). It will be important for future studies to further investigate the impacts of CXCL12, IL-10 and other cytokines and chemokines on the addictive effects of opioids.

In summary, sub-therapeutic doses of opioids in combination with CRAs may provide a new approach to pain in inflammatory conditions resulting from surgery or injury. Eisenstein et al. (2020) reported the most pronounced results when the drugs were provided post-surgery. The two CRAs selected for the opioid-chemokine combination studies were maraviroc and AMD3100, both of which are approved for human use by the U.S. Food and Drug Administration. Thus, the administration of opioids in lower doses post-surgery in combination with maraviroc or AMD3100 may reduce the number of individuals who subsequently develop an opioid use disorder. Use of opioids in lower doses may not only prevent tolerance and dependence, but also reduce side effects including respiratory depression and gastrointestinal transit inhibition (Eisenstein et al., 2020).

4. Cocaine

4.1 Background

Cocaine is a highly addictive psychostimulant drug derived from the *Erythroxylon coca* plant that is native to Central and South America (Aguayo et al., 2006). The current prevalence of cocaine use lies particularly in the western hemisphere. In 2018, an estimated 977,000 Americans had a cocaine use disorder the previous year, representing 0.4 percent of the population (Lipari and Park-Lee, 2019).

4.2 Cellular Pharmacology

Cocaine effects on reward-related brain circuits, including mesolimbic and nigrostriatal dopaminergic tracks, are well established (Trecki and Unterwald, 2009). The mesolimbic pathway is a collection of dopaminergic neurons that project form the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAc) in the forebrain. The nigrostriatal pathway connects the substantia nigra in the midbrain with the dorsal striatum, which includes the caudate nucleus and putamen, in the forebrain. Within these systems, cocaine acts as an indirect dopamine receptor agonist by blocking dopamine reuptake through inhibition of dopamine transporters, thereby increasing extracellular dopamine in the NAc and caudate putamen (Thomas et al., 2008; Haile et al., 2012). This enhanced dopaminergic transmission underlies motivation, attention, reward, and locomotor activity produced by cocaine (Trecki and Unterwald, 2009). Research also indicates that cocaine acts within brain reward circuits to block serotonin (5-HT) and norepinephrine reuptake and alter glutamate and GABA transmission (Hall et al., 2004; Haile et al., 2012).

4.3 Therapeutic Void

The role of dopamine, glutamate, and other classical neurotransmitter systems in the pharmacological effects of cocaine is well established, but therapeutic strategies directly targeting these systems have not yet resulted in FDA-approved medications for treating cocaine use disorder. The therapeutic gap indicates the need to explore new endogenous targets. Recent studies have explored how cocaine dysregulates the neuroimmune system (Bachtell et al., 2017; Cotto et al., 2018). Drugs that inhibit glial activation have demonstrated preclinical efficacy in reducing addictive-like behaviors, but clinical utility may be limited by undesirable immunosuppressant effects (Poland et al., 2016). Thus, studies are now investigating more specific elements within the immune system, including cytokines and chemokines, which may more selectively target behavioral effects of cocaine related to dependence and addiction (Nayak et al., 2020).

4.4 Cytokine and Chemokine Biomarkers in Predicting Cocaine Use Disorder

Cocaine regulates production of cytokines and chemokines that influence neurotransmitter systems targeted by drugs of abuse (Araos et al., 2014), suggesting that dysregulation of chemokine and cytokine signaling during cocaine exposure perpetuates cocaine use disorder (Guyon et al., 2009; Trecki and Unterwald, 2009; Trocello et al., 2011). Cocaine-induced changes in chemokines may contribute to a high prevalence of co-morbid mental disorders in cocaine users (Crews et al., 2011), as studies have suggested that deficits in immune function contribute to depression, anxiety, and neurodegenerative diseases (Stuart and Baune, 2014). In fact, the utility of chemokines as pathological biomarkers or therapeutic targets has been proposed for treating mental disorders (Stuart and Baune 2014).

