Published in final edited form as:
Exp Biol Med (Maywood). 2014 November ; 239(11): 1433–1442. doi:10.1177/1535370214537747.

Systems-Level View of Cocaine Addiction: The Interconnection of the Immune and Nervous Systems

Christina C. Marasco[1,2], **Cody R. Goodwin**[1,3], **Danny Winder**[4], **Nicole Schramm-Sapyta**[5], **John A. McLean**[1,3], and **John P. Wikswo**[1,2,4,6]

[1]Vanderbilt Institute for Integrative Biosystems Research and Education, Vanderbilt University, Nashville, TN, 37235

[2]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, 37235

[3]Department of Chemistry and Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN, 37235

[4]Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN, 37232

[5]Department of Psychiatry, Duke University Medical Center, Durham, NC, 27710

[6]Department of Physics and Astronomy, Vanderbilt University, Nashville, TN, 37235

Abstract

The human body is a complex assembly of physiological systems designed to manage the multidirectional transport of both information and nutrients. An intricate interplay between the nervous, circulatory, and secretory systems is therefore necessary to sustain life, allow delivery of nutrients and therapeutic drugs, and eliminate metabolic waste products and toxins. These systems also provide vulnerable routes for modification by substances of abuse. Addictive substances are, by definition, neurologically active, but as they and their metabolites are spread throughout the body via both the nervous, circulatory, respiratory and digestive systems, there is abundant opportunity for interaction with numerous cell and tissue types. Cocaine is one such substance that exerts a broad physiological effect. While a great deal of the research concerning addiction has addressed the neurological effects of cocaine use, only a few studies have been aimed at delineating the role that cocaine plays in various body systems. In this paper, we probe the current research regarding cocaine and the immune system, and map a systems-level view to outline a broader perspective of the biological response to cocaine. Specifically, our overview of the neurological and immunomodulatory effects of the drug will allow a broader perspective of the biological response to cocaine. The focus of this review is on the connection between the nervous and immune systems and the role this connection plays in the long-term complications of cocaine use. By describing the multiplicity of these connections, we hope to inspire detailed investigations into the immunological interplay in cocaine addiction.

Corresponding Author: John P. Wikswo, john.wikswo@vanderbilt.edu.

Declarations
None

Statement of Author Contributions
CCM and CRG wrote the paper. DW, NS-S, JAM, and JPW defined the overall scope and critically reviewed the manuscript.

Keywords

cocaine; immune system; nervous system; addiction; metabolism; signaling

I. Introduction

Cocaine has diverse physiological and pharmacological actions as a result of its affinity for a variety of transporters and receptors in the central and peripheral nervous system, as well as in the immune system. This affinity enables cocaine to affect highly complex dopamine and opioid receptor signaling networks[1–3] that lead to a range of behavioral effects, including euphoria, alertness, energy, and enhanced locomotion, as well as anxiety and paranoia.[4] Because of the complicated nature of these behavioral effects, it is possible that not all arise solely from neuronal interactions with cocaine. Chronic use leads not only to physical harm based on the mode of administration, but also to alterations in the chemical and molecular make-up of neurons affected by the drug.[4] A potential complication in understanding the actions of cocaine is the connection between the nervous and immune systems,[5] including the hypothalamic-pituitary-adrenal axis (HPA axis), the sympathetic nervous system (SNS), and the brain's innate immune system. The HPA axis is the primary stress-response network, which acts through signaling by hormones and cytokines.[6] The SNS nerve endings interact with lymphocytes in the spleen for the transmission of information (through neurotransmitters) to the lymphocytes,[7] while the return of information from the lymphocytes to the neurons occurs through cytokine signaling.[8] Cocaine can modify the immune system by elevating circulating levels of glucocorticoids.[6;9–11] The brain, though initially viewed as an immune-privileged organ, has now been found to have its own immune components, including astrocytes and microglial cells, which exhibit behaviors of both neural cells and immune cells.[12] Findings have also shown that the brain is a drug metabolizing organ.[13] When these communication pathways are viewed in light of chronic cocaine use and addiction, it becomes apparent that this systems-level connection may potentiate both the immune and neural adaptations caused by chronic cocaine use. We will explore this notion first by reviewing both the neurological and immune effects of cocaine administration, then by investigating the interconnection of the two systems. We recognize that the direction of some of these connections may not yet be established – correlation does not necessarily imply causality. However, a first step toward a deeper understanding of the relation between cocaine and addiction may be to recognize the breadth of physiological systems affected by cocaine. Hence this systems-level review, which we hope will lead to transdisciplinary explorations that might bring to light new perspectives on the problem.

II. Effects of Cocaine Use on the Central Nervous System

Cocaine is a stimulant of the central nervous system (CNS), and as a result, most research on cocaine use and addiction in the past few decades has been focused on neurological effects, with less attention given to non-CNS systemic actions. Though many pharmacological actions of cocaine in the nervous system have been explored, not all are completely understood. We now provide a brief synopsis of the direct effects of cocaine on the CNS.

A. Monoamine Reuptake Inhibition

The most well-known and studied action of cocaine is its role in blocking the reuptake of monoamine (norepinephrine, serotonin, and dopamine) neurotransmitters. As a small xenobiotic molecule exhibiting both lipophilic and hydrophilic properties, cocaine, upon administration, can cross the blood-brain barrier. Cocaine binds and blocks reuptake at catecholamine neurotransmitter transporters in the nucleus accumbens, ventral tegmental area, amygdala and other regions.[14;15] This blockade increases levels of monoamines (norepinephrine, serotonin, and dopamine) in the synaptic cleft, allowing greater ligand binding to their respective receptors on the postsynaptic and presynaptic neuron. The recruitment of these G-protein coupled receptors leads to multiple signaling events within the neuron,[16;17] leading to increased neuronal firing in the nucleus accumbens,[14;17] followed by presynaptically altered neurotransmitter release.[18–20] For instance, upon dopamine (D2) autoreceptor activation, further release of dopamine is inhibited and dopamine neuron firing is reduced.[21–23] Prolonged chronic exposure to cocaine can lead to downregulation of postsynaptic dopamine receptors,[24] producing tolerance to the effects of the drug. When this occurs, a higher dose is required to achieve the same results.[25]

Dopamine signaling plays a fundamental role in learning and memory systems, and as such, Pavlovian and operant conditioning in these systems has been hypothesized to contribute to cocaine addiction.[16;26;27] For example, in both chronic users and rats, a spike in dopamine occurs in response to anticipated cocaine[25;28;29] and also in response to the peripheral interoceptive cues resulting from administered cocaine.[30] Both of these effects occur before the cocaine molecule reaches the brain and begins to block dopamine reuptake.[30] These findings provide evidence of a conditioned response to cocaine-associated cues – both external and interoceptive. These conditioned responses are thought to be related to adaptive modulation of circuits involving multiple neurotransmitter systems, including GABA, norepinephrine, corticotropic-releasing factor, and the opioid receptors glutamate and acetylcholine.[25] Clearly, long-term drug abuse creates a generalized response involving multiple neurological signaling systems. To add to the complexity of this system, cocaine also interacts with additional classes of receptors, both neural and peripheral. We will begin this discussion by reviewing the prominent non-monoaminergic neural substrates.

