



Opportunities for the Development of Neuroimmune Therapies in Addiction

Lara A. Ray^{*,1}, Daniel J.O. Roche^{*}, Keith Heinzerling[†], Steve Shoptaw[†]

^{*}Department of Psychology, University of California, Los Angeles, Los Angeles, California, USA

[†]Department of Family Medicine, University of California, Los Angeles, Los Angeles, California, USA

¹Corresponding author: e-mail address: lararay@psych.ucla.edu

Contents

| | |
|--|-----|
| 1. Introduction | 382 |
| 1.1 Neuroinflammation and alcohol dependence | 382 |
| 1.2 Neuroinflammation and MA dependence | 383 |
| 1.3 Neuroinflammation and HIV | 385 |
| 2. Neuroimmune Treatments | 386 |
| 2.1 Ibudilast | 386 |
| 2.2 Minocycline and doxycycline | 388 |
| 2.3 Topiramate | 389 |
| 2.4 Indomethacin | 390 |
| 2.5 Rolipram | 390 |
| 2.6 Anakinra (IL-1Ra) | 391 |
| 2.7 PPAR agonists | 391 |
| 2.8 Naltrexone/naloxone | 392 |
| 2.9 Summary and conclusions | 393 |
| References | 394 |

Abstract

Studies have implicated neuroinflammatory processes in the pathophysiology of various psychiatric conditions, including addictive disorders. Neuroimmune signaling represents an important and relatively poorly understood biological process in drug addiction. The objective of this review is to update the field on recent developments in neuroimmune therapies for addiction. First, we review studies of neuroinflammation in relation to alcohol and methamphetamine dependence followed by a section on neuroinflammation and accompanying neurocognitive dysfunction in HIV infection and concomitant substance abuse. Second, we provide a review of pharmacotherapies with neuroimmune properties and their potential development for the treatment of addictions. Pharmacotherapies covered in this review include ibudilast, minocycline, doxycycline, topiramate, indomethacin, rolipram, anakinra (IL-1Ra), peroxisome proliferator-activated receptor agonists, naltrexone, and naloxone. Lastly, summary

and future directions are provided with recommendations for how to efficiently translate preclinical findings into clinical studies that can ultimately lead to novel and more effective pharmacotherapies for addiction.



1. INTRODUCTION

Multiple studies implicate neuroinflammatory processes in the pathophysiology of various psychiatric conditions (Hirsch & Hunot, 2009; Sidoryk-Wegrzynowicz, Wegrzynowicz, Lee, Bowman, & Aschner, 2011), including addictive disorders. As carefully reviewed in this issue of *International Review of Neurobiology*, neuroimmune signaling represents an important and relatively poorly understood biological process in drug addiction. As the field begins to more fully understand and appreciate the contribution of the innate immune system to addiction etiology and maintenance, these discoveries set up opportunities for the development of novel treatments for addiction targeting neuroimmune dysfunction. In this chapter, we briefly review findings implicating neuroinflammation in alcohol dependence, methamphetamine (MA) dependence, and HIV. We then discuss specific pharmacotherapies with neuroimmune properties and their development potential for the indication of alcohol and/or drug use disorders. Lastly, we place these findings in the context of medication development for addiction, including efforts to effectively translate preclinical findings into more efficacious treatments.

1.1. Neuroinflammation and alcohol dependence

Several studies have demonstrated that neuroinflammation plays a role in alcohol use and abuse, with chronic alcohol use being associated with microglia activation and increased innate immune cell signaling (Mayfield, Ferguson, & Harris, 2013). Glial cell line-derived neurotrophic factor (GDNF) is a protein that is essential for the maintenance and survival of dopamine (DA) neurons (Boger et al., 2006) and can inhibit microglial activation (Rocha, Cristovão, Campos, Fonseca, & Baltazar, 2012). Additionally, preclinical evidence suggests that infusion of GDNF into the ventral tegmental area (VTA) blocks the acquisition and expression of alcohol-induced conditioned place preference (Barak, Ahmadiantehrani, Kharazia, & Ron, 2011; Barak, Carnicella, Yowell, & Ron, 2011), rapidly reduces alcohol intake (Carnicella, Ahmadiantehrani, Janak, & Ron, 2009, Carnicella, Amamoto, &

Ron, 2009; Carnicella, Kharazia, Jeanblanc, Janak, & Ron, 2008), and blocks alcohol reinstatement following extinction (Carnicella et al., 2008). Furthermore, endogenous levels of GDNF have been found to negatively regulate the rewarding effect of alcohol after a period of abstinence (Carnicella, Ahmadiantehrani, et al., 2009; Carnicella, Amamoto, et al., 2009). In one human study, GDNF serum levels measured peripherally were found to be significantly reduced in alcohol-dependent patients versus healthy controls and to be negatively associated with measures of tolerance and withdrawal (Heberlein et al., 2010). It has been hypothesized that GDNF functions to reduce these alcohol-related behaviors in animal models by reversing an alcohol-induced allostatic DA deficiency in the mesolimbic system caused by prolonged excessive alcohol consumption and repeated withdrawal (Barak, Ahmadiantehrani, et al., 2011; Barak, Carnicella, et al., 2011). Furthermore, there is evidence that pharmacological inhibition of phosphodiesterase-4 (PDE4), an enzyme that hydrolyses cyclic adenosine monophosphate (cAMP), decreases alcohol intake in mice (Hu et al., 2011) and rat (Wen et al., 2012) models of alcoholism, as well as reduces neuroinflammation and neuronal death in rats (Wang et al., 2012). In addition, a recent study found that another phosphodiesterase, PDE10A, mRNA levels correlated with greater alcohol self-administration during a relapse model and with ethanol preference after acquisition (Logrip & Zorrilla, 2012), suggesting that inhibition of PDE10A may have behavioral effects on alcohol ingestion. PDE4 inhibitors are highly relevant because by increasing cAMP levels, PDE4 inhibitors show a broad spectrum of anti-inflammatory effects in almost all inflammatory cells (Page & Spina, 2011). While these studies are promising, they rely primarily on animal models. One of the primary limitations for the translation of these findings to human samples is the relative difficulty in assessing accurate central markers of inflammation coupled with the unclear nature of the relationship between peripheral (i.e., more readily accessible) and central markers of inflammation.

1.2. Neuroinflammation and MA dependence

Preclinical studies have shown that MA has multiple effects on neuroimmune activities. MA activates microglia, and blocking this glial activation subsequently attenuates MA-induced neurodegeneration (Flora et al., 2002; Ladenheim et al., 2000; Thomas, Francescutti-Verbeem, & Kuhn, 2008; Thomas & Kuhn, 2005). Importantly, MA-induced microglial activation precedes the development of pathological changes in striatal DA

neurons (LaVoie, Card, & Hastings, 2004), suggesting that microglial activation is involved in the development of MA-induced neurological changes and is not merely a reaction to neurodegeneration.

In a human imaging study, a marker for activated microglia was significantly increased in abstinent MA users versus nonusing controls, and binding levels correlated inversely with the duration of MA abstinence (Sekine et al., 2008). MA-dependent women exhibited severe reductions in glial tri-carboxylic acid cycle rate compared to healthy control subjects in a magnetic resonance spectroscopy study, providing further evidence of *in vivo* glial cell dysfunction in MA users (Sailasuta, Abulseoud, Harris, & Ross, 2010). Furthermore, emerging research suggests that microglial activation may mediate MA-induced synaptic plasticity (Narita et al., 2006), thereby contributing to the prolonged susceptibility to drug relapse. Among human MA users, increased plasma levels of proinflammatory cytokines (IFN- α , IL-1 β , IL-2, IL-6, and TNF- α) and chemokines (MCP-1, MIP-1 α , and MIP-1 β) were significantly associated with greater neurocognitive dysfunction (Loftis, Choi, Hoffman, & Huckans, 2011). Together, these results suggest that medications that counteract MA-induced neuroinflammation and microglial activation may reduce MA-induced neurodegeneration, thereby improving neurocognition and treatment outcomes in MA dependence and perhaps other substance use disorders as well.

