Inflammation and infection in human cocaine addiction

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Over the past 30 years, the effects of cocaine on the immune system have been subject to research mainly in animals, while relatively little work has been done in humans. This review focuses exclusively on the human work and the related findings in a way that is accessible to neuroscientists. The emerging picture suggests that cocaine may exert some direct effects on lymphocyte responses, as well as, and possibly more importantly, indirect effects via interactions with the sympathetic and neuroendocrine systems. Given the pressing need for more effective treatments for cocaine addiction and the high prevalence of medical complications associated with this disorder, this review leaves no doubt that drug addiction merits a place in the growing field of neuropsychoimmunology.

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Introduction

Cocaine – one of the most widely consumed illicit drugs amongst young adults worldwide – is associated with significant harm [1]. Although the negative consequences of regular cocaine use are most noticeable in the domain of psychosocial functioning, attention has been increasingly paid to the wide range of medical complications frequently seen in chronic cocaine users [2,3]. Yet, the true scale of the health burden associated with the use of cocaine is only slowly emerging. Many cocaine-related medical complications lack specificity, and may only be recognized once they deteriorate into medical emergencies. However, at this late stage a direct link with cocaine is difficult to establish [4]. A common adverse health consequence in cocaine-addicted individuals is the increased transmission and progression of infectious diseases [4]. Understanding this particular vulnerability for infections may not only help to prevent the worsening of medical problems, but could also open up new avenues for the development of effective medical treatments for cocaine addiction, which are presently still lacking. This review represents an attempt to elucidate the high infection risk in cocaine addiction from both a neuroscientific and an immunological perspective, with a particular focus on research in humans. A comprehensive introduction into the field of neuropsychoimmunology would be beyond the scope of this review, but can be found elsewhere [5,6,7••]. Instead, our aim is to give neuroscientists a glimpse into an emerging area of interdisciplinary research that has the potential to broaden and improve our understanding of cocaine addiction.

The neuroscientific perspective

Infections caused by maladaptive behaviour

For many neuroscientists, inflammation and infection in chronic cocaine users have been regarded as consequential to behaviours that occur in conjunction with cocaine-related changes in brain function. The dopamine system is one of the best studied in cocaine addiction, as it is critically involved in cocaine's highly reinforcing effects, thus determining its addictive properties [8]. As a central nervous stimulant, cocaine acutely increases levels of monoamines (specifically dopamine) by blocking their reuptake [9]. Acute cocaine intoxication is associated with compromised judgement and decision-making abilities, which may facilitate reward-seeking and risk-taking behaviours. Chronic cocaine use has been associated with a variety of neuroadaptive changes, resulting in reduced central dopamine neurotransmission [10,11] and significant abnormalities in brain structure and function [12]. Compromised 'higher level' cognitive processing is thus likely to underlie the erratic and ill-judged behaviour patterns frequently seen in cocaine-addicted individuals. No doubt risky behaviours, such as sharing unsterile straws and pipes or engagement in unprotected sex, increase the probability of contracting an infectious disease [13]. Moreover, cocaine users' failure to avoid adversity [14] may not only increase the likelihood for contracting infections even further [15], but also explain the limited success of harm avoidance strategies in the treatment of cocaine addiction [16]. A better understanding of the drug's immunomodulatory effects might therefore be critical in developing more effective means of protection.

The immunological perspective
## Infections caused by drug effects on cell-mediated immunity