B. Non-Monoaminergic Nervous System Substrates: Sigma-1 Receptor

As the main pathway leading to the reward associated with cocaine use, dopamine reuptake inhibition has received great attention from the scientific community. Investigation of the role of cocaine binding to additional neural substrates also has the potential to contribute to our understanding of cocaine's complex pharmacological actions. For example, although it is still unidentified, an additional neuronal receptor was discovered by Rothman et al. to be a potential binding site for cocaine, as the binding affinity of the drug to this receptor is within the concentration range of cocaine found in brain membrane preparations post-administration.[31] Smirnov et al. have implicated peripheral non-monoamine neural substrates in the immediate physiological response (desynchronization of cortical EEG and activation of the neck EMG) to cocaine prior to stimulation of the central nervous system.[32] Secondary effects of increased dopamine signaling may also occur. For instance, prolonged cocaine administration leads to upregulation of μ opioid receptors in the nucleus

accumbens and κ opioid receptors in the olfactory tubule, caudate putamen, and cingulate cortex as a result of increased dopamine transmission.[33] The sigma-1 (σ_1) receptor is one of the more extensively studied of the additional substrates for cocaine and will be reviewed here in greater detail.

The σ_1 receptor is found in high density in the central nervous system and throughout peripheral organs, tissues, and immune cells. This receptor was initially classified as an opioid receptor in 1976,[34] but it was found to have no homology and few shared ligands to the opioid receptors and was subsequently reclassified as a separate class of receptor.[35] It has been implicated in addiction, cognition, pain, depression and a wealth of human diseases, including cancer and cardiovascular disease.[36]

This receptor functions as both a molecular chaperone in the endoplasmic reticulum (ER),[37] and a modulator of ion channels (both voltage-gated and ligand-gated) on the cell surface and ER.[38;39] As molecular chaperones, σ_1 receptors redistribute to the ER in response to stress to the ER. This activity may play a role in the unfolded protein response (UPR), which suppresses release of misfolded proteins.[37] As the ion channel modulators, sigma receptors act in both the ER and outer cell membrane. In the ER, σ_1 agonists administered in neural cell lines caused a rise in Ca^{+2} flux through the IP3 receptor (IP3R) even in the presence of an IP3R inhibitor.[40] Sigma-1 receptors have also been shown to regulate the interorganelle Ca^{+2} signaling between the mitochondria and the ER.[37] Agonist-stimulated sigma receptors can also leave the endoplasmic reticulum and translocate to the cell membrane to inhibit the function of cell-surface ion channels. The first cell-surface ion channels to be associated with sigma receptors are the NMDA-type glutamate receptors, which are involved in memory and learning, although discrepancies exist between studies.[41–43] Through these actions, it is postulated that σ_1 receptors modulate neuronal firing and neurotransmitter release[44] and play a role in the behavioral and locomotor stimulus response associated with cocaine use.[45]

The affinity of cocaine for the σ_1 receptor is 2–10 μM, which is within typical blood concentrations of cocaine users.[36;44] Cocaine also augments the expression of the immediate early gene fos-related antigen 2 (*fra-2*), which in turn potentiates the gene expression of the σ_1 receptor and its subsequent nucleophilic attack expression.[46;47] As a σ_1 agonist, cocaine is capable of inhibiting voltage-gated ion channels while enhancing the activity of ligand-gated ion channels.[38] The relationship between calcium and cocaine is far from new information; however, the details of the relationship, beyond that of cocaine causing a decrease in mobilized cytosolic Ca^{+2}, potentially through a mechanism involving the σ_1 receptor, are unclear.

These studies of both monoamine and non-monoamine targets for cocaine binding shed light on the complex nature of the drug's pharmacological and behavioral effects. While many of these substrates, such as dopamine transporters, are well characterized, others are still in the early stages of identification and characterization. Understanding the diverse actions of cocaine will allow for the development of innovative methods for treatment of addiction or cocaine toxicity, yet investigating only the nervous system effects of the drug leaves an untapped resource for potential treatment strategies. One must also consider the immune

effects of cocaine, as well as how the immune and nervous systems interact, to truly understand the complete physiological reaction to the drug.

III. Immunological Effects of Cocaine Use

Investigation of the effects of cocaine on immune response began slowly in the 1980s with a study showing the suppressive effects of cocaine on the immune response of mice to sheep red blood cells,[48] followed by 10–15 studies published per year from the early 1990s through the present day. As the link between cocaine use and immune function has become stronger, the expectation of permanent immune changes grows more plausible, but it has not yet been investigated directly. Extensive research on the role of cocaine in the susceptibility to and progression of HIV, cancer, and cardiovascular diseases has been conducted and will be reviewed here alongside general immune function changes due to cocaine exposure.

A. Direct Immunomodulatory Effects

Cocaine is an immune suppressor that acts directly on the σ_1 receptor in a wide range of leukocyte populations, including T cells, B cells, and natural killer (NK) cells. Numerous peripheral mechanisms of action via the neuroimmune connection that result in immune function changes are also suspected (a summary of immunomodulatory effect is shown in Figure 2). In one of the earliest studies of the effects of cocaine on the immune system, Watson et al. described a suppression of the immune system following cocaine administration in mice as measured by ear swelling and plaque-forming cell (PFC) splenic assay.[48] As time progressed, more direct measures of immune function were incorporated. Change in white blood cell count post-cocaine exposure was one of these more direct immune differences, although there is some discrepancy in the nature of that change, with several reports of decrease[49] and even no change[50;51] in cell count or viability. When exposed to cocaine, and to a greater degree when incubated with cocaine for 24 hours, phytohemagglutinin (PHA)-induced proliferation of T cells is suppressed and associated with a decrease in the cytosolic free Ca^{+2} and diminished production of IL-2,[52] although other studies show no link between decreased T cell proliferation and Ca^{+2} flux or IL-2 production.[53] Disagreement between findings suggests a more complex signaling cascade, with Ca^{+2} most likely playing a critical role in need of further investigation. Faraj et al. report that lymphocytes possess a high affinity dopamine uptake process that cocaine blocks in a concentration-dependent manner.[54] Cytokine secretion has been shown to be altered in response to cocaine exposure in various leukocytes, including NK cells, T cells, neutrophils and macrophages.[55;56] Specifically, cocaine has been shown to increase T helper type 1 (Th1) cytokines and decrease T helper type 2 (Th2) cytokines, and thus promote Th1-mediated immune responses and degrade Th2-mediated responses.[56;57] This range of results is perhaps due to varying exposure parameters (chronic and acute administration are known even to cause differential effects in the central nervous system), experimental model or cell population, and potential tolerance to cocaine.[58;59] Pellegrino et al. released a compelling study on lymphocyte proliferation after exposure to cocaine and demonstrated that suppression of proliferation occurred as a result of peripheral activities of cocaine.[60] They additionally report that the need for a high dose of cocaine *in vitro,* in order to elicit a decrease in immune function, points to indirect methods of immune suppression, potentially

through alterations on neurotransmitters or the neuroendocrine system. Disagreement between results from numerous studies indicates the complexity of this biological system and drives the need for a more systematic approach that includes studies on both the humoral and cell-mediated immune responses in single and mixed immune cell populations across various animal models, especially from humans, under tightly controlled and easily adjustable experimental conditions.

