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Toll-like receptor 4, a novel target to tackle drug addiction?

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Abstract

Drug addiction is a chronic brain disease characterized by compulsive drug-seeking and drug-taking behaviors despite the major negative consequences. Current well-established neuronal underpinnings of drug addiction have promoted the substantial progress in understanding this disorder. However, non-neuronal mechanisms of drug addiction have long been underestimated. Fortunately, increased evidence indicates that neuroimmune system, especially Toll-like receptor 4 (TLR4) signaling, plays an important role in the different stages of drug addiction. Drugs like opioids, psychostimulants, and alcohol activate TLR4 signaling and enhance the proinflammatory response, which is associated with drug reward-related behaviors. While extensive studies have shown that inhibition of TLR4 attenuated drug-related responses, there are conflicting findings implicating that TLR4 signaling may not be essential to drug addiction. In this chapter, preclinical and clinical studies will be discussed to further evaluate whether TLR4-based neuroimmune pharmacotherapy can be used to treat drug addiction. Furthermore, the possible mechanisms underlying the effects of TLR4 inhibition in modulating drug-related behaviors will also be discussed.

Keywords

Toll-like receptor 4; drug addiction; non-neuronal mechanisms; opioid; psychostimulants; alcohol

1 Introduction

Drug addiction is a chronic brain disease characterized by compulsive drug-seeking and drug-taking behaviors despite the major negative consequences (1). It is one of the leading causes of disability and fatality worldwide today, with a huge annual cost related to crime, reduced work productivity and health care (2). Current studies focusing on neuronal adaptations have yield much progress in the research of drug addiction. For example,

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Conflict of interest

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it is suggested that molecular, synaptic, and neurocircuitry neuroadaptations combine to promote the transition to drug addiction, which is comprised of increased incentive salience, decreased reward, increased stress and decreased executive function (3). However, non-neuronal underpinnings of drug addiction have long been underestimated (4). Fortunately, a growing body of studies indicate that neuroimmune system plays an important role in the different stages of drug addiction, including binge/intoxication, withdrawal and relapse (5-7).

Toll-like receptors (TLRs) are a family of pattern recognition receptors (PPRs) in the innate immune system which detects and respond both to exogenous pathogen associated molecular patterns (PAMPs) and endogenous danger associated molecular patterns (DAMPs) (8-10). Toll-like receptor 4 (TLR4) is one of the TLRs and its activation leads to enhanced production of proinflammatory cytokines and chemokines. In the brain, TLR4 is mainly expressed in glial cells like microglia and astrocytes (11). Upon recognition of PAMPs or DAMPs, TLR4 signals through two distinct pathways, the myeloid differentiation primary response protein 88 (MyD88)-dependent and MyD88-independent pathway (12). In the MyD88-dependent pathway, the signal transduces through activation of Interleukin-1 receptor associated kinases (IRAKs, like IRAK1 and IRAK4) and TNF receptor associated factor 6 (TRAF6), which subsequently promotes the phosphorylation of inhibitors of nuclear factor κB kinases (IKK). The activation in turn leads to the NFκB activation and the production of proinflammtory cytokines and chemokines (13). Alternatively, in MyD88-independent pathway, the adaptor protein TRIF, TRAF3 and interferon regulatory factor 3 (IRF3) are involved (14).

TLR4 signaling is suggested to be involved in several neuropsychiatric disorders, including major depressive disorders, neurodegenerative disorders and impulsive control (15-19). As drugs of abuse can be considered as “exogenous”, it is recognized that drugs of different class activate TLR4 signaling and induce proinflammatory responses. Emerging evidence has suggested the important role of TLR4 signaling in regulating drug addiction (20). In this chapter, we will discuss the preclinical and clinical evidence of TLR4 signaling modulation in drug addiction (i.e. opioid, psychostimulants, and alcohol addiction), in order to evaluate whether TLR4-based neuroimmune pharmacotherapy can be used to as novel treatment for this disorder. Furthermore, we will also discuss the possible mechanisms underlying the effects of TLR4 antagonism in regulating drug-related behaviors.

