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Drug addiction: targeting dynamic neuroimmune receptor interactions as a potential therapeutic strategy

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Drug addiction and dependence have proven to be difficult psychiatric disorders to treat. The limited efficacy of neuronally acting medications, such as acamprosate and naltrexone, highlights the need to identify novel targets. Recent research has underscored the importance of the neuroimmune system in many behavioural manifestations of drug addiction. In this review, we propose that our appreciation for complex phenotypes such as drug addiction and dependence will come with a greater understanding that these disorders are the result of intricate, interconnected signalling pathways that are, if only partially, determined at the receptor level. The idea of receptor heteromerisation and receptor mosaics will be introduced to explain cross talk between the receptors and signalling molecules implicated in neuroimmune signalling pathways.

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Introduction

Drug addiction is a chronic complex relapsing disorder with substantial morbidity and mortality. Worldwide, the annual number of deaths attributable to illicit drug use and to the harmful use of alcohol is 99,000–253,000 and 3.3 million, respectively [1,2]. Conceptually, drug addiction is a perpetual pathological cycle consisting of three phases: binge, withdrawal and craving. As drug addiction progresses, there is an inherent shift in the reinforcement mechanisms underlying the motivation to consume the drug (from positive to negative reinforcement) which reflects maladaptive alterations in brain regions governing reward, salience, pain and anxiety [3,4]. These neuronal alterations form the targets of our current pharmacological therapies for addiction. Unfortunately, however, these interventions demonstrate extremely limited efficacy [5], leading to high relapse rates. This highlights the need to better understand the complex mechanisms behind drug addiction and then identify novel targets for the development of promising therapeutic interventions.

The importance of neuronal systems in the development of drug addiction cannot be understated. However, accumulating evidence demonstrates the crucial role of the neuroimmune system, specifically, microglia and astrocytes in many addiction behaviours [6]. Microglia and astrocytes (glia) are the primary immunocompetent cells within the central nervous system (CNS). These cells were traditionally considered passive elements within the CNS, thought only to provide structural support. However, evidence over the past two decades has suggested that these cells play a more pivotal role in brain physiology. Glia actively respond to many drugs of abuse such as alcohol, amphetamines, cocaine and opioids by producing a subinflammatory immune response [6,7]. The neuroimmune system is not comprised solely of glia; neurons, oligodendrocytes, endothelial cells and infiltrating monocytes and T cells additionally participate in creating this complex system. The extent of each participant's contribution varies substantially reflecting the type of drug of abuse. Indeed, the exact make up of the cellular environment may first allow the specific detection of the drugs of abuse and then determine the signalling outcome.

Evidence for neuroimmune system involvement in addiction

Unravelling the neuroimmune system's influence on drug addiction is complicated by the route of administration, the time of drug exposure, the stage of addiction, the analytical endpoint, the brain region, and the animal model used to interpret a particular aspect of addiction. Irrespective of these variables, alterations in the neuroimmune system are consistently found following administration or withdrawal from drugs of abuse. Here, we provide a brief overview of drug of abuse-induced neuroimmune signalling and highlight that this system acts at multiple levels within the CNS.

Receptors

Drugs of abuse directly and indirectly interact with immune receptors. Direct interactions include drug of

abuse-receptor binding. For example, *in silico* and *in vitro* evidence demonstrates that Toll-like receptor 4 (TLR4), an innate immune pattern recognition receptor, binds alcohol, cocaine and opioids within the same motif [8•,9•,10]. Activation of TLR4 culminates in the translocation of inflammatory transcription factors such as NFκB to the nucleus, and the release of inflammatory mediators [11]. This suggests a common pathway activating the neuroimmune system following exposure to drugs of abuse. Indirect interactions primarily arise from a drug-induced increase in inflammatory mediators, which subsequently bind to their cognate receptors. For example, cocaine-induced CCL2 release binds to $CCR2^{+}$ neurons. This, in turn, alters membrane hyperpolarisation and ERK1/2 phosphorylation, ultimately influencing neurotransmission [12]. Consequently, examining how and where neuroimmune receptor interactions occur following drug abuse is crucial to the progression of addiction research and the development of future pharmacological interventions.