B. Serum Protein Alteration and Resulting Immune Response

The body's response to recognizable foreign substances includes non-specific innate immune responses and primary and secondary adaptive immunological responses. These will occur if the foreign body, in this case cocaine, elicits an immune response. Immunological responses to antigen presentation should not occur in response to cocaine alone, as it is a small molecule; however, cocaine can elicit an immune response when attached to a large carrier molecule, such as a protein. Cocaine metabolites, specifically benzoylecognine, have been shown to covalently modify endogenous proteins (e.g., albumin) present in the plasma through the acylation of the ε-amino group of the protein lysine residues through a nucleophilic attack by benzoylecgonine.[61] Other mechanisms of cocaine modification of proteins are a topic of active interest.[62] The use of vaccines to treat substance abuse such as cocaine is beyond the scope of this review.[63–65] Though speculative in nature, these modified proteins have the potential to be recognized as foreign antigens through binding with major histocompatibility complexes (MHC) located on antigen-presenting cells (e.g., macrophages, dendritic cells). Binding, depending on whether the proteins are endogenous or exogenous, will occur on either MHC class I or MHC class II, respectively, for any antigen that is recognized. The modified proteins that have been documented are treated as exogenous, as they are highly abundant plasma proteins, such as albumin and IgG proteins. The exogenous modified proteins are endocytosed by antigen-presenting cells (APCs). This endocytosis occurs either non-specifically by dendritic cells whose primary job is to scavenge and present any protein they encounter, by receptors on macrophages, or through surface IgM antibodies on B cells. Once these endosomes are digested, through fusion with protease-containing lysosomes, the resultant digested peptides bind to MHC II, forming a complex that is then shipped to the plasma membrane for presentation to CD4+ T cells. Upon recognition, the CD4+ cells are activated by the antigen-presenting cell, and they then stimulate B cells to produce neutralizing antibodies against the cocaine-acylated proteins. T cell activation subsequently leads to increases in IL-2 production and upregulation in IL-2 receptor expression in addition to T cell growth and proliferation. These T cells differentiate into T helper cells, which then differentiate into Th1 cells through IL-12 promotion, or Th2 cells through IL-4 promotion (corroborating the results of Gardner et al.[56] and Gan et al.[57]). For this discussion, Th2 cells are most important, as they promote the production of antibodies through the activation of B cells.

B cell activation occurs through a similar antigen recognition procedure: a specific antigen binds to B cell surface antibodies (IgM and IgD antibodies) and is endocytosed and presented as a MHC class II complex. This MHC class II complex must then be recognized by an antigen-specific Th cell, which then activates the naïve B cell through cytokine secretion. This Th cell also expresses a CD40 receptor, which binds with the CD40

produced by the antigen-presenting B cell. These B cells then proliferate and differentiate into antibody-secreting B cells. As such, both memory T and B cells specific to the modified proteins are present in the body, along with antibodies for their neutralization in the plasma.

After the initial recognition, activation, and antibody-forming cascade, cocaine-modified proteins in the bloodstream are recognized by IgM or IgG antibodies, resulting in an immunological cascade.[64] The cocaine-modified proteins are bound to extracellular IgM or IgG antibodies, which in turn activate the complement system. This is considered the classical pathway of activation and results from an antigen:antibody complex. These antibodies are produced by B cells, each having a single specificity for a modified protein dictated by the variable region of the antibody. The activation of complements results in the opsonization of the antigen, the recruitment of inflammatory cells, and the subsequent clearance of the antibody:antigen complexes through phagocytosis.

During this process, macrophages become activated by binding inflammatory chemokine C5a. Activated macrophages also secrete cytokines and other signaling factors, such as leukotrienes and prostaglandins, in response to antigen recognition. These recruit lymphocytes and alert them that an antigen is present, eliciting an adaptive response. As a result of activation, a cocktail of interleukins (i.e., IL-1, IL-6, IL-8, IL-12), in addition to tumor necrosis factor alpha (TNF-α), are produced by macrophages. Important for this discussion is the production of IL-6, IL-8, and IL-12, as IL-6 activates lymphocytes and stimulates further antibody production, IL-12 activates Th 1 cells, and IL-8 recruits neutrophils, basophils, and T cells. Hence, as a result of cocaine's permanent covalent modification of plasma proteins, an immunological response that ultimately includes both innate and adaptive immune systems is mounted.

C. Progression of Diseases and Aging

Immune suppression as a result of cocaine administration leaves the user with an increased susceptibility to infection. While cocaine itself is able to cross the blood-brain barrier, in doing so it leads to alteration in the expression and conformation of tight junction proteins and cocaine-induced neuroinflammation, which causes an increase in blood-brain barrier permeability to toxins, bacteria and viruses[66] and leukocytes.[67] Additionally, the relation of cocaine use and prevalence of HIV and AIDS has frequently been studied, with reports indicating that increased susceptibility to HIV infection among cocaine users is not a result of intravenous drug use alone but also of the changes in the immune system caused by cocaine.[58] Baldwin et al. report an increase in infectivity or HIV replication in human cells when exposed to cocaine *in vitro*.[55] A decrease in CD4+ counts, lower CD4:CD8 ratio, and marked increase in viral load upon cocaine administration were found in mice implanted with HIV-infected human peripheral blood leukocytes.[68] In a supplementary study by the same investigators of the various mechanisms through which viral load was increased 150-fold, it was shown that cocaine both increases expression of HIV chemokine coreceptors and directly binds the σ_1 receptor of leukocytes, causing an increase in IL-10 and TGF-β – both significant factors in the progression of HIV.[50] However, a recent study focusing entirely on quiescent T cells, which comprise the largest subset of circulating T-cells, did not observe increased IL-10 and TFG-β in these cells. Interestingly, an increase in HIV infection

was attributed to bypassing the block in early reverse transcription in an independent manner, though the mechanistic rationale is currently under further investigation.[69] The striking impact of cocaine administration on risk and progression of HIV, along with the evidence of numerous mechanisms of action leading to these issues, necessitates further work before effective HIV treatment and prevention strategies can be developed.

HIV and other infections are not the only conditions worsened by cocaine use. Cancer progression has also been shown to be associated with the binding of cocaine to σ_1 receptors, which increases chemokine production, specifically IL-10, leading to suppression of the antitumor response.[56;70] It has also been reported that macrophage inhibition of tumor growth is diminished when exposed to cocaine *in vitro*.[71] As the antitumor response is a feature associated with the immune system, it follows that the suppression of the immune system by cocaine would also hamper the response to tumor formation.

Cocaine use is a culprit in many cardiovascular complications, including myocardial ischemia, apparent myocardial infarction, hypertrophy, myocarditis, thrombosis, stroke and sudden cardiac death, among others. Although the mechanisms by which cocaine plays a role in cardiovascular disorders remain to be determined, many studies investigate the connection.[72–77] A thorough review of the role of cocaine use in cardiovascular disorders has been conducted elsewhere.[78–80] It is, however, important to realize the broad range of physical effects caused by cocaine use.

In a related study on drug-induced accelerated aging, Reece reports that addicted populations of patients show higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), globulins, globulin/albumin ratio, and lymphocyte count when compared with non-addicted medical patients, and that since many of these factors are considered biomarkers of aging, it is possible that aging of addicted individuals follows a contracted time course.[81]

D. Current Strategies of Immune Modulation Research

Much of the research to determine the effects of cocaine on immune function discussed above was performed using immune cell lines and blood samples from animal models. The assessment of immune status is typically performed by quantifying parameters such as lymphocyte proliferation, cell count, cytolytic activity, plaque-forming activity, antibody titer, cytokine production, and corticosterone levels, to name a few. Immunoassays such as enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry combined with flow cytometry are the current techniques used in these types of studies. These techniques have their downfalls, though. For example, ELISA is plagued by potential complications of cross-reactivity and poor sensitivity, although digital ELISA might increase the sensitivity by orders of magnitude.[82] Flow cytometry, while fast and capable of detecting multiple wavelengths at a time, reports only population-based information, missing any variation between cell phenotypes and not allowing sequential measurements on individual cells. Further complicating such measurements in cultured lymphocyte cell lines are the large volumes associated with cell culture, which are known to dilute paracrine and autocrine signaling factors that provide critical information concerning the status of the immune system.[83] These concerns in the determination of immune status bring to light the need for

additional analytical techniques and instrumentation to delve further into these biological matters.