In addition to the potential negative impact of glial-mediated neuroinflammation on MA-related neurodegeneration, glial cells also produce neurotrophic factors that may ameliorate DA dysfunction in MA dependence. For example, GDNF selectively protects DA neurons, but not serotonergic neurons, from MA-induced neurodegeneration (Cass, 1996), and increased GDNF expression in the putamen actually regenerates DA neurons and restores DA functioning in a nonhuman primate model of Parkinson's disease (Kells et al., 2010). GDNF is found at high levels in the striatum including the nucleus accumbens (NAcc), and GFR α 1 and Ret, the receptors for GDNF, are highly expressed in DA neurons in the VTA (Carnicella & Ron, 2009). Preclinical studies suggest that increased GDNF expression and the activation of the GDNF pathway reduce the biochemical and behavioral response to a variety of drugs of abuse including cocaine, opioids, alcohol, and MA. GDNF expression is increased in the NAcc in mice following MA administration, and treatment with the peptide Leu-Ile, which is a GDNF inducer, blocked the development of MA conditioned place preference and behavioral sensitization in wild type but not heterozygous GDNF knockout (GDNF +/-) mice (Niwa et al., 2007).

GDNF +/- mice have lower levels of GDNF and exhibit greater MA conditioned place preference (Niwa et al., 2007). GDNF +/- mice acquire stable MA self-administration behavior more quickly than wild-type mice, exhibit greater motivation to self-administer MA (increased dose-response curve for MA self-administration and higher break point on progressive ratio schedule), and display greater reinstatement of prime- and cue-induced drug seeking following extinction, an effect that remained even 6 months after extinction training (Yan et al., 2007). In humans, polymorphisms in the GDNF gene have been associated with age of onset of MA dependence and addiction severity in Japanese MA users (Yoshimura et al., 2011). Together, these studies suggest that increasing GDNF is a promising approach to treating MA dependence due to its neurotrophic and neuroprotective effects that may restore DA functioning (Gramage & Herradon, 2011) and provide at least one mechanism that could not only reduce the reinforcing effect of MA but also reduce the use of MA itself (Carnicella & Ron, 2009; Ghitza et al., 2010).

1.3. Neuroinflammation and HIV

Neuroinflammation and accompanying neurocognitive dysfunction are also major clinical issues in HIV infection, and they are exacerbated by concomitant substance abuse. HIV-associated neurocognitive disorders (HANDs) are common even with antiretroviral therapy, with 52% of patients in a recent HIV clinical cohort exhibiting at least some level of neuropsychological impairment (Heaton et al., 2010). HIV does not directly infect central nervous system (CNS) neurons, and HAND is thought to result primarily from the infection and subsequent activation of CNS macrophages and microglia, which then secrete many of the same proinflammatory cytokines that are also secreted in response to MA and chronic alcohol use, including TNF- α , IL-1 β , IL-6, and MCP-1 (Yadav & Collman, 2009). HIV proteins gp120 and Tat are also neurotoxic and combined with MA exhibit synergistic toxicity on striatal DA neurons and the blood-brain barrier leading to enhanced CNS penetration by HIV (Silverstein et al., 2011). Not surprisingly, MA abuse increases the risk for neurocognitive impairment among HIV-infected persons (Carey et al., 2006; Rippeth et al., 2004), especially with HIV/Hepatitis C Virus (HCV) coinfection (Cherner et al., 2005; Letendre et al., 2007). Greater cognitive dysfunction is associated with poor HIV clinical outcomes including medication nonadherence (Becker, Thames, Woo, Castellon, & Hinkin, 2011) and worsened quality of life

(Parsons, Braaten, Hall, & Robertson, 2006). Therefore, medications that reduce neuroinflammation in HIV-infected substance users may improve HIV and substance-related clinical outcomes via improvements in neurocognitive functioning.



2. NEUROIMMUNE TREATMENTS

This section provides a review of pharmacotherapies with neuro-immune properties and their potential development for the treatment of addictions. Pharmacotherapies covered in this section include ibudilast, minocycline, doxycycline, topiramate, indomethacin, rolipram, anakinra (IL-1Ra), peroxisome proliferator-activated receptor (PPAR) agonists, naltrexone, and naloxone. A summary of the medications, their potential neuroimmune targets, and preclinical and clinical findings is provided in Table 12.1.

2.1. Ibudilast

Ibudilast (IBUD; MN-166/AV411) is a nonselective phosphodiesterase inhibitor with preferential inhibition of PDE3A, PDE4, PDE10, and PDE11 (Gibson et al., 2006) that also inhibits glial cell activation (Suzumura, Ito, Yoshikawa, & Sawada, 1999) and production of macrophage migration inhibitory factor (Cho et al., 2010). IBUD has been used clinically for over 20 years in Asia for the treatment of bronchial asthma and, more recently, for poststroke dizziness and ocular allergies for which it has proven to be safe and well tolerated (Rolan, Hutchinson, & Johnson, 2009). IBUD increases expression of GDNF in *in vitro* studies (Mizuno et al., 2004) suggesting that IBUD may ameliorate DA dysfunction among MA users and alcohol-dependent patients via the induction of GDNF expression. IBUD also reduces microglial activation *in vitro* in preclinical studies (Suzumura, Ito, & Mizuno, 1999, 2003; Suzumura et al., 1999). IBUD dose-dependently protected against microglial activation and the subsequent cerebrovascular white matter lesions following bilateral ligation of the carotid arteries (an animal model of vascular dementia/cognitive impairment) in rats (Wakita et al., 2003). IBUD also suppressed activated microglia-induced neuronal cell death *in vitro* via inhibiting production of proinflammatory cytokines (IL-1 β , IL-6, and TNF- α), reactive oxygen species, and nitric oxide and via increasing the secretion of anti-inflammatory mediators (IL-10, nerve growth factor, neurotrophin-4, and GDNF) by microglial cells (Mizuno et al., 2004).

Table 12.1 Neuroimmune medications with potential for the treatment of addictive disorders

| Medication | Potential immune targets | Findings in animal studies | Findings in human studies |
|---------------------------------|--|--|---|
| Ibudilast | Glia, PDE | ↓ MA self-administration, locomotor sensitization, and reinstatement | Clinical trials underway for MA, alcohol, and opioid dependence |
| Tetracyclines | Glia, NMDA receptors, oxidative stress signaling, NO | ↓ MA conditioned place preference, MA-induced DA release ↓ Alcohol self-administration ↑ Alcohol-induced motor impairment | ↓ D-Amphetamine subjective reward |
| Topiramate | T cells or antigen-presenting cells | ↓ Alcohol self-administration ^a | Mixed evidence supporting use for alcohol dependence ^a |
| Indomethacin | COX-2, iNOS | ↓ Alcohol-induced apoptosis and cognitive/motor dysfunction | Did not affect acute response to alcohol or pentobarbital |
| Rolipram | PDE | ↓ Alcohol self-administration and preference | |
| Anakinra | IL-1 receptor | ↓ Alcohol-induced sedation and liver damage | |
| Thiazolidinediones and fibrates | PPAR | ↓ Alcohol self-administration, reinstatement, and withdrawal ↓ MA locomotor sensitization ↓ Nicotine-induced DA release, nicotine self-administration, and reinstatement | |

Continued

Table 12.1 Neuroimmune medications with potential for the treatment of addictive disorders—cont'd

| Medication | Potential immune targets | Findings in animal studies | Findings in human studies |
|--------------------------------|--------------------------|---|---------------------------|
| (+)(-) Naltrexone and Naloxone | TLR4 | ↓ Cocaine and amphetamine locomotor activity ↓ Alcohol-induced apoptosis, motor impairment, and sedation | |

^aUnclear if medication effects are related to immune function.