Cocaine not only increases monoamine levels in the brain but also in the periphery, where it interacts with immune cells. The neurotransmitter dopamine is thought to play a pivotal role in regulating immunity [17]. Dopamine receptors are expressed on various lymphocyte subpopulations (i.e. T-cells, B-cells and NK-cells), where they contribute to the regulation of proliferation, differentiation and apoptosis of these cells [18]. Through binding to the dopamine transporter in peripheral lymphocytes, cocaine may thus be able to directly modulate immune functions [19••]. Dopamine has, therefore, been suggested to act as a mediator between the brain and the immune system, given its involvement in both [20]. Preclinical studies provide support for this hypothesis, showing that experimental lesions of the nigrostriatal dopaminergic system directly result in an increase in the number of circulating T-cells, B-cells, and neutrophil granulocytes in peripheral blood [21]. Clinical observations in neuropsychiatric disorders complement this evidence: Parkinson's disease and schizophrenia, both disorders that are characterized by significant abnormalities in central dopamine function, show significant alterations in the proliferative response of peripheral lymphocytes in these patients [18]. This invites the question of whether the widely studied central nervous dopamine dysfunction in cocaine addiction is also accompanied by changes in the number, proportion and function of CD4+ and CD8+ lymphocytes, natural killer (NK) cells, and macrophages in the periphery.

Although little studied in humans, the picture emerging from the literature suggests that cocaine administration acutely increases the number and activity of distinct lymphocyte populations, including CD4+, CD8+ and NK-cells [22–24]. However, it remains unclear as to whether these changes are long lasting, as reports in actively using cocaine-addicted individuals are inconsistent [23,25]. Our own data in stimulant-addicted individuals show significantly higher levels of CD4- and significantly lower levels of NK-cells compared with healthy control volunteers, and no measurable group differences with respect to CD8 and B-cells (Figure 1). Important to note is that these observed changes were not associated with differences in measures of depressed mood, although levels of depression were significantly higher in addicted individuals and depression itself has been associated with changes in immunity. Though perhaps surprising at first glance, these results are consistent with the notion of the dopamine-mediated control of lymphocyte function [26]. For instance, the significant decline in NK-cells could be explained by the suppression of NK-cell proliferation following prolonged dopamine-induced activation [27], which would be a plausible scenario in cocaine addiction. In light of the major role that NK-cells play in anti-viral immune defense, reduced levels of NK-cells may have repercussions on immunity. Furthermore, increased levels of CD4 T-cells would not be unusual following prolonged periods of infection.

Changes in immune regulation may be reflected not only in the cell count, but also in alterations in the cells' capacity to either produce or respond to cytokines. Cytokines are cell-signalling molecules that facilitate communication between cells and regulate immune responses. Changes in cytokine expression may thus impact on

Figure 1
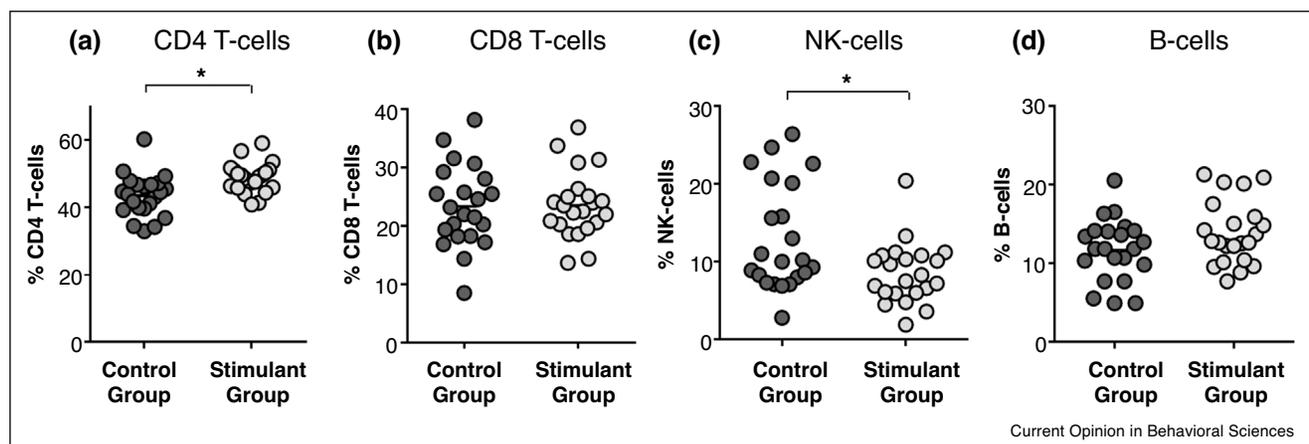
Comparisons of T-cells, NK-cells and B-cells between 22 actively using stimulant-dependent individuals and 22 matched healthy control volunteers. **(a)** The percentage of CD4 T-cells was significantly increased in the stimulant-dependent group compared with control volunteers ($t_{42} = 3.21$, $p = 0.003$). **(b)** The percentage of CD8 T-cells ($t_{42} = 0.11$, $p = 0.916$) and the CD4/CD8 ratio did not significantly differ between the groups ($t_{42} = 0.58$, $p = 0.568$). **(c)** The percentage of NK-cells is significantly reduced in the stimulant-dependent group ($t_{42} = 2.69$, $p = 0.010$) compared with the control group. **(d)** No differences were found with respect to the percentage of B-cells ($t_{42} = 1.79$, $p = 0.081$).