2 Role of TLR4 signaling in drug addiction

2.1 Opioid

Although the major targets of opioids in the brain are opioid receptors, which probably mediate most of the effects of opioids within the CNS, growing evidence has demonstrated that opioids can also interact with TLRs, among which the TLR4 is best-studied in opioid addiction. In vitro evidence suggests that the molecular interaction between the opioid system and TLR4 is complex. The opioid antagonist naloxone inhibited the classic TLR4 agonist LPS-induced secretion of IL-β and morphological changes of microglia in mixed brain cell cultures (21). In contrast, both morphine and fentanyl could activate TLR4 in unstimulated cells, even though the activation level was much lower than that was stimulated

by LPS (22). Morphine exposure could elevate TLR4 protein and mRNA expression as well as activate TLR4-related signaling pathways in the NAc (23). Interestingly, morphine and fentanyl could attenuate LPS-induced activation of TLR4 in a non-competitive manner (22). These findings suggest that opioids might interact with TLR4 and act as its partial agonists. Besides *in vitro* reports, many behavioral studies have explored the role of TLR4 in mediating the effects of opioids, including addictive properties (24).

Many pharmacological studies using the TLR4 antagonists such as (+)-naloxone and LPS-RS have implicated that TLR4 participates in the development of opioid addiction and relapse. (+)-Naloxone blocked morphine-induced CPP, remifentanil self-administration, drug-induced reinstatement of heroin-seeking behavior, and dopamine release in the NAc (5, 25). Another study found that microinjection of TLR4 antagonist LPS-RS into the VTA prevented the conditioning and maintenance, but not expression, of morphine-induced CPP (26). In the same study, it was suggested that the STAT3 might mediate the function of TLR4 since LPS-RS prevented morphine-induced activation of STAT3 in the VTA (26). Interestingly, microinjection of LPS-RS into the NAc did not affect drug-induced reinstatement of heroin-seeking, suggesting that the NAc might not be the critical brain site where TLR4 regulates opioid addiction (25). Consistent with pharmacological findings, global deletion of tlr4 or myd88 gene prevented oxycodone-induced CPP in mice (5). Studies that evaluated the effects of ibudilast also provided some implications on the role of TLR4 in opioid addiction. Ibudilast is principally a PDE4 inhibitor but also exerts antagonist property at TLR4. Moreover, ibudilast could decrease morphine-induced dopamine release in the NAc in rodents (27).

Opioid withdrawal has been demonstrated to participate in the development of opioid addiction via a negative reinforcing mechanism (28). Several pharmacological studies have indicated that TLR4 also regulates opioid withdrawal. The TLR4 antagonist (+)-naloxone could significantly attenuate the μ opioid receptor antagonist (−)-naloxone-precipitated withdrawal behavior in morphine-dependent rats (22). The TLR4 antagonist ibudilast reduced spontaneous withdrawal-induced hyperactivity in rats (29). In contrast, the genetic deletion of TLR4 genes did not affect opioid withdrawal. Compared to wildtype Balb/c mice, both TLR4-KO or MyD88-KO mice (Balb/c background) showed similar degrees of naloxone-precipitated jumping behavior, an animal model of opioid withdrawal (30). A more recent study also reported similar findings that both TLR4 mutant and null mice showed normal morphine withdrawal behaviors (31). These findings suggest that the tlr4 gene might not be critical for opioid withdrawal. However, it should be noted that global deletion of TLR4 or MyD88 genes may result in changes in many other genes that could compensate for the loss in the function of TLR4 signaling. Therefore, future studies using conditional deletion of TLR4 are required to address the role of the tlr4 gene in the development of opioid addiction.