Preclinical studies have found that IBUD has significant effects on behavior in multiple rodent models of MA dependence including reinstatement, locomotor sensitization, and self-administration. Importantly, IBUD demonstrated a dose-dependent effect on behavior in all three models with the greatest effect at higher doses. In the MA-reinstatement model, rats were trained to lever press for MA after which MA infusions were discontinued and lever pressing extinguished. IBUD significantly reduced MA prime- and stress-induced reinstatement of active lever pressing (Beardsley, Shelton, Hendrick, & Johnson, 2010) suggesting that IBUD may be effective in reducing relapse during clinical treatment for MA dependence. While both high and low IBUD doses reduced stress-induced reinstatement, only the higher IBUD dose reduced prime-induced reinstatement. Our research group is actively engaged in studies of IBUD for the indications of MA (ClinicalTrial.Gov identifier: NCT01860807, NCT01217970) and alcohol dependence (ClinicalTrial.Gov identifier: NCT02025998). Additionally, a clinical study of IBUD for opiate dependence is underway (ClinicalTrial.Gov identifier: NCT00723177). In brief, IBUD is a potentially promising medication for addiction with supportive preclinical studies and several human trials underway. Importantly, the neuroinflammatory actions of IBUD represent novel targets in the field of psychiatry, and addiction in particular.

2.2. Minocycline and doxycycline

Minocycline is a tetracycline antibiotic typically used to treat acne. Recent studies have focused on minocycline as a therapeutic agent for psychiatric disorders in light of its antioxidant properties, which in turn are thought

to target deficits in oxidative defense associated with psychiatric disorders (Dean, Data-Franco, Giorlando, & Berk, 2012). For addiction, in particular, studies have highlighted the glutamatergic and DA effects of minocycline, which in turn have been implicated in addiction etiology (Kalivas & Volkow, 2005). In addition, the effects of minocycline on neuroimmune and cytokine expression have been emphasized as potential therapeutic targets for this medication (Fan et al., 2007; Mishra & Basu, 2008).

Preclinical studies have found that minocycline attenuated NMDA receptor antagonist-induced cognitive impairment in rodents (Fujita et al., 2008; Munzar, Li, Nicholson, Wiley, & Balster, 2002). Further, minocycline was protective against the deleterious effects of MA on DA transporter levels in monkeys (Hashimoto et al., 2007). Additional preclinical studies suggested that minocycline blocked the rewarding effects of MA (Fujita, Kunitachi, Iyo, & Hashimoto, 2012) and reduced ethanol administration in mice (Agrawal, Hewetson, George, Syapin, & Bergeson, 2011). A study of doxycycline, another anti-inflammatory mediator in the tetracycline derivative family, also observed reductions in alcohol consumption in mice, along with increased sensitivity to the motor-impairing effects of alcohol (McIver, Muccigrosso, & Haydon, 2012). One study to date has examined the effects of minocycline in healthy human volunteers and found that minocycline reduced the subjective rewarding effects of dextroamphetamine, increased reaction times on a Go No-Go task, and reduced plasma levels of cortisol compared to placebo (Sofuoglu, Mooney, Kosten, Waters, & Hashimoto, 2011). In summary, while there are no studies of clinical populations to date, the preclinical literature suggests that tetracycline antibiotic drugs such as minocycline, and possibly doxycycline, may have therapeutic effects for addiction and that these effects may be, at least in part, mediated by their neuroinflammatory properties.

2.3. Topiramate

Topiramate is an anticonvulsant medication with demonstrated clinical effects on drinking outcomes among alcohol-dependent individuals (Johnson & Ait-Daoud, 2010). In addition, studies have found that topiramate has anti-inflammatory properties and that it decreases alcohol consumption in animal models (Breslin, Johnson, & Lynch, 2010; Zalewska-Kaszubska et al., 2013). A preclinical study found that topiramate inhibited the production of several proinflammatory cytokines, including IL-17, IFN- γ , TNF, IL-6, and IL-10, which are generally produced by

either T cells or antigen-presenting cells (Bhat et al., 2010). This study demonstrates that GABAergic drugs such as topiramate can act on T cells or antigen-presenting cells to suppress inflammatory signalling. Notably, no studies to date have implicated the anti-inflammatory properties of topiramate in its clinical or preclinical efficacy for alcohol or other substance use disorders. Nonetheless, recognizing that these anti-inflammatory effects are present for medications with known clinical efficacy, such as topiramate and opioid antagonists (discussed below), provides intriguing evidence to suggest that neuroinflammatory process may be common mechanisms across efficacious pharmacotherapies for addiction.

2.4. Indomethacin

Indomethacin is a nonsteroidal anti-inflammatory and a cyclooxygenase (COX-2) enzyme inhibitor. A preclinical study found that administration of indomethacin prevented ethanol-induced behavioral deficits caused by the ethanol-induced COX-2 and nitric oxide synthase (iNOS) expression and subsequent neuronal death. These findings indicate that indomethacin had protective effects against ethanol-induced brain damage by reducing inflammatory signalling and, in turn, prevented ethanol-related cognitive and motor decrements (Pascual, Blanco, Cauli, Minarro, & Guerri, 2007). However, a human pharmacology study found that indomethacin pretreatment did not alter the effects of alcohol or pentobarbital on subjective drug ratings, heart rate, and cognitive/psychomotor performance (Pickworth, Fant, & Henningfield, 1997). Perhaps the neuroprotective effects of indomethacin may be better observed after chronic alcohol consumption in humans, yet extensive controlled studies are needed before establishing whether indomethacin may have therapeutic value for substance use disorders.

2.5. Rolipram

The cAMP signaling cascade is thought to subserve the behavioral responses to alcohol. As previously described, PDE4 catalyzes the hydrolysis of cAMP and regulates intracellular cAMP levels. Rolipram is a selective PDE4 inhibitor thought to represent a novel treatment option for alcoholism due to its effects on the cAMP cascade. A recent preclinical study found that rolipram acutely reduced ethanol self-administration in a dose-dependent fashion and also, after chronic dosing, reduced ethanol preference and

consumption (Wen et al., 2012). This is consistent with a previous study showing that acute rolipram administration substantially reduced ethanol consumption and preference in mice (Hu et al., 2011). Together, these findings suggest that rolipram as well as other PDE4 inhibitors, may have potential for the treatment of alcoholism and perhaps other substance use disorders.

2.6. Anakinra (IL-1Ra)

Anakinra is an interleukin (IL-1) receptor antagonist frequently used in the treatment of rheumatoid arthritis. Studies have found that anakinra (IL-1Ra) crosses the blood–brain barrier in rodents (Shavit, Wolf, Goshen, Livshits, & Yirmiya, 2005) and also reduces CNS inflammation in humans (Goldbach-Mansky et al., 2006). Perhaps most intriguing, an animal study found that anakinra reduced alcohol-induced sedation in mice (Wu et al., 2011). More recently, a rodent study found that IL-1Ra's inhibition of IL-1 signaling was associated with a significant reduction in alcohol-induced liver inflammation, fat accumulation, and damage (Petrasek et al., 2012). Although preliminary, these intriguing studies advance IL-1 receptor antagonists as possible therapeutics for alcoholism. One ongoing trial of Anakinra for patients with severe and acute hepatitis and alcoholism was identified through a search of ClinicalTrial.Gov database (ClinicalTrial.Gov identifier: NCT01809132).