IV. The Neuroimmune Connection and Its Role in Potential Long-Term Effects of Cocaine Use

One theory of addiction is that drug use, especially when repeated, leads to long-lasting behavioral sensitization in the form of psychosis or craving for the drug, which is thought to arise from potentially permanent[84–87] neuroplastic changes in certain areas and circuitry of the brain as a result of increased dopamine transmission.[88] De Vries et al. report that reinstatement of drug-seeking behavior after withdrawal is associated with this long-term behavioral sensitization.[89] Activation of the σ_1 receptor has been implicated in drug-seeking relapse in mice as determined through the use of the conditioned place preference (CPP) behavioral assessment.[90] Ecke et al. link the cocaine-induced differences in long-term alterations of genes typically viewed as stress- or immune-related to the level of cAMP response element-binding protein (CREB), a factor in stress-induced reinstatement.[91] The evidence of long-term effects in the nervous system suggests that permanent changes take place that have a subsequent effect on immune function potentially through the brain-immune communication network (Figure 3)[92–94] or by some other, yet undiscovered, means. Brain-mediated immune responses involve not only neuroendocrine, neurochemical, metabolic and autonomic responses, but also changes in mood, motivational state, sleeping patterns, eating behavior, and social and locomotor activities.[95]

Cocaine has long been shown to increase levels of adrenocorticotropin hormone (ACTH), β-endorphin, and corticosterone in rats in a manner dependent upon cocaine or dopamine regulation of corticotropin-releasing hormone (CRH), the initiator of HPA axis activation.[6;10;11] Likewise, cocaine use is associated with the maintenance of increased cortisol levels.[9] Upregulation of these stress hormones leads to increases in glucocorticoid receptor gene expression and potentiates cocaine self-administration.[96] HPA axis activation, along with the increased secretion of these signaling molecules, leads to downregulation of the inflammatory response.[94] Most investigations into the combined modulation of the immune system through the brain signaling in addition to cocaine are relatively short-term studies, and their findings have mixed responses due to the difficulty of controlling studies for collective cell-mediated immunity and peripheral effects relating to the humoral immune response. In one of the few long-term studies, Avila et al. suggest several valid explanations for prolonged immune suppression after withdrawal from chronic cocaine use that imply long-term or even permanent alterations in the immune system.[97] They discuss how the immune system's vulnerability caused periodic release of corticosteroids initiated by cocaine administration, the sustained stress response release of corticosteroids during withdrawal, or the combination of the two as potential mechanisms of sustained T cell suppression after withdrawal.[97] In separate studies by the same group, the activated neuroendocrine stress response was implicated in the suppression of cellular immunity during the early withdrawal period.[98;99] Johnson et al. investigated the immune markers during acute cocaine withdrawal in pregnant women, and over this short period of data collection saw significant changes in complement receptor expression (with most

receptor expression increasing transiently during withdrawal), which plays a role in the host-pathogen response.[100] The correlation of these changes with the course of withdrawal does not mean that these changes were necessarily directly related to the addiction.

The interaction between the brain and the immune system is bidirectional, resulting in the brain interpreting immune cell activation as a stressor through signaling of cytokines.[92;93] Since cocaine is capable of eliciting an immune response by binding to serum proteins and thereby activating the release of cytokines, the effects of cocaine may be potentiated through the HPA axis.

A recent review published on the neuroimmunopharmacology of opioids provides an in-depth discussion of the role of the central immune system – i.e., astrocytes and microglial cells, which exhibit behaviors of both neural cells and immune cells – in this interconnection of the neurological and immunological systems.[12] Hutchinson comments that "[c]entral immune signaling cannot be thought of as a parallel system separate from that of neuronal synaptic transmission and neuronal communication," which, taken together with the research findings of the neuroimmune connection, can be extended to include peripheral immune signaling.[12] Cocaine has been found to further potentiate the neuroimmune connection by serving as an inflammatory stressor that causes leukocytes to adhere to endothelial cells of the blood-brain barrier, which leads to leaking of the tight junctions and allows leukocytes to traverse the barrier.[67] This connection complicates the determination of potential mechanisms of immunosuppressive effects of cocaine, but further establishes the likelihood of both direct and peripheral mechanisms of action, the interactions of which may serve as a feedback system that could lead to prolonged and long-term effects in both the immune and nervous systems.

Experienced researchers in the field of drug-modulated immunology also speculate on the matter of long-term immune effects. For instance, Pacifici et al. comment that "… the possibility that some kind of immune memory mechanism could also play a role cannot be discarded."[101] Evidence of these potential sustained effects, however, may lie in the neuroimmune communication, including the HPA axis and the autonomic nervous system. With the increasing attention toward psychoneuroimmunology and the link between the brain and the immune system, in addition to the continuing quest to understand addiction, future studies may be able to bring to light any long-term or permanent immune effects and the connection between those of the long-lasting or permanent behavioral changes in the nervous system.

V. Conclusions

Cocaine, while often considered to plague a single physiological system, is capable of eliciting a range of effects on both the nervous and immune systems, thereby creating a cascade of physiological responses. Many of the effects on the nervous system are due to modifications of dopamine signaling, though there is evidence of additional actions through the σ_1 receptor, as well as receptors that are still to be identified. The suppression of the immune system by cocaine is highly dependent on dose and administration frequency, and although cocaine alone does not elicit an immune response, it may lead to activation of the

immune system and production of cytokines through modifications to serum proteins. When viewing the modulations of both the immune and nervous systems in light of the bi-directional communication network, it is likely that further regulatory interactions occur, specifically through upregulated stress hormones and a variety of changes to particular immune-signaling molecules, producing a complex interaction network that leads to adaptations in gene transcription. While there is no published evidence of a permanent change in immune function as a result of either chronic or acute cocaine use, the long-lasting or permanent behavioral changes, in addition to the link between the brain and the immune system, lead one to speculate regarding this possibility. Immune adaptations could further explain the relationship between cocaine use and diseases and aging.

In order to best treat addiction, it is important to understand how addictive drugs affect not only the brain, but also the immune system. Though the recent advances in developing vaccines against cocaine addiction[102] could serve to benefit many individuals, they focus on preventing the neural effects of the drug and ignore the immune response to the drug-modified serum proteins (which begins as soon as cocaine enters the bloodstream) and subsequent neuroimmune signaling capable of perpetuating addictive effects. Yet these endeavors may serve to propel interest in the effects of cocaine on the immune system in addition to the neurological effects. Continuing to look at cocaine modulations on a systems level, thus further investigating the neuroimmune connection, could lead to additional treatment strategies that ameliorate the long-term or permanent changes associated with chronic drug use.

Ideally, this systems-level review of the interconnections between the immune and nervous systems will enable further explorations that cross physiological and disciplinary boundaries. Possibly we raise more questions than we answer, but that reflects the status of the current understanding of these complex interconnections.

Acknowledgments

The authors thank Allison Price for editorial assistance.

Funding Statement

This work has been supported in part by NIH grants 1R01GM092218-01 and RC2DA028981, and, through the National Center for Advancing Translational Sciences of the NIH, UH2TR000491; the U.S. Defense Threat Reduction Agency (HDTRA-09-1-0013); and the Vanderbilt Institute for Integrative Biosystems Research and Education.

References

1. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev. 2011; 63(1):182–217. [PubMed: 21303898]
2. Law PY, Wong YH, Loh HH. Molecular mechanisms and regulation of opioid receptor signaling. Annu Rev Pharmacol Toxicol. 2000; 40:389–430. [PubMed: 10836142]
3. Nestler EJ. Historical review: Molecular and cellular mechanisms of opiate and cocaine addiction. Trends Pharmacol Sci. 2004; 25(4):210–8. [PubMed: 15063085]
4. World Health Organization. Neuroscience of psychoactive substance use and dependence. Geneva: World Health Organization; 2004.