Nevertheless, not all literature supports the view that TLR4 mediates opioid addiction. Acute injection of (+)-naltrexone did not affect incubated cue-induced heroin-seeking or extended access heroin self-administration. Whereas chronic administration of (+)-naltrexone reduced incubated cue-induced heroin-seeking but did not affect ongoing extended access heroin self-administration (32). One explanation is that TLR4 signaling might only participate

in some particular opioid addiction-related behaviors. Furthermore, many factors such as opioid dose, history of drug use, and treatment strategy (i.e., acute or chronic treatment) are essential factors that might dramatically influence the pharmacological effects of TLR4 antagonists on opioid addiction.

In clinical settings, TLR4 antagonist ibudilast was tested for its efficacy in attenuating opioid-related effects. ibudilast was shown to reduce ratings of drug liking following 15 mg of oxycodone and heroin craving (33). Meanwhile, ibudilast also decreased drug breakpoint under the 15 mg but not 30 mg oxycodone condition in a progressive-ratio oxycodone self-administration task, suggesting that ibudilast attenuated, at least to some extent, the reinforcing effects of oxycodone (33). In contrary, ibudilast was unable to consistently affect subjective effect ratings of oxycodone in opioid-dependent volunteers in another study (34). Nevertheless, it decreased ratings of withdrawal symptoms on some SOWS items during detoxification (35).

2.2 Psychostimulants

2.2.1 Cocaine—Cocaine activates innate immune system within the brain through its interaction with TLR4 (36, 37), possibly in a region-specific manner (38). Cocaine docked to the same binding site of MD-2 as the classical TLR4 agonist LPS and increased the proinflammatory responses. This effect is associated with cocaine-induced dopamine release and cocaine reward, an effect that can be blocked by TLR4 antagonist (+)-naloxone (7). Pretreatment of (+)-naloxone or LPS-RS attenuated cocaine-induced elevation of extracellular dopamine in the NAc, while they alone did not affect the dopamine signaling. Meanwhile, non-TLR4 modulator, neurotensin, did not affect cocaine-induced dopamine elevation, suggesting the specificity to TLR4 receptor. Moreover, pretreatment of TLR4 antagonists blocked the development of cocaine CPP and self-administration, while sparing food-maintained responses (7). Consistently, TLR4 mutant mice showed less responses to cocaine self-administration and cocaine reward learning, suggesting the importance of TLR4 in cocaine reinforcement (4, 7).

However, inconsistent findings suggest that TLR4 may not be crucial for cocaine-related behavioral and neurochemical alterations. Tanda and colleagues found that (+)-naloxone or (+)-naltrexone did not decrease cocaine or heroin-induced dopamine levels in the NAc shell (39). Both antagonists attenuated cocaine or remifentanil self-administration at a higher dose that decreased food-maintained responding as well, suggesting a lack of selectivity on reward behaviors (39). In addition, (+)-naloxone did not interact with cocaine subjective effects in the drug-discrimination studies (39). It is further shown that a TLR4 agonist reactivated microglia, suppressed striatal synaptic strength and finally decreased cocaine-induced sensitization (40). These results challenge the current knowledge of TLR4 in cocaine addiction, yet call for further examination and clarification of the role of TLR4 in cocaine-related responses.

A recent clinical study showed that cocaine users had a significant increase in IL-6 compared with control group, demonstrating an activation of the immune system (41). Nonetheless, there are few clinical studies examining the effect of neuroimmune modulators

in regulating cocaine addiction. More clinical investigations focusing on the possibility of neuroimmune signaling as novel therapeutic target for cocaine addiction are needed.

2.2.2 Methamphetamine—Methamphetamine(METH) exposure activates glia cells and enhances proinflammtory cytokines release (42-44). Indeed, METH was shown to bind to MD-2, the key receptor of TLR4 and enhanced CD11b and IL-6 in mRNAs in the VTA (45). Increased evidence suggests that modulation of TLR4 can reduce METH-related behavioral and neurochemical effects (46-48). TLR4 antagonists (+)-naloxone and LPS-RS reduced METH-induced elevation of dopamine in the NAc (45). Ibudilast, AV1013, and minocycline decreased METH-induced behavioral sensitization, drug-primed and cue-induced METH-seeking (49, 50), METH-induced conditioned place preference (CPP) (46, 51) and METH self-administration(52). These findings indicate an essential role of glia activation underlying the rewarding effects of METH. Interestingly, it is also implicated that cannabinoids Δ9-tetrahydrocannabinol and cannabidiol might be effective for protection of METH-induced inflammation though modulation of TLR4 and NF-κB signaling (53).