2.7. PPAR agonists

PPARs are ligand-activated nuclear receptors that function as transcription factors. There are three known PPAR isoforms, PPAR α , PPAR β/δ , and PPAR γ , which are located throughout most peripheral tissues, as well as in neurons and glia in the brain (Gofflot et al., 2007; Moreno, Farioli-Vecchioli, & Ceru, 2004; Sarruf et al., 2009; Woods et al., 2003). Activation of PPAR attenuates innate immune signaling, thereby mediating anti-inflammatory and neuroprotective processes (Berger & Moller, 2002; Kapadia, Yi, & Vemuganti, 2008; Landreth & Heneka, 2001; Pistis & Melis, 2010). Importantly, PPAR α and PPAR γ receptors are densely expressed in the lateral hypothalamus, are located in VTA DA neurons, and can modulate DA release from the VTA into the NAcc (Melis et al., 2010, 2008; Moreno et al., 2004; Sarruf et al., 2009), all of which suggest a potential role in addiction-related processes. In support, recent studies that have pharmacologically manipulated PPAR in rodents and nonhuman

primates have provided promising results advocating PPAR agonists as potential addiction-related treatments. Two selective PPAR γ agonists, the thiazolidinediones pioglitazone and rosiglitazone, reduced alcohol consumption, abolished reinstatement of alcohol-seeking behavior, and reduced alcohol withdrawal symptoms in rats (Stopponi et al., 2011). Pioglitazone and ciglitazone, which is another thiazolidinedione selective for PPAR γ , blocked the expression of locomotor sensitization to MA in mice (Maeda et al., 2007). Additionally, in rodents and nonhuman primates, clofibrate, a fibrate medication and selective PPAR α agonist, blocked nicotine-induced VTA firing and DA release in the NAcc at the molecular level, and at the behavioral level it blocked the acquisition of nicotine-seeking behavior in nondependent animals, decreased nicotine self-administration in dependent animals, and prevented relapse to nicotine seeking in abstinent animals (Panlilio et al., 2012). Thus, in rodents and nonhuman primates, PPAR agonists may be effective in reducing the motivational and salient properties of multiple drugs (i.e., MA, alcohol, and nicotine) by modulating neurotransmission within the common reward pathway by which drugs of abuse are thought to exert their positively reinforcing effects. One ongoing clinical study of pioglitazone was identified as an adjunct treatment to opioid and nicotine dependence (ClinicalTrial.Gov identifier: NCT01395797). While these medications have not yet been tested in humans for this purpose, fibrates and thiazolidinediones are already approved for use in humans as treatments for elevated cholesterol and diabetes, respectively, and thus, repositioning these medications for use as addiction pharmacotherapies may provide a fast and economically feasible alternative in treatment development.

2.8. Naltrexone/naloxone

Naltrexone is an opioid antagonist approved for the treatment of alcoholism and heroin dependence and is currently under investigation for treatment of nicotine dependence. Naloxone is also an opioid receptor antagonist with similar affinity to mu opioid receptors as naltrexone, but relatively lower affinity to kappa and delta opioid receptors. Each of these medications is available in two isomers: the (–) isomer is the common opioid receptor antagonist form of each drug, whereas the (+) isomer does not bind (or has significantly reduced binding affinity) to opioid receptors (Hutchinson et al., 2008, 2011). However, both the (+) and (–) forms of each drug are antagonists at the Toll-like receptor 4 (TLR4; Hutchinson et al.,

2008). Interestingly, despite its inability to antagonize opioid receptors, (+) naloxone was found to reduce stimulant-induced locomotor activity (Chatterjie, Alexander, Sechzer, & Lieberman, 1996; Chatterjie, Sechzer, Lieberman, & Alexander, 1998), which is congruent with findings suggesting that TLR4 contributes to the acute effects of drugs of abuse (Hutchinson et al., 2012) and the ability of opioid receptor antagonists to affect such responses (Wu et al., 2012). The activation of TLR4 predominantly contributes to glial activation and the subsequent release of numerous proinflammatory cytokines (Mayfield et al., 2013). Importantly, these TLR4-related processes are involved in the behavioral and neuroinflammatory effects of drugs of abuse (Mayfield et al., 2013), as TLR4 activation has been shown to be integral to alcohol-induced glial activation and proinflammatory signaling (Alfonso-Loeches, Pascual-Lucas, Blanco, Sanchez-Vera, & Guerri, 2010; Blanco, Pascual, Valles, & Guerri, 2004; Blanco, Valles, Pascual, & Guerri, 2005; Fernandez-Lizarbe, Pascual, & Guerri, 2009), as well as alcohol's behavioral effects in rodents (Wu et al., 2012). Furthermore, in rodents, naltrexone attenuates proinflammatory TLR4-related signaling (Hutchinson et al., 2011) and blocks ethanol-induced glial activation and neuronal death (Qin & Crews, 2012), while (+) naloxone reduces acute alcohol-induced sedation and motor impairment (Wu et al., 2012). In sum, these findings may indicate that TLR4 signaling is involved in both the acute behavioral and chronic inflammatory effects of alcohol and other drugs of abuse and also that such TLR4-mediated processes may be ameliorated by the opioid receptor antagonists naltrexone and naloxone.

2.9. Summary and conclusions

The literature on the role of neuroinflammatory processes in psychiatric disorders broadly, and addiction, in particular, is in its infancy. As the field quickly develops a more refined understanding of the effects of the innate immune system in addiction etiology, the opportunities for intervention become clearer and hopefully more targeted. One of the important recognitions from this review is that while largely predicated on preclinical studies, there is compelling evidence to suggest that medications modulating neuroinflammatory processes represent promising alternatives for addiction treatment and do so by targeting novel pathways. In addition, one quickly recognizes that medications with established efficacy for addiction, such as naltrexone and topiramate, also have neuroinflammatory properties. As

such, a plausible question is the degree to which such inflammatory effects contribute to their clinical efficacy.

Importantly, the promise of newer and more effective treatments for substance use disorders ought to be considered in light of an efficient pathway from preclinical to clinical science. As outlined recently by Litten and colleagues, the effective translation of treatments from bench to bedside involves carefully addressing translational questions at all levels of analyses (Litten et al., 2012). To that end, proof-of-concept laboratory studies offer an important bridge between preclinical findings and clinical application to treatment-seeking samples. Human laboratory models can be used to guide identification of medications with promise of efficacy by collecting both safety and alcohol/drug interaction data along with initial demonstration of subjective responses to alcohol/drug, cue-reactivity, and self-administration models (Plebani et al., 2012). Human laboratory models can also aid in the effective translation of preclinical findings by elucidating the biobehavioral mechanisms by which pharmacotherapies may be efficacious for addiction (Ray, Hutchison, & Tarter, 2010; Ray, Mackillop, & Monti, 2010). Such findings on safety and mechanisms are vital to deciding whether to invest resources for efficacy testing for a putative addiction medication. Our team has used human laboratory paradigms to test several medications for addiction, including naltrexone (Ray, Bujarski, Chin, & Miotto, 2012; Ray & Hutchison, 2007), topiramate (Miranda et al., 2008; Ray et al., 2009), quetiapine (Moallem & Ray, 2012; Ray, Chin, Heydari, & Miotto, 2011), and varenicline (Ray et al., 2014, 2013). Given the new opportunities presented by recent discoveries on the role of neuroinflammation in addiction as well as new advancements in the technology of medication development, including the refinement of powerful human laboratory models, the stage is set for the discovery of novel treatments for substance use disorders. The ultimate goal is to develop treatments for addiction that are more efficacious than the available ones and to further boost the efficacy of these novel compounds through personalized approaches, including genomics and behavioral science. Together, these approaches have the potential to mitigate the many costs of addiction to the individual and to society at large.