5. Quan N, Banks WA. Brain-immune communication pathways. Brain Behav Immun. 2007; 21(6): 727–35. [PubMed: 17604598]
6. Goeders NE. The HPA axis and cocaine reinforcement. Psychoneuroendocrinology. 2002; 27(1–2): 13–33. [PubMed: 11750768]
7. Straub RH. Complexity of the bi-directional neuroimmune junction in the spleen. Trends Pharmacol Sci. 2004; 25(12):640–6. [PubMed: 15530642]
8. Deleo JA, Tanga FY, Tawfik VL. Neupoimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. Neuroscientist. 2004; 10(1):40–52. [PubMed: 14987447]
9. Heesch CM, Negus BH, Keffer JH, Snyder RWI, Risser RC, Eichhorn EJ. Effects of cocaine on cortisol secretion in humans. Am J Med Sci. 1995; 310(2):61–4. [PubMed: 7631644]
10. Goeders NE. A neuroendocrine role in cocaine reinforcement. Psychoneuroendocrinology. 1997; 22(4):237–59. [PubMed: 9226728]
11. Goeders NE, Bienvenu OJ, Desouza EB. Chronic cocaine administration alters corticotropin-releasing factor receptors in the rat-brain. Brain Res. 1990; 531(1–2):322–8. [PubMed: 1963104]
12. Hutchinson MR, Shavit Y, Grace PM, Rice KC, Maier SF, Watkins LR. Exploring the neuroimmunopharmacology of opioids: An integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. Pharmacol Rev. 2011; 63(3):772–810. [PubMed: 21752874]
13. Ghosh C, Marchi N, Hossain M, Rasmussen P, Alexopoulos AV, Gonzalez-Martinez J, Yang H, Janigro D. A pro-convulsive carbamazepine metabolite: Quinolinic acid in drug resistant epileptic human brain. Neurobiol Dis. 2012; 46(3):692–700. [PubMed: 22426401]
14. Robbins TW, Everitt BJ. Drug addiction: bad habits add up. Nature. 1999; 398(6728):567–70. [PubMed: 10217139]
15. Civelli O, Bunzow JR, Grandy DK. Molecular diversity of the dopamine-receptors. Annu Rev Pharmacol Toxicol. 1993; 33:281–307. [PubMed: 8494342]
16. Dalley JW, Everitt BJ. Dopamine receptors in the learning, memory and drug reward circuitry. Semin Cell Dev Biol. 2009; 20(4):403–10. [PubMed: 19560045]
17. Nestler EJ. Molecular mechanisms of opiate and cocaine addiction. Curr Opin Neurobiol. 1997; 7(5):713–9. [PubMed: 9384550]
18. Sulzer D. How Addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron. 2011; 69(4):628–49. [PubMed: 21338876]
19. Blakely RD, DeFelice LJ, Hartzell HC. Molecular physiology of norepinephrine and serotonin transporters. J Exp Biol. 1994; 196:263–81. [PubMed: 7823027]
20. Schoemaker H, Pimoule C, Arbilla S, Scatton B, Javoyagid F, Langer SZ. Sodium-dependent [H-3] cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopaminergic denervation and in Parkinsons-Disease. Naunyn Schmiedebergs Arch Pharmacol. 1985; 329(3):227–35. [PubMed: 3927176]
21. Zhang H, Sulzer D. Regulation of striatal dopamine release by presynaptic auto- and heteroreceptors. Basal Ganglia. 2012 Mar; 2(1):5–13. [PubMed: 22712055]
22. Cragg SJ, Greenfield SA. Differential autoreceptor control of somatodendritic and axon terminal dopamine release in substantia nigra, ventral tegmental area, and striatum. J Neurosci. 1997; 17(15):5738–46. [PubMed: 9221772]
23. Bello EP, Mateo Y, Gelman DM, Noain D, Shin JH, Low MJ, Alvarez VA, Lovinger DM, Rubinstein M. Cocaine supersensitivity and enhanced motivation for reward in mice lacking dopamine D-2 autoreceptors. Nat Neurosci. 2011; 14(8):1033–U128. [PubMed: 21743470]
24. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacol. 2010; 35(1):217–38.
25. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: Beyond dopamine reward circuitry. PNAS (US). 2011; 108(37):15037–42.
26. Everitt BJ, Dickinson A, Robbins TW. The neuropsychological basis of addictive behaviour. Brain Res Rev. 2001; 36(2–3):129–38. [PubMed: 11690609]
27. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: The role of reward-related learning and memory. An Rev Neurosci. 2006; 29:565–98.

28. Wheeler RA, Aragona BJ, Fuhrmann KA, Jones JL, Day JJ, Cacciapaglia F, Wightman RM, Carelli RM. Cocaine cues drive opposing context-dependent shifts in reward processing and emotional state. Biol Psychiatry. 2011; 69(11):1067–74. [PubMed: 21481843]
29. Aragona BJ, Day JJ, Roitman MF, Cleaveland NA, Wightman RM, Carelli RM. Regional specificity in the real-time development of phasic dopamine transmission patterns during acquisition of a cue-cocaine association in rats. Eur J Neurosci. 2009; 30(10):1889–99. [PubMed: 19912327]
30. Wise RA, Kiyatkin EA. Differentiating the rapid actions of cocaine. Nat Rev Neurosci. 2011; 12(8):479–84. [PubMed: 21633381]
31. Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. Eur J Pharmacol. 2003; 479(1–3):23–40. [PubMed: 14612135]
32. Smirnov MS, Kiyatkin EA. Cocaine action on peripheral, non-monoamine neural substrates as a trigger of electroencephalographic desynchronization and electromyographic activation following IV administration in freely moving rats. Neuroscience. 2010; 165(2):500–14. [PubMed: 19861149]
33. Unterwald EM, Rubenfeld JM, Kreek MJ. Repeated cocaine administration up-regulates kappa-opioid and mu-opioid, but not delta-opioid receptors. NeuroReport. 1994; 5(13):1613–6. [PubMed: 7819531]
34. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. Effects of morphine-like and nalorphine-like drugs in nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976; 197(3):517–32. [PubMed: 945347]
35. Vaupel DB. Naltrexone fails to antagonize the sigma-effects of PCP and SKF 10,047 in the dog. Eur J Pharmacol. 1983; 92(3–4):269–74. [PubMed: 6313397]
36. Su TP, Hayashi T. Understanding the molecular mechanism of sigma-1 receptors: Towards a hypothesis that sigma-1 receptors are intracellular amplifiers for signal transduction. Curr Med Chem. 2003; 10(20):2073–80. [PubMed: 12871086]
37. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca2+ signaling and cell survival. Cell. 2007; 131(3):596–610. [PubMed: 17981125]
38. Maurice T, Su TP. The pharmacology of sigma-1 receptors. Pharmacol Ther. 2009; 124(2):195–206. [PubMed: 19619582]
39. Su TP, Hayashi T. Cocaine affects the dynamics of cytoskeletal proteins via sigma(1) receptors. Trends Pharmacol Sci. 2001; 22(9):456–8. [PubMed: 11543872]
40. Hayashi T, Su TP. Regulating ankyrin dynamics: Roles of sigma-1 receptors. PNAS (US). 2001; 98(2):491–6.
41. Sabeti J, Nelson TE, Purdy RH, Gruol DL. Steroid pregnenolone sulfate enhances NMDA-receptor-independent long-term potentiation at hippocampal CA1 synapses: Role for L-type calcium channels and sigma-receptors. Hippocampus. 2007; 17(5):349–69. [PubMed: 17330865]
42. Martina M, Turcotte MEB, Halman S, Bergeron R. The sigma-1 receptor modulates NMDA receptor synaptic transmission and plasticity via SK channels in rat hippocampus. J Physiol Lond. 2007; 578(1):143–57. [PubMed: 17068104]
43. Chen L, Dai XN, Sokabe M. Chronic administration of dehydroepiandrosterone sulfate (DHEAS) primes for facilitated induction of long-term potentiation via sigma 1 (sigma(1)) receptor: Optical imaging study in rat hippocampal slices. Neuropharmacology. 2006; 50(3):380–92. [PubMed: 16364377]
44. Hayashi T, Su TP. sigma-1 receptor ligands - Potential in the treatment of neuropsychiatric disorders. CNS Drugs. 2004; 18(5):269–84. [PubMed: 15089113]
45. Matsumoto RR, McCracken KA, Pouw B, Zhang Y, Bowen WD. Involvement of sigma receptors in the behavioral effects of cocaine: evidence from novel ligands and antisense oligodeoxynucleotides. Neuropharmacology. 2002; 42(8):1043–55. [PubMed: 12128006]
46. Liu Y, Matsumoto RR. Alterations in fos-related antigen 2 and sigma(1) receptor gene and protein expression are associated with the development of cocaine-induced behavioral sensitization: Time course and regional distribution studies. J Pharmacol Exp Ther. 2008; 327(1):187–95. [PubMed: 18591217]