immunity. Although several studies identified differences in cytokine concentration in the blood of cocaine-addicted individuals compared with control volunteers [28–33] (Table 1), these results are difficult to interpret. Cross-sectional measurements only give a snapshot of participants' current inflammatory status, without providing any details about potential causes or mechanisms underlying the observed deviations. Measurements of cytokine expression in response to cocaine exposure are more informative, as these might elucidate the functional implications of cocaine use on immunity and inflammation.

Though only a few studies have examined blood samples after volunteers had taken cocaine, they consistently report anti-inflammatory effects. Cocaine administration *in vivo* seems to significantly reduce the synthesis of pro-inflammatory cytokines such as tumor-necrosis factor (TNF) alpha and interleukin (IL) 6 [34[•],35[•]], irrespective of whether these volunteers had prior experiences with cocaine. By contrast, cocaine-addicted participants in our studies, who are using cocaine almost on a daily basis, show significantly higher levels of IL-6 compared with control volunteers, both in circulating blood (unpublished) as well as in saliva [15]. This suggests that cocaine may acutely exert anti-inflammatory effects but, when used chronically, may have the opposite effect, which increases the risk of systemic inflammation.

The functional implications of altered cytokine secretion can be examined by experimentally activating immune cell populations *in vitro*. T-cells can be stimulated by the lectin phythohemagglutin (PHA), whereas innate immune cells can be stimulated by the endotoxin lipopolysaccharide (LPS). Cocaine administration *in vivo* has been shown to acutely alter the cytokine balance between cellular (Th1) and humoral (Th2) immunity by increasing the PHA-stimulated secretion of interferon (IFN) gamma and decreasing the secretion of IL-10 [22]. Another study, which also administered cocaine to their volunteers *in vivo* before challenging their blood *in vitro* with LPS reported that cocaine had a significant inhibitory effect on the secretion of TNF-α whilst preserving the secretion of IL-6 [34]. However, we could not replicate the aforementioned findings in our own data, which we obtained by stimulating blood samples of healthy volunteers *in vitro* with PHA and LPS both with and without using cocaine as a co-stimulator. One account for the observed discrepancies in results may lie in the nature of conditions for cocaine exposure within different experiments: namely the difference between *in vivo* versus *in vitro* exposure. Cocaine exposure *in vivo* may enable the action of indirect effects of cocaine on neurotransmitters and hormones, which could mediate cocaine's effect on the immune response, in a way that *in vitro* exposure may not capture [36[••]].