REFERENCES

- Agrawal, R. G., Hewetson, A., George, C. M., Syapin, P. J., & Bergeson, S. E. (2011). Minocycline reduces ethanol drinking. *Brain, Behavior, and Immunity*, 25(Suppl. 1), S165–S169. <http://dx.doi.org/10.1016/j.bbi.2011.03.002>.
- Alfonso-Loeches, S., Pascual-Lucas, M., Blanco, A. M., Sanchez-Vera, I., & Guerri, C. (2010). Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain

- damage. *Journal of Neuroscience*, 30(24), 8285–8295. <http://dx.doi.org/10.1523/jneurosci.0976-10.2010>.
- Barak, S., Ahmadiantehrani, S., Kharazia, V., & Ron, D. (2011). Positive autoregulation of GDNF levels in the ventral tegmental area mediates long-lasting inhibition of excessive alcohol consumption. *Translational Psychiatry*, 419, 456–459. <http://dx.doi.org/10.1038/tp.2011.57>.
- Barak, S., Carnicella, S., Yowell, Q. V., & Ron, D. (2011). Glial cell line-derived neurotrophic factor reverses alcohol-induced allostasis of the mesolimbic dopaminergic system: Implications for alcohol reward and seeking. *Journal of Neuroscience*, 31(27), 9885–9894. <http://dx.doi.org/10.1523/JNEUROSCI.1750-11.2011>.
- Beardsley, P. M., Shelton, K. L., Hendrick, E., & Johnson, K. W. (2010). The glial cell modulator and phosphodiesterase inhibitor, AV411 (ibudilast), attenuates prime- and stress-induced methamphetamine relapse. *European Journal of Pharmacology*, 637(1–3), 102–108. <http://dx.doi.org/10.1016/j.ejphar.2010.04.010>.
- Becker, B. W., Thames, A. D., Woo, E., Castellon, S. A., & Hinkin, C. H. (2011). Longitudinal change in cognitive function and medication adherence in HIV-infected adults. *AIDS and Behavior*, 15(8), 1888–1894. <http://dx.doi.org/10.1007/s10461-011-9924-z>.
- Berger, J., & Moller, D. E. (2002). The mechanisms of action of PPARs. *Annual Review of Medicine*, 53(1), 409–435.
- Bhat, R., Axtell, R., Mitra, A., Miranda, M., Lock, C., Tsien, R. W., et al. (2010). Inhibitory role for GABA in autoimmune inflammation. *Proceedings of the National Academy of Sciences of the United States of America*, 107(6), 2580–2585. <http://dx.doi.org/10.1073/pnas.0915139107>.
- Blanco, A. M., Pascual, M., Valles, S. L., & Guerri, C. (2004). Ethanol-induced iNOS and COX-2 expression in cultured astrocytes via NF-kappa B. *Neuroreport*, 15(4), 681–685.
- Blanco, A. M., Valles, S. L., Pascual, M., & Guerri, C. (2005). Involvement of TLR4/type I IL-1 receptor signaling in the induction of inflammatory mediators and cell death induced by ethanol in cultured astrocytes. *Journal of Immunology*, 175(10), 6893–6899.
- Boger, H. A., Middaugh, L. D., Huang, P., Zaman, V., Smith, A. C., Hoffer, B. J., et al. (2006). A partial GDNF depletion leads to earlier age-related deterioration of motor function and tyrosine hydroxylase expression in the substantia nigra. *Experimental Neurology*, 202, 336–347. <http://dx.doi.org/10.1016/j.expneurol.2006.06.006>.
- Breslin, F. J., Johnson, B. A., & Lynch, W. J. (2010). Effect of topiramate treatment on ethanol consumption in rats. *Psychopharmacology*, 207(4), 529–534. <http://dx.doi.org/10.1007/s00213-009-1683-4>.
- Carey, C. L., Woods, S. P., Rippeth, J. D., Gonzalez, R., Heaton, R. K., & Grant, I. (2006). Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. *AIDS and Behavior*, 10(2), 185–190. <http://dx.doi.org/10.1007/s10461-005-9056-4>.
- Carnicella, S., Ahmadiantehrani, S., Janak, P. H., & Ron, D. (2009). GDNF is an endogenous negative regulator of ethanol-mediated reward and of ethanol consumption after a period of abstinence. *Alcoholism, Clinical and Experimental Research*, 33(6), 1012–1024. <http://dx.doi.org/10.1111/j.1530-0277.2009.00922.x>.
- Carnicella, S., Amamoto, R., & Ron, D. (2009). Excessive alcohol consumption is blocked by glial cell line-derived neurotrophic factor. *Alcohol*, 43(1), 35–43. <http://dx.doi.org/10.1016/j.alcohol.2008.12.001>.
- Carnicella, S., Kharazia, V., Jeanblanc, J., Janak, P. H., & Ron, D. (2008). GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse. *Proceedings of the National Academy of Sciences of the United States of America*, 105(23), 8114–8119. <http://dx.doi.org/10.1073/pnas.0711755105>.

- Carnicella, S., & Ron, D. (2009). GDNF—A potential target to treat addiction. *Pharmacology & Therapeutics*, *122*(1), 9–18.
- Cass, W. A. (1996). GDNF selectively protects dopamine neurons over serotonin neurons against the neurotoxic effects of methamphetamine. *Journal of Neuroscience*, *16*(24), 8132–8139.
- Chatterjie, N., Alexander, G. J., Sechzer, J. A., & Lieberman, K. W. (1996). Prevention of cocaine-induced hyperactivity by a naloxone isomer with no opiate antagonist activity. *Neurochemical Research*, *21*(6), 691–693.
- Chatterjie, N., Sechzer, A., Lieberman, K., & Alexander, G. (1998). Dextro-naloxone counteracts amphetamine-induced hyperactivity. *Pharmacology, Biochemistry, and Behavior*, *59*(2), 271–274.
- Cherner, M., Letendre, S., Heaton, R. K., Durelle, J., Marquie-Beck, J., Gragg, B., et al. (2005). Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*, *64*(8), 1343–1347. <http://dx.doi.org/10.1212/01.WNL.0000158328.26897.0D>.
- Cho, Y., Crichlow, G. V., Vermeire, J. J., Leng, L., Du, X., Hodsdon, M. E., et al. (2010). Allosteric inhibition of macrophage migration inhibitory factor revealed by ibudilast. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(25), 11313–11318. <http://dx.doi.org/10.1073/pnas.1002716107>.
- Dean, O. M., Data-Franco, J., Giorlando, F., & Berk, M. (2012). Minocycline: Therapeutic potential in psychiatry. *CNS Drugs*, *26*(5), 391–401. <http://dx.doi.org/10.2165/11632000-000000000-00000>.
- Fan, R., Xu, F., Previti, M. L., Davis, J., Grande, A. M., Robinson, J. K., et al. (2007). Minocycline reduces microglial activation and improves behavioral deficits in a transgenic model of cerebral microvascular amyloid. *Journal of Neuroscience*, *27*(12), 3057–3063. <http://dx.doi.org/10.1523/JNEUROSCI.4371-06.2007>.
- Fernandez-Lizarbe, S., Pascual, M., & Guerri, C. (2009). Critical role of TLR4 response in the activation of microglia induced by ethanol. *Journal of Immunology*, *183*(7), 4733–4744. <http://dx.doi.org/10.4049/jimmunol.0803590>.
- Flora, G., Lee, Y. W., Nath, A., Maragos, W., Hennig, B., & Toborek, M. (2002). Methamphetamine-induced TNF-alpha gene expression and activation of AP-1 in discrete regions of mouse brain: Potential role of reactive oxygen intermediates and lipid peroxidation. *Neuromolecular Medicine*, *2*(1), 71–85. <http://dx.doi.org/10.1385/NMM:2:1:71>.
- Fujita, Y., Ishima, T., Kunitachi, S., Hagiwara, H., Zhang, L., Iyo, M., et al. (2008). Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antibiotic drug minocycline. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *32*(2), 336–339. <http://dx.doi.org/10.1016/j.pnpbp.2007.08.031>.
- Fujita, Y., Kunitachi, S., Iyo, M., & Hashimoto, K. (2012). The antibiotic minocycline prevents methamphetamine-induced rewarding effects in mice. *Pharmacology, Biochemistry, and Behavior*, *101*(2), 303–306. <http://dx.doi.org/10.1016/j.pbb.2012.01.005>.
- Ghitza, U. E., Zhai, H., Wu, P., Airavaara, M., Shaham, Y., & Lu, L. (2010). Role of BDNF and GDNF in drug reward and relapse: A review. *Neuroscience & Biobehavioral Reviews*, *35*(2), 157–171.
- Gibson, L. C., Hastings, S. F., McPhee, I., Clayton, R. A., Darroch, C. E., Mackenzie, A., et al. (2006). The inhibitory profile of Ibudilast against the human phosphodiesterase enzyme family. *European Journal of Pharmacology*, *538*(1–3), 39–42. <http://dx.doi.org/10.1016/j.ejphar.2006.02.053>.
- Gofflot, F., Chartoire, N., Vasseur, L., Heikkinen, S., Dembele, D., Le Merrer, J., et al. (2007). Systematic gene expression mapping clusters nuclear receptors according to their function in the brain. *Cell*, *131*(2), 405–418.