47. Liu Y, Chen GD, Lerner MR, Brackett DJ, Matsumoto RR. Cocaine up-regulates Fra-2 and sigma-1 receptor gene and protein expression in brain regions involved in addiction and reward. J Pharmacol Exp Ther. 2005; 314(2):770–9. [PubMed: 15879001]
48. Watson ES, Murphy JC, Elsohly HN, Elsohly MA, Turner CE. Effects of the administration of coca alkaloids on the primary immune-responses of mice - Interaction with delta-9-tetrahydrocannabinol and ethanol. Toxicol Appl Pharmacol. 1983; 71(1):1–13. [PubMed: 6314602]
49. Bagasra O, Forman L. Functional-analysis of lymphocytes subpopulations in experimental cocaine abuse.1. Dose-dependent activation of lymphocyte subsets. Clin Exp Immunol. 1989; 77(2):289–93. [PubMed: 2528433]
50. Roth MD, Whittaker KM, Choi R, Tashkin DP, Baldwin GC. Cocaine and sigma-1 receptors modulate HIV infection, chemokine receptors, and the HPA axis in the huPBL-SCID model. J Leukoc Biol. 2005; 78(6):1198–203. [PubMed: 16204638]
51. Chao C, Jacobson LP, Tashkin D, Martinez-Maza O, Roth MD, Margolick JB, Chmiel JS, Rinaldo C, Zhang ZF, Detels R. Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men. Drug Alcohol Depend. 2008; 94(1–3):165–71. [PubMed: 18180115]
52. Klein TW, Matsui K, Newton CA, Young J, Widen RE, Friedman H. Cocaine suppresses proliferation of phytohemagglutinin-activated human peripheral-blood T-cells. Int J Immunopharmacol. 1993; 15(1):77–86. [PubMed: 8432625]
53. Piccotti JR, BrissetteStorkus CS, Chambers WH, Bricker JD. Suppression of splenic T lymphocyte proliferation by acute cocaine administration. Life Sci. 1997; 61(10):967–76. [PubMed: 9296335]
54. Faraj BA, Olkowski ZL, Jackson RT. A cocaine-sensitive active dopamine transport in human-lymphocytes. Biochem Pharmacol. 1995; 50(7):1007–14. [PubMed: 7575655]
55. Baldwin GC, Roth MD, Tashkin DP. Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. J Neuroimmunol. 1998; 83(1–2):133–8. [PubMed: 9610681]
56. Gardner B, Zhu LX, Roth MD, Tashkin DP, Dubinett SM, Sharma S. Cocaine modulates cytokine and enhances tumor growth through sigma receptors. J Neuroimmunol. 2004; 147(1–2):95–8. [PubMed: 14741436]
57. Gan XH, Zhang L, Newton T, Chang SL, Ling W, Kermani V, Berger O, Graves MC, Fiala M. Cocaine infusion increases interferon-gamma and decreases interleukin-10 in cocaine-dependent subjects. Clin Immunol Immunopathol. 1998; 89(2):181–90. [PubMed: 9787120]
58. Pellegrino T, Bayer BM. In vivo effects of cocaine on immune cell function. J Neuroimmunol. 1998; 83(1–2):139–47. [PubMed: 9610682]
59. Kubera M, Filip M, Basta-Kaim A, Nowak E, Siwanowicz J, Zajicova A, Holan V, Maes M, Lasori W. The effect of cocaine sensitization on mouse immunoreactivity. Eur J Pharmacol. 2004; 483(2–3):309–15. [PubMed: 14729122]
60. Pellegrino TC, Dunn KL, Bayer BM. Mechanisms of cocaine-induced decreases in immune cell function. Int Immunopharmacol. 2001; 1(4):665–75. [PubMed: 11357879]
61. Deng SX, Bharat N, Fischman MC, Landry DW. Covalent modification of proteins by cocaine. PNAS (US). 2002; 99(6):3412–6.
62. Schneider KJ, DeCaprio AP. Covalent thiol adducts arising from reactive intermediates of cocaine biotransformation. Chem Res Toxicol. 2013; 26(11):1755–64. [PubMed: 24112049]
63. Kinsey BM, Jackson DC, Orson FM. Anti-drug vaccines to treat substance abuse. Immunol Cell Biol. 2009; 87(4):309–14. [PubMed: 19333250]
64. Orson FM, Rossen RD, Shen X, Lopez AY, Wu Y, Kosten TR. Spontaneous development of IgM anti-cocaine antibodies in habitual cocaine users: Effect on IgG antibody responses to a cocaine cholera toxin B conjugate vaccine. Am J Addiction. 2013; 22(2):169–74.
65. Kosten TR, Domingo CB. Can you vaccinate against substance abuse? Expert Opin Biol Ther. 2013 Apr 18; 13(8):1093–7. [PubMed: 23594123]
66. Kousik SM, Napier TC, Carvey PM. The effects of psychostimulant drugs on blood brain barrier function and neuroinflammation. Front Pharmacol. 2012; 3:Article 121.