Araos et al. (2014) found plasma levels of TNFα, IL-1β, CXCL12, CCL2, and CX3CL1 to be elevated during acute cocaine exposure in mice but reduced during abstinence in human cocaine users. Furthermore, plasma levels of IL-1β, CXCL12, and CX3CL1 were positively associated with a number of criteria met for cocaine abuse and dependence in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSMIV), suggesting that the severity of cocaine use disorder may be monitored through circulating cytokine and

chemokine levels (Araos et al., 2014). Cytokines and chemokines may therefore serve as predictors of cocaine addiction, cocaine symptom severity, and psychiatric comorbidity in cocaine users (Araos et al., 2014). In summary, cocaine alters the plasma levels of inflammatory cytokines and chemokines, which may be used to predict the pathological use of cocaine and establish a better stratification of cocaine users seeking treatment (Araos et al., 2014).

4.5 Chemokine Receptor Antagonists in Reducing Behavioral Effects of Cocaine

Chemokine receptor systems are altered by cocaine exposure and contribute to the behavioral effects of cocaine (Nayak et al., 2020). A characteristic behavioral feature of cocaine resulting from increased dopamine transmission is hyperlocomotion. The administration of CXCR4 agonist CXCL12 intracerebroventricularly (icv) enhanced cocaine-induced hyperlocomotion (Trecki and Unterwald, 2009). Furthermore, synaptic dopamine levels in the dorsal striatum were enhanced following CXCL12 injection into the substantia nigra and subsequent CXCR4 receptor activation (Skrzydelski et al., 2007; Guyon, 2014). These observations are supported by data identifying CXCR4 receptor expression by dopamine neurons in the substantia nigra (Banisadr et al., 2002) and GABAergic medium spiny neurons in the nucleus accumbens (Trecki et al., 2010).

Kim et al. (2017) further demonstrated the role of the CXCL12/CXCR4 receptor system on the behavioral effects of cocaine. This preclinical study found that administration of the CXCR4 antagonist AMD3100 inhibited cocaine-induced hyperlocomotion and CPP. The researchers also reported increased CXCL12 mRNA levels in the VTA following repeated cocaine exposure, potentially identifying the VTA as the source of interaction between CXCL12 and dopamine. It is hypothesized that cocaine elevates extracellular dopamine levels in the VTA, which increases the expression of TNFα mRNA levels and in turn increases CXCL12 levels. Elevated CXCL12 then activates the CXCR4 receptor, enhancing mesolimbic dopamine activity and mediating the behavioral effects of cocaine (Kim et al., 2017). Thus, interactions between the neuroimmune and brain reward systems contribute to the abuse liability of cocaine (Kim et al., 2017). Interestingly, Oliver et al. (2018) found that AMD3100 also reduced CPP and locomotor activation following administration of the ‘bath salt’ synthetic cathinone MDPV (3,4-methlylenedioxypyrovalerone).

CCR2 and its cognate ligand, CCL2, may also contribute to behavioral and neurochemical effects of cocaine as both are constitutively expressed in dopaminergic neurons in the substantia nigra (Banisadr et al., 2002, 2005a, b, c). CCL2 administration into the rat substantia nigra increased extracellular dopamine levels and locomotor activity in the nigrostriatal pathway (Guyon et al., 2009). Trocello et al. (2011) demonstrated that locomotor activity is reduced in CCR2 knockout mice, suggesting that the CCR2 chemokine receptor system contributes to cocaine-induced sensitization. Thus, development of CCR2 antagonists may present a new therapeutic approach for individuals with cocaine use disorder (Trocello et al., 2011).

Recent evidence suggests that the CCR5 chemokine receptor system may also influence dopamine systems that contribute to cocaine dependence (Nayak et al., 2020). CCR5 knockout animals, compared to wild types, displayed fewer dopamine neurons in the

substantia nigra, decreased dopamine levels in the striatum, and reduced locomotion (Choi et al., 2013). Dopamine neurons in the mesolimbic pathway have been suggested to produce and express the CCR5 agonist, CCL5 (Lanfranco et al., 2018). The CCR5 ligand CCL3 is also reportedly expressed by dopamine neurons and astrocytes in the substantia nigra (Kalkonde et al., 2007). Nayak et al. (2020) demonstrated enhanced CCR5 mRNA levels in the nucleus accumbens and VTA following repeated cocaine exposure. Furthermore, inhibition of CCR5 with the antagonist maraviroc reduced hyperlocomotion and CPP. It is hypothesized that cocaine-induced increases in dopamine transmission promotes downstream activation of the mesolimbic CCR5 system, thus increasing CCR5 gene expression and enhancing the reward and locomotor effects of cocaine. These results suggest that, similar to those observed with CXCR4 and CCR2, mesolimbic CCR5 receptors are altered by cocaine exposure and may influence behavioral effects that contribute to abuse liability (Nayak et al., 2020). As maraviroc is FDA-approved, the antagonist may serve as a potential therapeutic for individuals with cocaine use disorder.