- Goldbach-Mansky, R., Dailey, N. J., Canna, S. W., Gelabert, A., Jones, J., Rubin, B. I., et al. (2006). Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *New England Journal of Medicine*, *355*(6), 581–592. <http://dx.doi.org/10.1056/NEJMoa055137>.
- Gramage, E., & Herradon, G. (2011). Connecting Parkinson's disease and drug addiction: Common players reveal unexpected disease connections and novel therapeutic approaches. *Current Pharmaceutical Design*, *17*(5), 449–461. <http://dx.doi.org/10.2174/138161211795164103>.
- Hashimoto, K., Tsukada, H., Nishiyama, S., Fukumoto, D., Kakiuchi, T., & Iyo, M. (2007). Protective effects of minocycline on the reduction of dopamine transporters in the striatum after administration of methamphetamine: A positron emission tomography study in conscious monkeys. *Biological Psychiatry*, *61*(5), 577–581. <http://dx.doi.org/10.1016/j.biopsych.2006.03.019>.
- Heaton, R. K., Clifford, D. B., Franklin, D. R., Jr., Woods, S. P., Ake, C., Vaida, F., et al. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, *75*(23), 2087–2096. <http://dx.doi.org/10.1212/WNL.0b013e318200d727>.
- Heberlein, A., Muschler, M., Wilhelm, J., Frieling, H., Lenz, B., Groschl, M., et al. (2010). BDNF and GDNF serum levels in alcohol-dependent patients during withdrawal. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(6), 1060–1064. <http://dx.doi.org/10.1016/j.pnpbp.2010.05.025>.
- Hirsch, E. C., & Hunot, S. (2009). Neuroinflammation in Parkinson's disease: A target for neuroprotection? *Lancet Neurology*, *8*(4), 382–397. [http://dx.doi.org/10.1016/S1474-4422\(09\)70062-6](http://dx.doi.org/10.1016/S1474-4422(09)70062-6).
- Hu, W., Lu, T., Chen, A., Huang, Y., Hansen, R., Chandler, L. J., et al. (2011). Inhibition of phosphodiesterase-4 decreases ethanol intake in mice. *Psychopharmacology*, *218*(2), 331–339. <http://dx.doi.org/10.1007/s00213-011-2290-8>.
- Hutchinson, M. R., Northcutt, A., Hiranita, T., Wang, X., Lewis, S., Thomas, J., et al. (2012). Opioid activation of toll-like receptor 4 contributes to drug reinforcement. *The Journal of Neuroscience*, *32*(33), 11187–11200.
- Hutchinson, M. R., Shavit, Y., Grace, P. M., Rice, K. C., Maier, S. F., & Watkins, L. R. (2011). Exploring the neuroimmunopharmacology of opioids: An integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. *Pharmacological Reviews*, *63*(3), 772–810.
- Hutchinson, M. R., Zhang, Y., Brown, K., Coats, B. D., Shridhar, M., Sholar, P. W., et al. (2008). Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: Involvement of toll-like receptor 4 (TLR4). *European Journal of Neuroscience*, *28*(1), 20–29.
- Johnson, B. A., & Ait-Daoud, N. (2010). Topiramate in the new generation of drugs: Efficacy in the treatment of alcoholic patients. *Current Pharmaceutical Design*, *16*(19), 2103–2112. <http://dx.doi.org/10.2174/138161210791516404>.
- Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: A pathology of motivation and choice. *The American Journal of Psychiatry*, *162*(8), 1403–1413. <http://dx.doi.org/10.1176/appi.ajp.162.8.1403>.
- Kapadia, R., Yi, J.-H., & Vemuganti, R. (2008). Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists. *Frontiers in Bioscience: A Journal and Virtual Library*, *13*, 1813–1826.
- Kells, A. P., Eberling, J., Su, X., Pivrotto, P., Bringas, J., Hadaczek, P., et al. (2010). Regeneration of the MPTP-lesioned dopaminergic system after convection-enhanced delivery of AAV2-GDNF. *Journal of Neuroscience*, *30*(28), 9567–9577. <http://dx.doi.org/10.1523/JNEUROSCI.0942-10.2010>.
- Ladenheim, B., Krasnova, I. N., Deng, X., Oyler, J. M., Poletini, A., Moran, T. H., et al. (2000). Methamphetamine-induced neurotoxicity is attenuated in transgenic mice with a null mutation for interleukin-6. *Molecular Pharmacology*, *58*(6), 1247–1256.

- Landreth, G. E., & Heneka, M. T. (2001). Anti-inflammatory actions of peroxisome proliferator-activated receptor gamma agonists in Alzheimer's disease. *Neurobiology of Aging*, 22(6), 937–944.
- LaVoie, M. J., Card, J. P., & Hastings, T. G. (2004). Microglial activation precedes dopamine terminal pathology in methamphetamine-induced neurotoxicity. *Experimental Neurology*, 187(1), 47–57. <http://dx.doi.org/10.1016/j.expneurol.2004.01.010>.
- Letendre, S., Paulino, A. D., Rockenstein, E., Adame, A., Crews, L., Cherner, M., et al. (2007). Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. *The Journal of Infectious Diseases*, 196(3), 361–370. <http://dx.doi.org/10.1086/519285>.
- Litten, R. Z., Egli, M., Heilig, M., Cui, C., Fertig, J. B., Ryan, M. L., et al. (2012). Medications development to treat alcohol dependence: A vision for the next decade. *Addiction Biology*, 17(3), 513–527. <http://dx.doi.org/10.1111/j.1369-1600.2012.00454.x>.
- Loftis, J. M., Choi, D., Hoffman, W., & Huckans, M. S. (2011). Methamphetamine causes persistent immune dysregulation: A cross-species, translational report. *Neurotoxicity Research*, 20(1), 59–68. <http://dx.doi.org/10.1007/s12640-010-9223-x>.
- Logrip, M. L., & Zorrilla, E. P. (2012). Stress history increases alcohol intake in relapse: Relation to phosphodiesterase 10A. *Addiction Biology*, 17(5), 920–933. <http://dx.doi.org/10.1111/j.1369-1600.2012.00460.x>.
- Maeda, T., Kiguchi, N., Fukazawa, Y., Yamamoto, A., Ozaki, M., & Kishioka, S. (2007). Peroxisome proliferator-activated receptor gamma activation relieves expression of behavioral sensitization to methamphetamine in mice. *Neuropsychopharmacology*, 32(5), 1133–1140.
- Mayfield, J., Ferguson, L., & Harris, R. A. (2013). Neuroimmune signaling: A key component of alcohol abuse. *Current Opinion in Neurobiology*, 23(4), 513–520.
- McIver, S. R., Muccigrosso, M. M., & Haydon, P. G. (2012). The effect of doxycycline on alcohol consumption and sensitivity: Consideration for inducible transgenic mouse models. *Experimental Biology and Medicine (Maywood, N.J.)*, 237(10), 1129–1133. <http://dx.doi.org/10.1258/ebm.2012.012029>.
- Melis, M., Carta, S., Fattore, L., Tolu, S., Yasar, S., Goldberg, S. R., et al. (2010). Peroxisome proliferator-activated receptors-alpha modulate dopamine cell activity through nicotinic receptors. *Biological Psychiatry*, 68(3), 256–264.
- Melis, M., Pillolla, G., Luchicchi, A., Muntoni, A. L., Yasar, S., Goldberg, S. R., et al. (2008). Endogenous fatty acid ethanolamides suppress nicotine-induced activation of mesolimbic dopamine neurons through nuclear receptors. *The Journal of Neuroscience*, 28(51), 13985–13994.
- Miranda, R., Jr., MacKillop, J., Monti, P. M., Rohsenow, D. J., Tidey, J., Gwaltney, C., et al. (2008). Effects of topiramate on urge to drink and the subjective effects of alcohol: A preliminary laboratory study. *Alcoholism, Clinical and Experimental Research*, 32(3), 489–497. <http://dx.doi.org/10.1111/j.1530-0277.2007.00592.x>.
- Mishra, M. K., & Basu, A. (2008). Minocycline neuroprotects, reduces microglial activation, inhibits caspase 3 induction, and viral replication following Japanese encephalitis. *Journal of Neurochemistry*, 105(5), 1582–1595. <http://dx.doi.org/10.1111/j.1471-4159.2008.05238.x>.
- Mizuno, T., Kurotani, T., Komatsu, Y., Kawanokuchi, J., Kato, H., Mitsuma, N., et al. (2004). Neuroprotective role of phosphodiesterase inhibitor ibudilast on neuronal cell death induced by activated microglia. *Neuropharmacology*, 46(3), 404–411. <http://dx.doi.org/10.1016/j.neuropharm.2003.09.009>.
- Moallem, N., & Ray, L. A. (2012). Quetiapine improves response inhibition in alcohol dependent patients: A placebo-controlled pilot study. *Pharmacology, Biochemistry, and Behavior*, 100(3), 490–493. <http://dx.doi.org/10.1016/j.pbb.2011.10.012>.
- Moreno, S., Farioli-Vecchioli, S., & Ceru, M. (2004). Immunolocalization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS. *Neuroscience*, 123(1), 131–145.