67. Gan XH, Zhang L, Berger O, Stins MF, Way D, Taub DD, Chang SL, Kim KS, House SD, Weinand M, Witte M, Graves MC, Fiala M. Cocaine enhances brain endothelial adhesion molecules and leukocyte migration. Clin Immunol. 1999; 91(1):68–76. [PubMed: 10219256]
68. Roth MD, Tashkin DP, Choi R, Jamieson BD, Zack JA, Baldwin GC. Cocaine enhances human immunodeficiency virus replication in a model of severe combined immunodeficient mice implanted with human peripheral blood leukocytes. J Infect Dis. 2002; 185(5):701–5. [PubMed: 11865430]
69. Kim SG, Jung JB, Dixit D, Rovner R, Zack JA, Baldwin GC, Vatakis DN. Cocaine exposure enhances permissiveness of quiescent T cells to HIV infection. J Leukoc Biol. 2013 Oct 1; 94(4): 835–43. [PubMed: 23817564]
70. Zhu LX, Sharma S, Gardner B, Escuadro B, Atianzar K, Tashkin DP, Dubinett SM. IL-10 mediates sigma(1) receptor-dependent suppression of antitumor immunity. J Immunol. 2003; 170(7):3585–91. [PubMed: 12646621]
71. Xu W, Flick T, Mitchel J, Knowles C, Ault K. Cocaine effects on immunocompetent cells: an observation of in vitro cocaine exposure. Int J Immunopharmacol. 1999; 21(7):463–72. [PubMed: 10454020]
72. Fischman MW, Schuster CR, Javaid J, Hatano Y, Davis J. Acute tolerance development to the cardiovascular and subjective effects of cocaine. J Pharmacol Exp Ther. 1985; 235(3):677–82. [PubMed: 4078729]
73. Pitts DK, Udom CE, Marwah J. Cardiovascular effects of cocaine in anesthetized and conscious rats. Life Sci. 1987; 40(11):1099–111. [PubMed: 3821374]
74. Foltin RW, Fischman MW. Smoked and intravenous cocaine in humans - acute tolerance, cardiovascular and subjective effects. J Pharmacol Exp Ther. 1991; 257(1):247–61. [PubMed: 2019989]
75. Mendelson JH, Sholar M, Mello NK, Teoh SK, Sholar JW. Cocaine tolerance: Behavioral, cardiovascular, and neuroendocrine function in men. Neuropsychopharmacol. 1998; 18(4):263–71.
76. Karch SB. Cocaine cardiovascular toxicity. South Med J. 2005; 98(8):794–9. [PubMed: 16144174]
77. Restrepo C, Rojas C, Martinez S, Riascos R, Marmol-Velez A, Carrillo J, Vargas D. Cardiovascular complications of cocaine: Imaging findings. Emerg Radiol. 2009 Jan 1; 16(1):11–9. [PubMed: 18773229]
78. Knuepfer MM. Cardiovascular disorders associated with cocaine use: myths and truths. Pharmacol Ther. 2003; 97(3):181–222. [PubMed: 12576134]
79. Afonso L, Mohammad T, Thatai D. Crack whips the heart: A review of the cardiovascular toxicity of cocaine. Am J Cardiol. 2007; 100(6):1040–3. [PubMed: 17826394]
80. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. N Engl J Med. 2001 Aug 2; 345(5):351–8. [PubMed: 11484693]
81. Reece A. Evidence of accelerated ageing in clinical drug addiction from immune, hepatic and metabolic biomarkers. Immun Ageing. 2007; 4(1):6. [PubMed: 17892544]
82. Rissin DM, Kan CW, Campbell TG, Howes SC, Fournier DR, Song L, Piech T, Patel PP, Chang L, Rivnak AJ, Ferrell EP, Randall JD, Provuncher GK, Walt DR, Duffy DC. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nat Biotechnol. 2010; 28(6):595–9. [PubMed: 20495550]
83. Faley SL, Copland M, Wlodkowic D, Kolch W, Seale KT, Wikswo JP, Cooper JM. Microfluidic single cell arrays to interrogate signalling dynamics of individual, patient-derived hematopoietic stem cells. Lab Chip. 2009; 9(18):2659–64. [PubMed: 19704981]
84. Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. Neuron. 2000; 25(3):515–32. [PubMed: 10774721]
85. Robinson TE, Berridge KC. The neural basis of drug craving - an incentive-sensitization theory of addiction. Brain Res Rev. 1993; 18(3):247–91. [PubMed: 8401595]
86. Self DW, Nestler EJ. Molecular mechanisms of drug reinforcement and addiction. An Rev Neurosci. 1995; 18:463–95.
87. Kuhar MJ, Pilotte NS. Neurochemical changes in cocaine withdrawal. Trends Pharmacol Sci. 1996; 17(7):260–4. [PubMed: 8756185]

88. Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug-induced and stress-induced sensitization of motor-activity. Brain Res Rev. 1991; 16(3):223–44. [PubMed: 1665095]

89. De Vries TJ, Schoffelmeer ANM, Binnekade R, Murder AH, Vanderschuren LJMJ. Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization. Eur J Neurosci. 1998; 10(11):3565–71. [PubMed: 9824469]

90. Romieu P, Meunier J, Garcia D, Zozime N, Martin-Fardon R, Bowen WD, Maurice T. The sigma(1) (sigma(1)) receptor activation is a key step for the reactivation of cocaine conditioned place preference by drug priming. Psychopharmacol. 2004; 175(2):154–62.

91. Ecke LE, Cleck JN, White P, Schug J, Mifflin L, Blendy JA. CREB-mediated alterations in the amygdala transcriptome: coordinated regulation of immune response genes following cocaine. Int J Neuropsychopharmacol. 2011; 14(8):1111–26. [PubMed: 21138621]

92. Maier SF, Watkins LR. Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev. 1998; 105(1):83–107. [PubMed: 9450372]

93. Anisman H. Cascading effects of stressors and inflammatory immune system activation: implications for major depressive disorder. J Psychiatry Neurosci. 2009; 34(1):4–20. [PubMed: 19125209]

94. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol. 2006; 6(4):318–28. [PubMed: 16557263]

95. Tilders, JH.; Schmidt, ED. Cross-sensitization between immune and non-immune stressors. In: Dantzer, R.; Wollman, EE.; Yirmiya, R., editors. Cytokines, Stress, and Depression. 461. Springer US; 1999. p. 179-97.

96. Ambroggi F, Turiault M, Milet A, Deroche-Gamonet V, Parnaudeau S, Balado E, Barik J, van der Veen R, Maroteaux G, Lemberger T, Schutz G, Lazar M, Marinelli M, Piazza PV, Tronche F. Stress and addiction: glucocorticoid receptor in dopaminoceptive neurons facilitates cocaine seeking. Nat Neurosci. 2009; 12(3):247–9. [PubMed: 19234455]

97. Avila, AH.; Alonzo, NC.; Bayer, BM. Effects of cocaine and morphine withdrawal on the immune response. In: Friedman, H.; Klein, TW.; Bendinelli, M., editors. Infectious Diseases and Substance Abuse. Springer US; 2005. p. 1-11.

98. Avila AH, Morgan CA, Bayer BM. Stress-induced suppression of the immune system after withdrawal from chronic cocaine. J Pharmacol Exp Ther. 2003; 305(1):290–7. [PubMed: 12649381]

99. Avila AH, Alonzo NC, Bayer BM. Immune cell activity during the initial stages of withdrawal from chronic exposure to cocaine or morphine. J Neuroimmunol. 2004; 147(1–2):109–13. [PubMed: 14741439]

100. Johnson TR, Knisely JS, Christmas JT, Schnoll SH, Ruddy S. Changes in immunologic cell surface markers during cocaine withdrawal in pregnant women. Brain Behav Immun. 1996; 10(4):324–36. [PubMed: 9045748]

101. Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Palmi I, Ortuno J, Menoyo E, Segura J, de la Torre R. Cell-mediated immune response in MDMA users after repeated dose administration. Ann New York Acad Sci. 2002; 965(1):421–33. [PubMed: 12105117]

102. Hicks MJ, De BP, Rosenberg JB, Davidson JT, Moreno AY, Janda KD, Wee S, Koob GF, Hackett NR, Kaminsky SM, Worgall S, Toth M, Mezey J, Crystal RG. Cocaine analog coupled to disrupted adenovirus: A vaccine strategy to evoke high-titer immunity against addictive drugs. Mol Ther. 2011; 19(3):612–9. [PubMed: 21206484]

103. Su TP, Hayashi T, Vaupel DB. When the endogenous hallucinogenic trace amine N,N-dimethyltryptamine meets the sigma-1 receptor. Sci Signal. 2009; 2(61):Article pe12.