5. Methamphetamine

5.1 Background

Methamphetamine (METH) is a psychostimulant and amphetamine derivative used in the form of a crystalline hydrochloride that causes severe cognitive impairments often persisting after discontinuation of use (Loftis et al., 2011). METH consumption increased 4-fold between 2015 and 2016, and age-adjusted drug overdose deaths involving METH increased 3-fold between 2011 and 2016 (Piper et al., 2018; Hedegaard et al., 2018). In 2018, approximately 1.1 million Americans aged 12 or older had a METH use disorder the previous year, representing 0.4 percent of the population (Lipari and Park-Lee, 2019).

5.2 Cellular Pharmacology

METH acts as an indirect agonist at dopamine, noradrenaline, and serotonin receptors, thereby increasing the release of these monoamines from nerve terminals in the central and peripheral nervous systems (Paulus and Stewart, 2020). METH dysregulates vesicular monoamine transporters (VMAT) that displaces monoamines from storage vesicles into the cytosol (Cruickshank and Dyer, 2009). This process further disrupts monoamine transporters at cell surface membranes, which results in the release of dopamine, noradrenaline, and serotonin into synapses. In addition, METH reduces the metabolism of these monoamines by inhibiting the enzyme monoamine oxidase (Cruickshank and Dyer, 2009).

5.3 Therapeutic Approaches

There are no approved medications with demonstrated efficacy for the treatment of METH use order as the neurobiology of the drug is more complex than just monoamine dysregulation, and pharmacological interventions targeting the monoaminergic pathways have largely failed (Paulus and Stewart, 2020). Preclinical and clinical research proposes a new therapeutic strategy targeting factors involved in METH-induced neuroinflammation (Beardsley et al., 2010; Birath et al., 2017; DeYoung et al., 2016; Loftis and Janowsky, 2014; Snider et al., 2013; Worley et al., 2016). Studies have demonstrated that cytokines, chemokines, and cell adhesion molecules may contribute to METH-induced neuronal injury

and cognitive impairments (Loftis et al., 2011; Tocharus et al., 2010; Loftis et al., 2009; Narita et al., 2008). METH-induced neuroinflammation is mediated in part by activation of the TLR4 transmembrane protein within the VTA, which is highly expressed in microglia (Wendeln et al., 2018). This TLR4-mediated microglia activation then stimulates the secretion of cytokines (*e.g.* TNFα, IL-1β, and IL-6) and chemokines (*e.g.* CCL2) that can cause neuroinflammation, neuronal damage, and behavioral impairments (Clark et al., 2013; Loftis et al., 2011; Yamamoto et al., 2010; Yamamoto and Raudensky, 2008). In fact, Loftis et al. (2011) found increased plasma levels of CCL2 and the cellular adhesion molecule ICAM-1 following repeated METH exposure in both mice and humans. The cytokine and chemokine changes were also associated with increased cognitive impairments in human participants (Loftis et al., 2011). These studies suggest a critical role for CNS immune dysregulation in METH neurotoxicity and addiction.

Ibudilast is a nonspecific phosphodiesterase and glial activation inhibitor that has been shown to reduce METH locomotor activity, self-administration, and relapse in preclinical studies (Brensilver et al., 2013; Worley et al., 2016). Li et al. (2020) demonstrated clinically that ibudilast treatment reduced METH-induced levels of proinflammatory mediators, including adhesion molecules sICAM-1 and sVCAM-1 and the lysosomal protease cathepsin D. These findings identify glial cell activity as a critical regulator of the behavioral effects of METH and put forward ibudilast as a compound to be further studied as a putative therapeutic for METH use disorder (Li et al., 2020).