- Munzar, P., Li, H., Nicholson, K. L., Wiley, J. L., & Balster, R. L. (2002). Enhancement of the discriminative stimulus effects of phencyclidine by the tetracycline antibiotics doxycycline and minocycline in rats. *Psychopharmacology*, *160*(3), 331–336. <http://dx.doi.org/10.1007/s00213-001-0989-7>.
- Narita, M., Miyatake, M., Shibasaki, M., Shindo, K., Nakamura, A., Kuzumaki, N., et al. (2006). Direct evidence of astrocytic modulation in the development of rewarding effects induced by drugs of abuse. *Neuropsychopharmacology*, *31*(11), 2476–2488. <http://dx.doi.org/10.1038/sj.npp.1301007>.
- Niwa, M., Nitta, A., Yamada, Y., Nakajima, A., Saito, K., Seishima, M., et al. (2007). An inducer for glial cell line-derived neurotrophic factor and tumor necrosis factor- α protects against methamphetamine-induced rewarding effects and sensitization. *Biological Psychiatry*, *61*(7), 890–901. <http://dx.doi.org/10.1016/j.biopsych.2006.06.016>.
- Page, C. P., & Spina, D. (2011). Phosphodiesterase inhibitors in the treatment of inflammatory diseases. *Handbook of Experimental Pharmacology*, *204*, 391–414. http://dx.doi.org/10.1007/978-3-642-17969-3_17.
- Panlilio, L. V., Justinova, Z., Mascia, P., Pistis, M., Luchicchi, A., Lecca, S., et al. (2012). Novel use of a lipid-lowering fibrate medication to prevent nicotine reward and relapse: Preclinical findings. *Neuropsychopharmacology*, *37*(8), 1838–1847.
- Parsons, T. D., Braaten, A. J., Hall, C. D., & Robertson, K. R. (2006). Better quality of life with neuropsychological improvement on HAART. *Health and Quality of Life Outcomes*, *4*, 11. <http://dx.doi.org/10.1186/1477-7525-4-11>.
- Pascual, M., Blanco, A. M., Cauli, O., Minarro, J., & Guerri, C. (2007). Intermittent ethanol exposure induces inflammatory brain damage and causes long-term behavioural alterations in adolescent rats. *European Journal of Neuroscience*, *25*(2), 541–550. <http://dx.doi.org/10.1111/j.1460-9568.2006.05298.x>.
- Petrasek, J., Bala, S., Csak, T., Lippai, D., Kodys, K., Menashy, V., et al. (2012). IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *Journal of Clinical Investigation*, *122*(10), 3476–3489. <http://dx.doi.org/10.1172/JCI60777>.
- Pickworth, W. B., Fant, R. V., & Henningfield, J. E. (1997). Inhibition of prostaglandin synthesis and effects of ethanol and pentobarbital in humans. *Journal of Pharmacology and Experimental Therapeutics*, *283*(1), 274–280.
- Pistis, M., & Melis, M. (2010). From surface to nuclear receptors: The endocannabinoid family extends its assets. *Current Medicinal Chemistry*, *17*(14), 1450–1467.
- Plebani, J. G., Ray, L. A., Morean, M. E., Corbin, W. R., MacKillop, J., Amlung, M. T., et al. (2012). Human laboratory paradigms in alcohol research. *Alcoholism, Clinical and Experimental Research*, *36*(6), 972–983. <http://dx.doi.org/10.1111/j.1530-0277.2011.01704.x>.
- Qin, L., & Crews, F. T. (2012). Chronic ethanol increases systemic TLR3 agonist-induced neuroinflammation and neurodegeneration. *Journal of Neuroinflammation*, *9*, 130. <http://dx.doi.org/10.1186/1742-2094-9-130>.
- Ray, L. A., Bujarski, S., Chin, P. F., & Miotto, K. (2012). Pharmacogenetics of naltrexone in Asian Americans: A randomized placebo-controlled laboratory study. *Neuropsychopharmacology*, *37*(2), 445–455. <http://dx.doi.org/10.1038/npp.2011.192>.
- Ray, L. A., Chin, P. F., Heydari, A., & Miotto, K. (2011). A human laboratory study of the effects of quetiapine on subjective intoxication and alcohol craving. *Psychopharmacology*, *217*(3), 341–351. <http://dx.doi.org/10.1007/s00213-011-2287-3>.
- Ray, L. A., Courtney, K. E., Ghahremani, D. G., Miotto, K., Brody, A., & London, E. D. (2014). Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers: Human laboratory findings. *Psychopharmacology*. <http://dx.doi.org/10.1007/s00213-014-3519-0>.
- Ray, L. A., & Hutchison, K. E. (2007). Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: A double-blind placebo-controlled study.