Clinical studies also yielded inspiring results that neuroimmune modulators could be effective against METH-related symptoms. Initially, a case study reported that minocycline significantly improved the psychotic symptoms in METH use disorders (54). Later, in an early-stage study, ibudilast reduced several METH-related subjective effects including High, Good, Stimulated and Like, suggesting its effect in attenuating the reward-associated subjective effects of METH (55). Moreover, ibudilast is also shown to improve the attention performance during the early abstinence from METH dependence (56). All these results implicated that neuroimmune modulators may have protective effects on METH-related disorders. However, a most recent clinical trial showed that ibudilast did not affect METH abstinence (57). This randomized, placebo-controlled trial included 64 patients with METH use disorders for the 12-week ibudilast treatment and urine specimen was collected for drug screen and study assessments (57). Ibudilast was well tolerated yet did not alter METH absitinence (57). No significant correlation between serum ibudilast levels and METH use during treatment for patients was observed (57). These results seem discouraging, yet it is still early to conclude that ibudilast has no effect on METH-related actions. No further assessment on the effect of ibudilast on METH intake or craving was provided. Indeed, a pilot clinical study showed that ibudilast could reduce METH-induced elevation of peripheral markers of inflammation, which may underlie the mechanisms of METH addiction. As such, more research investigating the effects of TLR4 modulation in METH-taking or relapse could add valuable information to the field.

2.2.3 Nicotine—Currently, there are no study examining the role of TLR4 in nicotine addiction. Although it is suggested that nicotine increased the expression of TLR4 and also up-regulated TLR4-related proinflammatory responses *in vitro*(58-60*),* less is known about whether TLR4 is involved in nicotine reward or withdrawal. Interestingly, a recent clinical study showed a potential association between *TLR4* polymorphism and lifetime smoking (61). Based on the study from 514 bipolar disorder patients, El-Hadi and colleagues found that rs10759932 was significantly associated with tobacco smoking (61). This finding suggests the involvement of TLR4 in smoking, or further, nicotine addiction.

However, studies also suggest that nicotine attenuates neuroinflammation induced by microglia activation in the brain (62, 63), possibly through TLR4 signaling (64). Nicotine and its metabolite cotinine targeted TLR4 co-receptor, MD-2, and inhibited LPS-induced production of TNF-α and nitric oxide, and further blocked microglia activation (64). Moreover, this effect cannot be abolished by nicotinic acetylcholine receptor (nAChR) inhibitor or nAChRs siRNA (64). These results seem inconsistent and add more complexity to the role of TLR4 in nicotine response.

2.3 Ethanol

Neuroinflammation contributes to the establishment of addiction of several substances, including alcohol. *In vitro* and *in vivo* studies have shown that ethanol produces neuroinflammation at least partially through TLR4 signaling pathway and leads to the activation of NFκB (65, 66). For example, adolescent binge drinking increases the TLR4 expression in the adult prefrontal cortex, which is correlated with deficits in reversal learning and increased preservative behaviors (67). Bing drinking also promoted the IL-1β mRNA expression in the basolateral amygdala (BLA). Consistently, intra-BLA infusions of IL-1 receptor antagonist (IL-1Ra) decreased the alcohol consumption without altering sucrose drinking and locomotion in mice (68). Furthermore, studies utilized TLR4 transgenic animal models showed that TLR4 deficiency prevented ethanol-induced neuroinflammation along with synaptic changes and long-term behavioral and cognitive alterations (66, 69-73). Consistently, TLR4 antagonists like (+)-Naltrexone and Nalmefene prevented TLR4 activation and inhibited alcohol-induced upregulations of proinflammatory responses as well as alcohol intake and reward (74-76). However, a recent comprehensive study showed that TLR4 may not be essential to excessive alcohol drinking (77). Using different species, different tests of alcohol consumption and different methods to inhibit TLR4 signaling, they found that TLR4 inhibition did not affect the drinking-in-the-dark or two-bottle choice chronic ethanol intake or ethanol self-administration (77). This study questioned the essentiality of TLR4 in alcohol reward. Nevertheless, they did agree on the effect of TLR4 modulation in alcohol-induced sedation and GABA receptor function (77).

