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Invited review

Why is neuroimmunopharmacology crucial for the future of addiction research?

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ABSTRACT

A major development in drug addiction research in recent years has been the discovery that immune signaling within the central nervous system contributes significantly to mesolimbic dopamine reward signaling induced by drugs of abuse, and hence is involved in the presentation of reward behaviors. Additionally, in the case of opioids, these hypotheses have advanced through to the discovery of the novel site of opioid action at the innate immune pattern recognition receptor Toll-like receptor 4 as the necessary triggering event that engages this reward facilitating central immune signaling. Thus, the hypothesis of major proinflammatory contributions to drug abuse was born. This review will examine these key discoveries, but also address several key lingering questions of how central immune signaling is able to contribute in this fashion to the pharmacodynamics of drugs of abuse. It is hoped that by combining the collective wisdom of neuroscience, immunology and pharmacology, into Neuroimmunopharmacology, we may more fully understanding the neuronal and immune complexities of how drugs of abuse, such as opioids, create their rewarding and addiction states. Such discoveries will point us in the direction such that one day soon we might successfully intervene to successfully treat drug addiction.

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1. Drugs of abuse: where to begin?

The neurocircuitries that contribute to the adaptive and beneficial aspects of hedonia, learning, and memory are crucial for an organism's long-term survival. In contrast to activation of these multi-nuclei networked/patterned response systems by natural rewards (palatable food, salt, sex, etc.), several classes of foreign compounds (xenobiotics) are capable of directly "high-jacking" these systems, creating states of pharmacologically induced euphoria and reward. Repeated exposure to xenobiotics with these pharmacological properties can lead to neuronal and behavioral adaptations that produce states of addiction and dependence to the xenobiotic, which is self reinforcing leading to escalation of drug use, and in the absence of drug produces states of withdrawal; hence these agents are collectively termed drugs of abuse. These abused xenobiotics have diverse structures and pharmacologies of both biologically-derived and fully synthetic origins. And yet, the action of many drugs of abuse converge on the mesolimbic dopamine reward pathway, in which exposure to these xenobiotics results in activation of the dopamine neurons projecting from the ventral tegmental area to the nucleus accumbens shell and/or elevation of extracellular dopamine within the nucleus accumbens shell itself (Ikemoto, 2007). These xenobiotic effects occur via bypassing classical adaptive signaling pathways and directly manipulating neurotransporter function, altering activation and inhibition pathways and vesicular displacement of neurotransmitters. Additional neuronal-mediated complexities to this system have also been observed (Laviolette et al., 2002; Vargas-Perez et al., 2009).

These xenobiotics can be from both legal and illicit drug origins, but, irrespective of origin, when these drugs are administered purely for their rewarding properties their use causes a profound social and economic burden on the individual and the community around them. The state of addiction and dependence leads the individual to repeatedly administer these xenobiotics, resulting in extensive exposure of the central nervous system to the parent xenobiotic and/or its metabolites. This xenobiotic exposure has a

Abbreviations: TLR, Toll-like receptor; LPS, Lipopolysaccharide.

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variety of consequences for the central nervous system, including neuronal adaptation and toxicity (Büttner, 2011; Cappon et al., 1998; Fantegrossi et al., 2008; Salazar et al., 2008; Tilleux and Hermans, 2007; Weber et al., 2006). These xenobiotic-induced alterations in central nervous system homeostasis often lead to increased allosteric load. Thus, in the absence of the xenobiotic, or when its pharmacological action is blocked, behavioral signs of dependence and relapse are precipitated. However, these responses are varied across abused xenobiotics, thus demonstrating specificity of adaptation (Hyman et al., 2006).

Owing to the profound, abundant neuronal actions of these abused xenobiotics, much of the research focus over several decades has been on understanding the neurocircuitry, neuronal receptors, intra-neuronal signaling pathways and neuronal-sensitization events that lead to the physiological state of addiction and dependence. However, in the past two decades, a trickle of manuscripts examining the non-neuronal central nervous system immune consequences of drugs of abuse has now swollen to a significant body of work. Initially, these studies reported correlative evidence of central nervous system proinflammation resulting from exposure to the drugs of abuse demonstrating key implications for neurotoxicity and disease progression associated with, for example, HIV infection (Coller and Hutchinson, 2012). However, more recently, this drug-induced activation of central immune signaling is now understood to contribute substantially to the pharmacodynamic actions of drugs of abuse, by enhancing the engagement of classical mesolimbic dopamine reward pathways and withdrawal centers. Thus the hypothesis of major proinflammatory contributions to drug abuse was formed through the unification of the collective wisdoms of neuroscience, immunology and pharmacology; hence, Neuroimmunopharmacology.