- Archives of General Psychiatry*, 64(9), 1069–1077. <http://dx.doi.org/10.1001/archpsyc.64.9.1069>.
- Ray, L. A., Hutchison, K. E., & Tarter, M. (2010). Application of human laboratory models to pharmacotherapy development for alcohol dependence. *Current Pharmaceutical Design*, 16(19), 2149–2158. <http://dx.doi.org/10.2174/138161210791516422>.
- Ray, L. A., Lunny, K., Bujarski, S., Moallem, N., Krull, J. L., & Miotto, K. (2013). The effects of varenicline on stress-induced and cue-induced craving for cigarettes. *Drug and Alcohol Dependence*, 131(1–2), 136–142. <http://dx.doi.org/10.1016/j.drugalcdep.2012.12.015>.
- Ray, L. A., Mackillop, J., & Monti, P. M. (2010). Subjective responses to alcohol consumption as endophenotypes: Advancing behavioral genetics in etiological and treatment models of alcoholism. *Substance Use and Misuse*, 45(11), 1742–1765. <http://dx.doi.org/10.3109/10826084.2010.482427>.
- Ray, L. A., Miranda, R., Jr., MacKillop, J., McGeary, J., Tidey, J. W., Rohsenow, D. J., et al. (2009). A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. *Experimental and Clinical Psychopharmacology*, 17(2), 122–129. <http://dx.doi.org/10.1037/a0015700>.
- Rippeth, J. D., Heaton, R. K., Carey, C. L., Marcotte, T. D., Moore, D. J., Gonzalez, R., et al. (2004). Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. *Journal of the International Neuropsychological Society: JINS*, 10(1), 1–14. <http://dx.doi.org/10.1017/S1355617704101021>.
- Rolan, P., Hutchinson, M., & Johnson, K. (2009). Ibudilast: A review of its pharmacology, efficacy and safety in respiratory and neurological disease. *Expert Opinion on Pharmacotherapy*, 10(17), 2897–2904. <http://dx.doi.org/10.1517/14656560903426189> (Review).
- Rocha, S. M., Cristovão, A. C., Campos, F. L., Fonseca, C. P., & Baltazar, G. (2012). Astrocyte-derived GDNF is a potent inhibitor of microglial activation. *Neurobiology of Disease*, 47(3), 407–415. <http://dx.doi.org/10.1016/j.nbd.2012.04.014>.
- Sailasuta, N., Abulseoud, O., Harris, K. C., & Ross, B. D. (2010). Glial dysfunction in abstinent methamphetamine abusers. *Journal of Cerebral Blood Flow and Metabolism*, 30(5), 950–960. <http://dx.doi.org/10.1038/jcbfm.2009.261>.
- Sarruf, D. A., Yu, F., Nguyen, H. T., Williams, D. L., Printz, R. L., Niswender, K. D., et al. (2009). Expression of peroxisome proliferator-activated receptor-gamma in key neuronal subsets regulating glucose metabolism and energy homeostasis. *Endocrinology*, 150(2), 707–712. <http://dx.doi.org/10.1210/en.2008-0899>.
- Sekine, Y., Ouchi, Y., Sugihara, G., Takei, N., Yoshikawa, E., Nakamura, K., et al. (2008). Methamphetamine causes microglial activation in the brains of human abusers. *Journal of Neuroscience*, 28(22), 5756–5761. <http://dx.doi.org/10.1523/JNEUROSCI.1179-08.2008>.
- Shavit, Y., Wolf, G., Goshen, I., Livshits, D., & Yirmiya, R. (2005). Interleukin-1 antagonizes morphine analgesia and underlies morphine tolerance. *Pain*, 115(1–2), 50–59. <http://dx.doi.org/10.1016/j.pain.2005.02.003>.
- Sidoryk-Wegrzynowicz, M., Wegrzynowicz, M., Lee, E., Bowman, A. B., & Aschner, M. (2011). Role of astrocytes in brain function and disease. *Toxicologic Pathology*, 39(1), 115–123. <http://dx.doi.org/10.1177/0192623310385254>.
- Silverstein, P. S., Shah, A., Gupte, R., Liu, X., Piepho, R. W., Kumar, S., et al. (2011). Methamphetamine toxicity and its implications during HIV-1 infection. *Journal of Neurovirology*, 17(5), 401–415. <http://dx.doi.org/10.1007/s13365-011-0043-4>.
- Sofuoglu, M., Mooney, M., Kosten, T., Waters, A., & Hashimoto, K. (2011). Minocycline attenuates subjective rewarding effects of dextroamphetamine in humans. *Psychopharmacology*, 213(1), 61–68. <http://dx.doi.org/10.1007/s00213-010-2014-5>.
- Stopponi, S., Somaini, L., Cippitelli, A., Cannella, N., Braconi, S., Kallupi, M., et al. (2011). Activation of nuclear PPAR γ receptors by the antidiabetic agent pioglitazone suppresses alcohol drinking and relapse to alcohol seeking. *Biological Psychiatry*, 69(7), 642–649.
- Suzumura, A., Ito, A., & Mizuno, T. (2003). Phosphodiesterase inhibitors suppress IL-12 production with microglia and T helper 1 development. *Multiple Sclerosis*, 9(6), 574–578.

- Suzumura, A., Ito, A., Yoshikawa, M., & Sawada, M. (1999). Ibudilast suppresses TNF α production by glial cells functioning mainly as type III phosphodiesterase inhibitor in the CNS. *Brain Research*, *837*(1–2), 203–212. [http://dx.doi.org/10.1016/S0006-8993\(99\)01666-2](http://dx.doi.org/10.1016/S0006-8993(99)01666-2).
- Thomas, D. M., Francescutti-Verbeem, D. M., & Kuhn, D. M. (2008). Methamphetamine-induced neurotoxicity and microglial activation are not mediated by fractalkine receptor signaling. *Journal of Neurochemistry*, *106*(2), 696–705. <http://dx.doi.org/10.1111/j.1471-4159.2008.05421.x>.
- Thomas, D. M., & Kuhn, D. M. (2005). MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. *Brain Research*, *1050*(1–2), 190–198. <http://dx.doi.org/10.1016/j.brainres.2005.05.049>.
- Wakita, H., Tomimoto, H., Akiguchi, I., Lin, J. X., Ihara, M., Ohtani, R., et al. (2003). Ibudilast, a phosphodiesterase inhibitor, protects against white matter damage under chronic cerebral hypoperfusion in the rat. *Brain Research*, *992*(1), 53–59. <http://dx.doi.org/10.1016/j.brainres.2003.08.028>.
- Wang, C., Yang, X. M., Zhuo, Y. Y., Zhou, H., Lin, H. B., Cheng, Y. F., et al. (2012). The phosphodiesterase-4 inhibitor rolipram reverses A β -induced cognitive impairment and neuroinflammatory and apoptotic responses in rats. *The International Journal of Neuropsychopharmacology*, *15*(6), 749–766. <http://dx.doi.org/10.1017/S1461145711000836>.
- Wen, R. T., Zhang, M., Qin, W. J., Liu, Q., Wang, W. P., Lawrence, A. J., et al. (2012). The phosphodiesterase-4 (PDE4) inhibitor rolipram decreases ethanol seeking and consumption in alcohol-preferring Fawn-Hooded rats. *Alcoholism, Clinical and Experimental Research*, *36*(12), 2157–2167. <http://dx.doi.org/10.1111/j.1530-0277.2012.01845.x>.
- Woods, J. W., Tanen, M., Figueroa, D. J., Biswas, C., Zycband, E., Moller, D. E., et al. (2003). Localization of PPAR δ in murine central nervous system: Expression in oligodendrocytes and neurons. *Brain Research*, *975*(1), 10–21.
- Wu, Y., Lousberg, E. L., Moldenhauer, L. M., Hayball, J. D., Coller, J. K., Rice, K. C., et al. (2012). Inhibiting the TLR4-MyD88 signalling cascade by genetic or pharmacological strategies reduces acute alcohol-induced sedation and motor impairment in mice. *British Journal of Pharmacology*, *165*(5), 1319–1329. <http://dx.doi.org/10.1111/j.1476-5381.2011.01572.x>.
- Wu, Y., Lousberg, E. L., Moldenhauer, L. M., Hayball, J. D., Robertson, S. A., Coller, J. K., et al. (2011). Attenuation of microglial and IL-1 signaling protects mice from acute alcohol-induced sedation and/or motor impairment. *Brain, Behavior, and Immunity*, *25*(Suppl. 1), S155–S164. <http://dx.doi.org/10.1016/j.bbi.2011.01.012>.
- Yadav, A., & Collman, R. G. (2009). CNS inflammation and macrophage/microglial biology associated with HIV-1 infection. *Journal of Neuroimmune Pharmacology: The Official Journal of the Society on NeuroImmune Pharmacology*, *4*(4), 430–447. <http://dx.doi.org/10.1007/s11481-009-9174-2>.
- Yan, Y., Yamada, K., Niwa, M., Nagai, T., Nitta, A., & Nabeshima, T. (2007). Enduring vulnerability to reinstatement of methamphetamine-seeking behavior in glial cell line-derived neurotrophic factor mutant mice. *The FASEB Journal*, *21*(9), 1994–2004. <http://dx.doi.org/10.1096/fj.06-7772com>.
- Yoshimura, T., Usui, H., Takahashi, N., Yoshimi, A., Saito, S., Aleksic, B., et al. (2011). Association analysis of the GDNF gene with methamphetamine use disorder in a Japanese population. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(5), 1268–1272. <http://dx.doi.org/10.1016/j.pnpbp.2011.04.003>.
- Zalewska-Kasubaska, J., Bajer, B., Gorska, D., Andrzejczak, D., Dyr, W., & Bienkowski, P. (2013). Effect of repeated treatment with topiramate on voluntary alcohol intake and beta-endorphin plasma level in Warsaw alcohol high-preferring rats. *Psychopharmacology*, *225*(2), 275–281. <http://dx.doi.org/10.1007/s00213-012-2812-z>.