Despite the complex results from preclinical studies, much efforts have been put on whether TLR4-related neuroimmune responses regulate alcohol intake in patients with alcohol use disorders (AUD). Studies showed that AUD patients had altered TLR4 methylation, which is correlated with alcohol consumption patterns (78, 79). Post-mortem human also showed upregulated TLR4-related immunoreactivity cells that correlated with lifetime alcohol consumption (80), although alcohol withdrawal may have differentiated effects (81). In a randomized, placebo controlled clinical study, however, ibudilast did not affect the subjective responses to alcohol. Meanwhile, it attenuated alcohol-induced stimulant and mood-altering effects in patients with more depressive symptoms (82), while other appetitive responses, like craving for high-fat/ high-sugar diet, was not altered (83). These results raised a question whether improvement of depressive symptomatology should be considered as a measurement for potential pharmacotherapies. Nevertheless, we are still at the very beginning to examine TLR4 as promising therapeutic target for the treatment of alcohol addiction, more comprehensive studies with larger sample size are warranted.

3 Possible mechanisms underlying the role of TLR4 signaling in drug addiction

Apart from the traditional neuronal mechanisms which involves dopaminergic, glutamatergic and GABAergic system, drugs of abuse-induced glia activation are believed to contribute to the development of drug addiction. Opioid, psychostimulants, and alcohol all bind to the accessory receptor MD-2 and activate TLR4. This activation promotes the release of proinflammatory cytokines and chemokines, which subsequently alters the neuroadaptations and synaptic plasticity that is related to drug-induced aberrant behaviors. TLR4 is showed to play a role in NAc synaptic physiology and drug reward behavior (4). TLR4-KO animals demonstrated a significantly decreased AMPA receptor/NMDA receptor ratio (A/N ratio) in the NAc core, suggesting a decrease in postsynaptic strength caused by a reduced AMPAR transmission or increased NMDAR transmission (4). Meanwhile, TLR4-KO D1(−) MSNs showed significant slower NMDAR decay kinetics compared with WT, suggesting an altered NMDAR stoichiometry (4). Because altered NMDARs in the NAc MSNs are related to behavioral adaptations affecting motivation and reward-associated learning, it is further shown that TLR4-KO mice exhibit deficits in long-term depression in the NAc core, paralleled with deficits in drug reward learning (4). These resluts showed a direct association between TLR4 and drug-induced neuroadaptations.

The downstream effectors of TLR4 may also play a part in regulating drug addiction. Our recent study examined the role of IRAK4, a downstream molecule of TLR4 signaling, in opioid addiction. We found that IRAK4 antagonist PF06650833 reduced cue-induced reinstatement of morphine-seeking and fentanyl-seeking (84). Morphine self-administration induced activation of IRAK4 in the NAc, which was accompanied by increases in IKKα/β activity and expression level of soluble TNFα (84). Furthermore, microinjection of RF06650833 into the NAc reduced cue-induced reinstatement of morphine-seeking (84). As IRAK4 is one of the keynotes of the TLR4 signaling cascade, our results might suggest that TLR4 might participate in the cue-induced reinstatement of morphine-seeking via the IRAK4 signaling pathway.