CCL2 is derived from neurons and glial cells and enhances dopamine release from neurons in the substantia nigra into the striatum (Wakida et al., 2014). It is suggested that CCL2-mediated neuroinflammation is associated with the pathogenesis of drug abuse (Crews et al., 2011). Ikegami et al. (2010) demonstrated upregulation of the CCL2 receptor CCR2 following METH administration; CCR2 may therefore be involved in maintaining sensitization to MA-induced hyperlocomotion as this behavior was significantly decreased in CCR2 knockout mice. Wakida et al. (2014) reported increased CCL2 mRNA levels following METH administration in both the prefrontal cortex and nucleus accumbens. METH-induced CPP was also suppressed by a CCR2 antagonist, RS504393 (Wakida et al., 2014). METH-induced increases in phosphorylated tyrosine hydroxylase (pTH) levels, the rate-limiting enzyme for dopamine synthesis, was also attenuated by RS504393 in the VTA. Thus, CCL2-CCR2 activation of dopamine neurons enhances physiological systems that facilitate METH addiction, and therapeutics targeting CCL2-CCR2 may be effective in treating METH dependence (Wakida et al., 2014).

In addition to activation of the CCR2 chemokine receptor system, Basova et al. (2018) found enhanced CCR5 gene expression following METH administration in a THP1 human macrophage cell line. Dopamine acting on the dopamine receptor DRD1 appeared to be the main factor in suppressing the CCR5 gene promoter toward transcription, thus suggesting a role for DRD1 agonists in regulating CCR5 expression (Basova et al., 2018). Future studies should explore both the CCR2 and CCR5 chemokine receptor systems as potential therapeutic targets for METH use disorder.

6. Conclusion

Central functions of cytokines and chemokines are not restricted to neuroinflammation and chemotaxis but extend to regulation of physiological systems that underlie addiction. In the present review, we discussed how these highly versatile inflammatory proteins facilitate the intersection between the immune and central nervous systems in the context of substance use disorders. In addition to providing a critical review of cytokine and chemokine mechanisms underlying substance use disorders, we also discussed cytokine- and chemokine-based therapeutic strategies. These approaches are entirely different from more conventional strategies directed toward receptors, transporters and enzymes that facilitate the biological actions of established neurotransmitters such as dopamine, glutamate, acetylcholine, and serotonin. Although speculative, an advantage of targeting cytokine and chemokine systems is their potential capability to inhibit the rewarding and reinforcing efficacy of different classes of drugs of abuse, including alcohol, opioids and psychostimulants by reducing cytokine- and chemokine-induced increases in mesolimbic dopaminergic transmission (Fig. 1). In terms of opioids, antagonists of chemokine receptors, especially CXCR4 and CCR5, may act as bifunctional opioid modulators by 1) preventing μ-opioid receptor desensitization, thus enhancing and preserving analgesic efficacy, while 2) simultaneously reducing the abuse liability of opioids through inhibition of mesolimbic dopamine transmission. Given that antagonists of some chemokine receptors (*e.g.* CXCR4, CCR5) enhance opioid-induced analgesia (Inan et al., 2018, 2019), it will be important in future studies to determine how specific cytokine and chemokine receptor antagonists affect adverse effects of opioids, such as dependence, relapse, constipation, and respiratory depression. In summary, these recent advances appear promising for developing cytokine- and chemokine-based pharmacotherapies for the prevention and treatment of substance use disorders.

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Research Highlights

- Cytokines offer new therapeutic targets for substance use disorders.
- Chemokines offer new therapeutic targets for substance use disorders.
- Cytokine and chemokine dysregulation by ethanol, opioids and stimulants is reviewed.
- Putative cytokine- and chemokine-based anti-addictive therapies are reviewed.