Molecules

Although behaviour cannot be modelled *in vitro*, the use of cell lines for exploring the physiological effects of drugs of abuse have provided valuable insights towards understanding the key signalling components in addiction. For example, alcohol at physiologically relevant concentrations increases the release of pro-inflammatory mediators (CCL2, COX-2, IL-1β, IL-6 and TNFα,) from primary microglial and astrocyte cultures [13]. Similarly, morphine increases the expression of CCL2, CCL5 and IFNγ-inducible protein [14]. *In vivo*, systemic injections of either opioids and alcohol increase the expression of inflammatory mediators in key neuroanatomical areas associated with addiction, such as the prefrontal cortex and the hippocampus but not the cortex in mice [14–16]. Furthermore, both opioids and alcohol increase inflammatory-related transcription factor activation in microglia and astrocytes in the aforementioned brain regions in both rodents and humans [10,17]. However, just as these drugs of abuse have specific neurotransmitter profiles, as determined by the neurotransmitters released following exposure to drugs of abuse, there is also a neuroimmune profile. This has been demonstrated by the differences in the inflammatory mediator expression following morphine and alcohol exposure [14,18]. It is worth highlighting, an immune challenge results in systemic release of inflammatory mediators, whereas an immune response to drugs of abuse within the CNS results in a more localised immune response. This localised response is mediated by neurokine signalling, whereby cytokines and chemokines act on neighbouring neurons to induce alterations to synaptic function, influencing neuronal processing and therefore behavioural output [7]. For example, TNFα and CCL2 decrease the threshold for firing action potentials from central amygdala neurons and increase the excitability of dopaminergic neurons, respectively [19,20].

Gene transcription

Gene analysis (transcriptome or network analysis) has primarily focused on alcohol addiction with fewer studies examining the gene networks of other abused drugs. However, network analysis of alcohol-addiction, opioid-addiction or smoking-addiction all demonstrate neuroimmune involvement [21]. Specifically, toll-like receptor and chemokine receptor (indirectly linked to NFκB)-related genes were over-represented among these three forms of addiction. Importantly, opioids and alcohol demonstrated the most immune gene overlap relative to smoking addiction, further supporting the concept of specific neuroimmune profiles of drugs of abuse [21]. Despite very little overlap of genes between amygdala, nucleus accumbens and prefrontal cortex regions (~20%), studies examining gene networks (*via* transcriptome) in the context of alcohol have determined that all three regions were enriched with astrocyte and microglia-associated pathways [22]. This identified the most persistent gene alterations primarily associated with the immune response. Finally, an epigenetic neuroimmune link to abuse liability following maladaptive early life experiences has been established. Schwarz *et al.* demonstrated that early life events in rodents caused specific adaptions in the methylation of the *IL-10* gene within nucleus accumbens microglia, which, in turn, was associated with an increase in morphine's rewarding properties [23].

Behaviour

There is a wealth of behavioural literature supporting the neuroimmune system's involvement in addiction phenotypes in both animals and humans. Ibudilast, an inhibitor of glial activation, blocks self-administration of a variety of drugs such as alcohol, methamphetamine and opioids in rodents [14,24,25]. In humans, ibudilast successfully reduced characteristics of opioid withdrawal compared to placebo controls [26]. Furthermore, in preclinical models, global knockout and selective knockout (*via* siRNA) of immune receptors and related molecules attenuate addiction-like behaviours such as impulsive consumption and craving [27,28•].

Drugs of abuse act at the cellular, receptor and molecular level, engaging multiple overlapping neuroimmune pathways. However, it is important to appreciate that these systems do not work in isolation. Rather, the behavioural and signalling outcomes are a result of complex interactions between receptors and the resulting integrated signalling networks that complement and coordinate with one another to generate complex addiction behaviours.

Molecular mechanisms underlying addiction

The molecular mechanisms underlying addiction are as varied as the drugs of abuse themselves. At first glance, it may therefore be surprising to find that a few key receptors and their ligands have been implicated in the signalling mechanisms responsible for addiction. However, fine