Immune factors like TNF-α and IL-β that are involved in the modulation of synaptic functions probably participate in drug reward as well. TNF-α is a key effector in the TLR4 signaling, and inhibition of TNF-α abolishes TLR4-mediated responses (85, 86). It is reported that TNF-α is involved in cocaine-induced plasticity (40). Drugs of abuse activate the glia cells in the NAc, which subsequently enhance the production of TNF-α. TNF-α is known to regulate the internalization of synaptic AMPA receptors (87). A recent study showed that cocaine activates striatal microglia and promotes TNF-α production, which suppresses the glutamatergic synaptic strength in the NAc core (40). Besides the AMPARs, TNF-α is also suggested to regulate the activity of presynaptic metabotropic glutamate receptors and $GABA_A$ receptors (88-91). Like TNF-α, IL-β is also activated by TLR4 (92). IL-β is associated with long-term potentiation which underlies learning and memory, thus is implicated with drug-related aberrant memory (93). IL-β decreases glutamate supply through the inhibition of glial glutamate transporter activity, resulting in the attenuation of glutamate-glutamine cycle-dependent GABA synthesis. Moreover,

IL-β also participates in the regulation of postsynaptic GABA receptor activity. These modulations are widely associated with synaptic plasticity which may contribute to TLR4 signaling-related neuroadaptations (94).

The activation of TLR4 by drugs of abuse produces neuroinflammation as well as neurodegeneration within key brain regions that are involved in drug addiction (95-97). Conversely, inhibition of TLR4 abolishes the proinflammatory responses and blocks cell damage (65). For example, neurodegenerations in the prefrontal cortex are associated with the loss of executive functions over behavioral inhibition or a lack of inhibitory control over mesolimbic areas, which may consequently promote the drug-taking behaviors (98, 99). Generally, the loss of control over progression from initial recreational drug use to compulsive drug-taking may promote the development of drug addiction (100). Although much evidence has implicated the role of TLR4 and its signaling in drug addiction, the exact mechanisms and process remain unknown. Nevertheless, it should be kept in mind that drugs of abuse activation of TLR4 signaling may work in conjunction with the traditional well-established neuronal mechanisms, as the modulation of central immune system alone did not alter drug-related behaviors (37).

4 Future directions

While extensive studies have suggested that TLR4 and its signaling play an important role in drug addiction, many questions remain to be answered before TLR4 modulators could be used as potential treatments for alleviating drug abuse-related symptoms. Firstly, conflicting results from preclinical studies suggest the complex effects of TLR4 in regulating drug addiction. Future comprehensive studies that examine the effect of TLR4 modulation in different drug class from different drug addiction stages (i.e. binge/intoxication, withdrawal and relapse) will help establish whether TLR4 is a promising and novel therapeutic target to treat drug addiction. Secondly, the mechanism underlying the effect of TLR4 modulations in drug addiction is no clear. More studies carefully investigate how TLR4-related activation contribute to the progression of drug addiction are urgently needed. More importantly, to answer how TLR4-related non-neuronal system communicate and synergize with the well-known neuronal system will help tremendously in understanding the mechanisms underlying drug addiction. Last but not least, increased recognition of TLR4 in regulating drug addiction leads to a growing interest in clinical investigations. However, we are still far away from reaching a solid conclusion from clinical settings that TLR4 modulators could be potential pharmacotherapies for drug addiction. Future randomized and placebo-controlled clinical studies with large sample size, which examine the long-term safety, tolerability and efficacy of TLR4-based neuroimmune pharmacotherapies are warranted.

5 Conclusion

Drugs of abuse activate TLR4 and its signaling and enhance the production of proinflammatory cytokines and chemokines. Modulations of TLR4 and its signaling are shown to be involved in addiction to drugs from different class, including psychostimulants, opioids and alcohol. Furthermore, increased evidence has suggested that TLR4 and related glial cell modulators could be potential treatments for addiction-related behaviors. This is

a thriving topic that requires more comprehensive studies for both target validation and clinical efficacy verification to reshape the treatment for drug addiction.

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