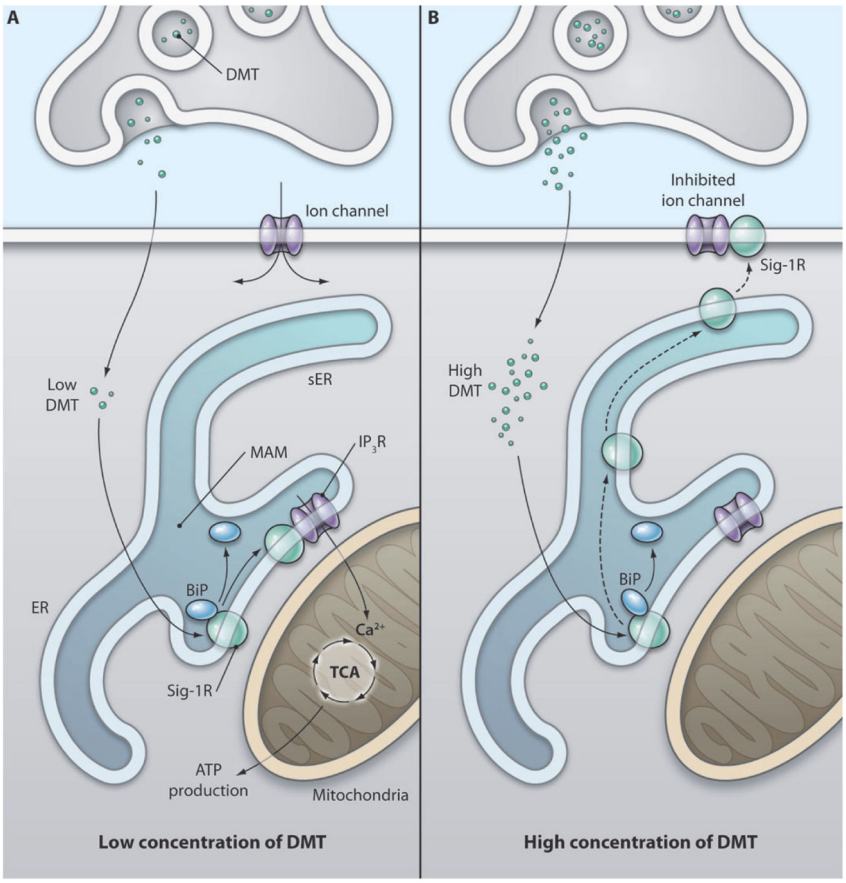

Figure 1.

Schematic representation of the signaling of N,N-dimethyltryptamine (DMT) by vesicular release from the pre-synaptic neuron (upper) through sigma-1 receptors (Sig-1R). A) At low concentrations of DMT, Sig-1Rs in the mitochondrion-associated endoplasmic reticulum (ER) membrane (i.e., the MAM) serve as ligand-activated molecular chaperones, particularly when Sig-1R ligands, including DMT, are present at concentrations close to the Ki value for that ligand-receptor pair.[103] In this case, DMT binding leads to the dissociation of binding immunoglobulin protein (BiP), another ER chaperone, from the Sig-1Rs. The Sig-1Rs can then co-localize with inositol 1,4,5-trisphosphate receptors (IP 3Rs) at the MAM,[103] enhancing Ca2+ signaling from the ER into mitochondria,[103], which activates the tricarboxylic acid (TCA) cycle and increases the production of adenosine triphosphate (ATP) that is released into the cytosol.[103] B) Higher concentrations of DMT cause the translocation of Sig-1Rs from the MAM to the plasma membrane, leading to the inhibition of other ion channels. Thus, Sig-1R ligands might shift the site of action of Sig-1R chaperones from the center of the cell to its periphery. In the present scheme, Sig-1Rs and related molecules or organelles are illustrated in the postsynaptic region for the sake of simplicity, although they may also be present presynaptically or in glia. Figure from Su et. al.,[103] with permission.

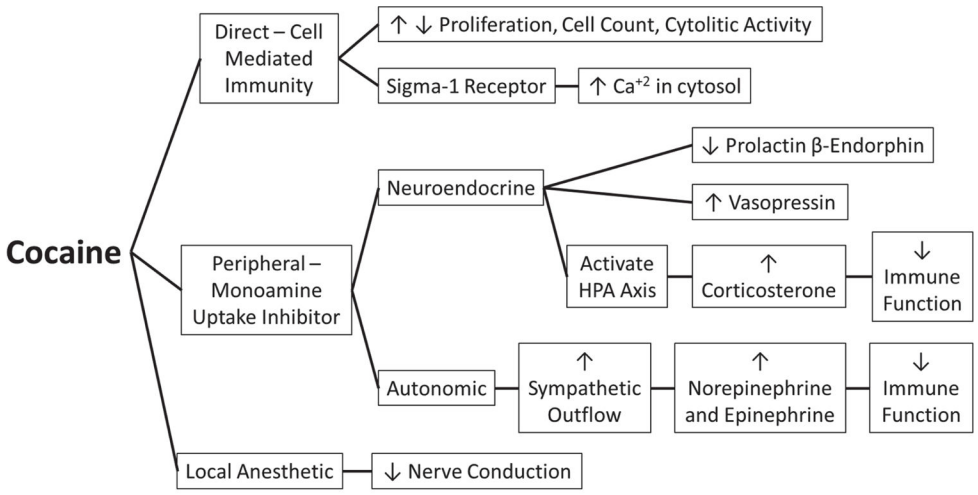

Figure 2.

Summary of effects of cocaine on immune function. Both up and down arrows indicate mixed results. Cocaine also alters antibody and cytokine production, though it is not clear by which route these alterations occur. Adapted from Pellegrino and Bayer.[58]

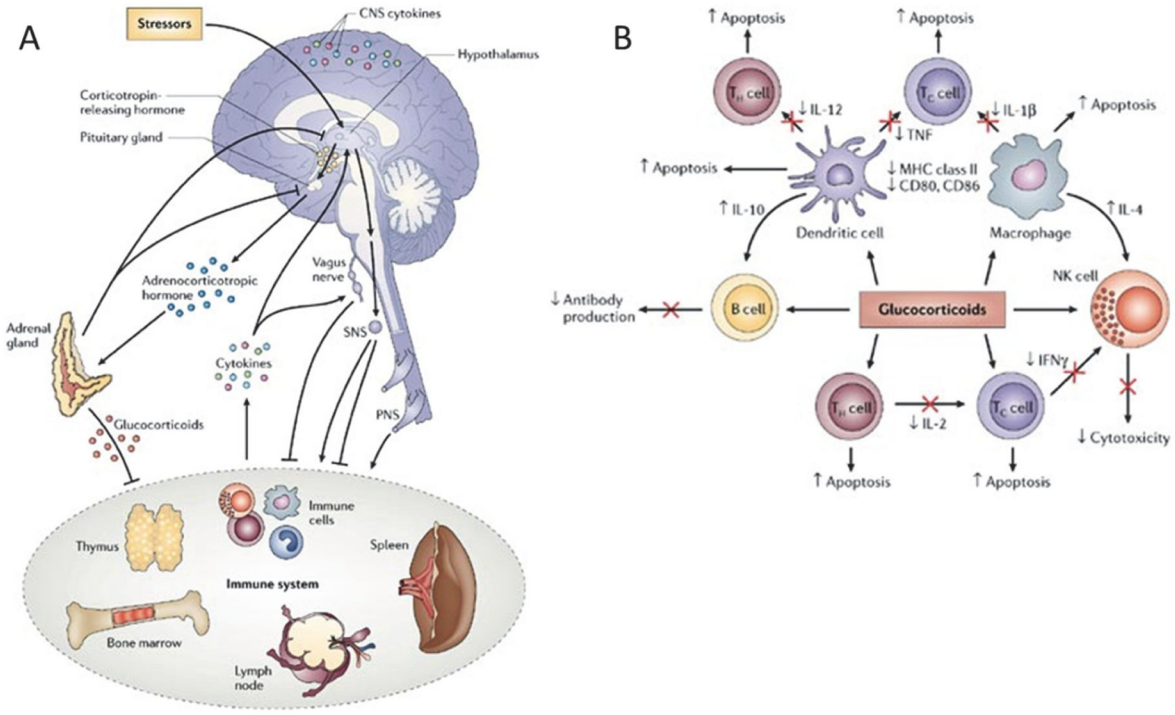

Figure 3.

A) Brain-immune bi-directional connections: the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS), and the peripheral nervous system (PNS). B) Glucocorticoids' mechanisms of action on immune cells resulting in alteration of function. From Sternberg.[94] Reprinted by permission of the author and from Macmillan Publishers Ltd: *Nature Reviews Immunology* 6(4), © 2006.