Such discoveries of central nervous system immune involvement in the mesolimbic dopamine reward pathway have significant implications for how we understand reward to be modulated in beneficial adaptive situations versus maladaptive pathogen- and xenobiotic-induced reward conditions. However, whilst exciting in its implications, the hypothesis of major proinflammatory contributions to drug abuse also presents a series of quandaries which have rightly been raised by the addiction neuroscience establishment. None are less critical than the question: How can proinflammatory immune signaling be involved in drug reward and addiction when we don't like being sick?

Thus, the aim of this review is to introduce and review the literature of the central immunology targets of drugs of abuse, highlighting the common mediators and mechanisms and the exciting opportunities these new targets have in identifying 'at risk' individuals and novel therapeutic opportunities. Additionally, some of the key conceptual and intellectual stumbling blocks that have impeded the proinflammatory hypothesis of drug abuse will be highlighted and explained in detail. Finally, the future of addiction research through "*Neuroimmunopharmacology tinted glasses*" will be surveyed to paint a picture of what the future of addiction research might hold.

Owing to the breadth of xenobiotics abused it will be difficult to cover all the developments in Neuroimmunopharmacology for each class. For a detailed review of these topics for abused xenobiotics where central immune signaling involvement has been established see our recent review (Coller and Hutchinson, 2012). Instead, here we will focus in this review on the evidence that we, and others, have generated over the past decade for opioid activation of central immune signaling and the impact this has on opioid reward and dependence.

2. An introduction to central immune signaling

Given that the hypothesis of major proinflammatory contributions to drug abuse requires both the knowledge of, and an appreciation for, neuroscience, immunology and pharmacology, a few key concepts need to be introduced in order to make this fascinating area optimally accessible. Firstly, the concept of immune-to-brain communication, which result in central immune signaling and subsequent altered behavior via neuronal-dependent adaptations will be examined.

It is very uncommon in an Immunology 101 course for any references to the central nervous system to be included, except perhaps when referring to immune involvement in neuroinflammatory diseases, such as Alzheimer's and Multiple Sclerosis. The predominant focus of most basic immunology courses, and in fact the collective wisdom held by the general public, is that the immune system's role is to defend the host organism from invading pathogens and to fight off infections. Whilst this host defense dogma is correct, the immune system has a far more nuanced role than we in western medicine and medical research currently give it credit for. The potential impact of peripheral immune cells, or immune signaling factors on brain function is commonly not discussed. However, this limited view of immune function is rapidly changing owing to a wealth of literature over more than 50 years.

Few of us will be unfamiliar with feeling sick at some point in our lives. But how do we feel sick and why don't we like it? A standard systemic immune response to an insult such as endotoxin (lipopolysaccharide from gram negative bacteria) causes a profound alteration in behavior, termed sickness behavior or the illness response. The anhedonic qualities associated with the illness response have been well established in multiple domains such as animal husbandry as well as the clinic (Yirmiya et al., 2000). Clearly anhedonia is only one facet of the complex sickness response, which also includes lethargy, depression, anxiety, anorexia, heightened pain states (hyperalgesia and allodynia), and cognitive impairment (Dantzer et al., 1999). Many of these behaviors require significant central nervous system engagement, demonstrating that this peripheral immune response is capable of profoundly modifying behavior and thus must have the capacity to alter central nervous system function. These discoveries of immune-to-brain communication are a cornerstone of Psychoneuroimmunology (Besedovsky and Rey, 2007).

The cause of the altered behavior induced by illness had been postulated to be due to changes in metabolic reserves resulting from the full activation of the immense power, but energy hungry, immune system. But when it was discovered that a blood borne factor resulting from endotoxin exposure was capable of altering behavioral function without the need for endotoxin to cross the blood brain barrier (Holmes and Miller, 1963), the age of immune-to-brain signaling was born. These immune derived cytokines have been characterized to act by various humoral and neuronal routes to alter central nervous system neuronal function (Capuron and Miller, 2011; Miller et al., 2009). But this is not the only alteration in the brain during an illness response. The non-neuronal cells of the central nervous system, glia, also respond following a similar peripheral immune challenge (Laflamme and Rivest, 1999), causing the generation of proinflammatory cytokines and a myriad of other neuronal adaptations and sensitizations within the brain and spinal cord. Hence, illness-induced immune responses are capable of profoundly altering central nervous system function via multiple parallel routes.

3. But is this too non-specific? Are all brain nuclei altered to the same extent? How can this peripheral immune response cause a specific behavioral phenotype such as the illness response?

The key concepts of bioavailability, neuroanatomy and immune heterogeneity come to the forefront. Firstly, much of the central