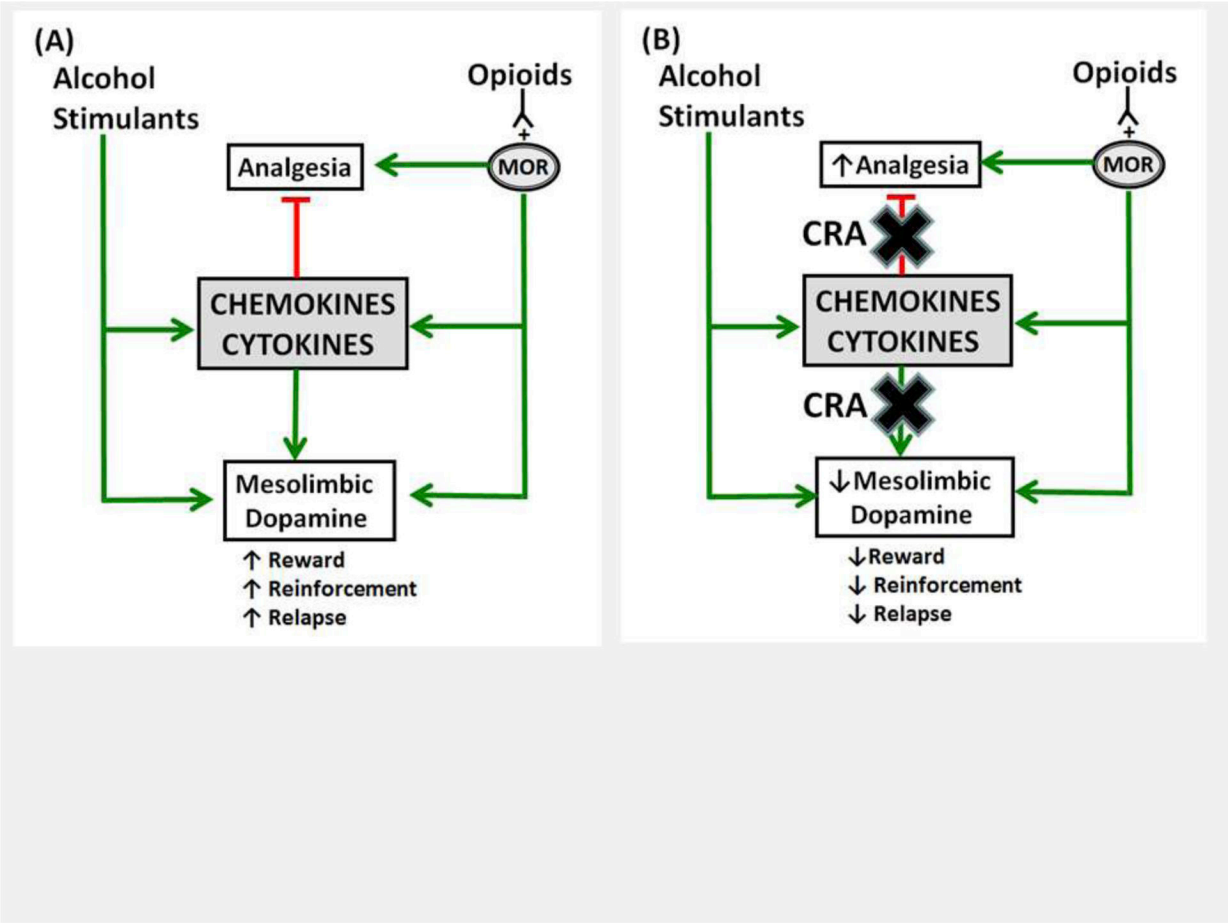

Fig. 1.

Model demonstrating potential interactions between drugs of abuse and cytokine/chemokine systems and putative therapeutic targets for substance use disorders (green lines = increase, red lines = decrease, MOR = μ-opioid receptor). **(A)** Exposure to different classes of drugs of abuse (psychostimulants, alcohol, opioids) causes an increase in brain levels of pro-inflammatory cytokines and chemokines (*e.g.* TNFα, IL-1β, CCL2, CCL5, and CXCL12). This leads to activation of specific receptors (*e.g.* CCR2, CCR5, and CXCR4) that enhances dopamine transmission in the limbic system, which exacerbates rewarding and reinforcing effects of drugs of abuse and relapse to drug seeking, and, in the case of opioids, reduces analgesic efficacy. **(B)** Cytokine and chemokine receptor antagonists (CRA) block the enhancement in dopamine transmission, thereby reducing drug reward, reinforcement and relapse, but enhance the analgesic efficacy of opioids by preventing desensitization of μ-opioid receptors (MOR).