Increasing the risk of infection through drug-induced physiological mechanisms

The brain and the immune system continuously crosstalk through soluble factors including cytokines, hormones and neurotransmitters, in order to maintain homeostasis. Communication is organized along two main pathways, comprising the autonomic nervous system and the neuroendocrine axis [36[••]]. Disruptions of homeostasis (by either internal or external stressors) activate these two pathways, resulting in increased peripheral levels of catecholamines (specifically noradrenaline) and cortisol respectively, which in turn activate or alter immune function through binding to their matching receptors on immune cells. Innervation of lymphoid tissue by the sympathetic system could be regarded as a direct link between the brain and the immune system [36]. Intriguingly, the effects of cocaine on both the sympathetic nervous and endocrine systems appear to mimic the stress response [35]. The similarities in the effects of stress and cocaine on immune cells are also exemplified by an increase in NK-cells, which has been reported in response to either acute stress or cocaine exposure [23,24,37]. Chronic stress, however, has been associated with a down-regulation in NK-cell activity [38], resembling our data in stimulant-addicted individuals. It is thus conceivable that the observed changes in NK-cells in cocaine-addicted individuals may not only be attributable to cocaine's direct effects on immune cells, but may also be caused by cocaine's modulatory effects on neuroendocrine hormones [35].

The role of cocaine in the progression of infectious diseases

Our growing knowledge about the immunomodulatory effects of cocaine has raised concerns around whether regular cocaine use may be associated not only with an increased risk for infections, but also with more rapid and severe progression of a contracted infectious disease. An interaction between the drug and a virus have been shown for the human immunodeficiency virus (HIV), but this may well apply to other infections too. One example of such an interaction involves the dopamine transporter (DAT), to which both the HIV-TAT protein and cocaine bind. Whilst cocaine increases extracellular levels of dopamine by inhibiting the DAT and thereby blocking dopamine reuptake, TAT-protein acts as an allosteric modulator of the DAT [39]. The increase in dopamine concentration is thought to result in an augmentation of inflammatory macrophages and greater permeability of the blood–brain-barrier, which in turn promotes the progression of HIV-associated pathology. Importantly, the interactions between cocaine and HIV are complex and are not limited to the DAT. Further mechanisms have been described including cocaine-induced enhancement of HIV transcription and expression [39,40]. Clearly, the use of cocaine during HIV infection worsens the outcome by increasing inflammation, accelerating the progression

Table 1

List of studies that have investigated the effects of cocaine use on the human immune system over the past 30 years, which are highly heterogeneous in terms of the cell types/products being studied (cells, cytokines, chemokines), procedures conducted (*in vivo/in vitro*), type of stimulation being used (T-cell stimulation/innate), and composition of the samples analyzed (patients, healthy volunteers, level of dependency, state of abstinence)

Authors	Groups	Measures	Key findings
Moreira et al. [28]	• 12 self-reported cocaine users (abstinent) • 24 healthy controls	Serum IL6, IL10	IL6: cocaine > control IL10: cocaine < control
Araos et al. [30]	• 82 chronic cocaine users (abstinent) with co-morbid alcohol use disorder • 65 healthy controls	Plasma TNFα, IL1β, IL6, CX3CL1/fractalkine, CCL2/MCP-1, CXCL12/SDF-1	TNFα, CCL2/MCP-1 CXCL12/SDF-1: cocaine < control
Ersche et al. [15]	• 31 cocaine-dependent men (not abstinent) • 30 healthy male controls	Saliva Il1β, IL6, IL8, IL10, IL12p70, TNFα, IFNγ Serial sampling: pre/post provocation (2 conditions: disgust-evoking, neutral) Recordings: skin conductance, response time Questionnaires: attitudes towards disgust and hygiene behaviours	Il6 baseline: cocaine > control IL6 disgust provocation: cocaine > control
Levandowski et al. [31]	• 44 cocaine-dependent women (abstinent) • 25 female healthy controls	Plasma TNFα, sTNFRI, sTNFRII, TWEAK, TRAIL Questionnaires: childhood trauma, severity of tobacco smoking	Group differences mediated by history of childhood trauma.
Narvaez et al. [29]	• 37 cocaine-dependent individuals (abstinent) • 27 healthy controls	Serum Il1β, IL6, TNFα, IL8, IL10, IL12p70, BDNF, TBARS, PCC	IL1ß, TNFα, BDNF: cocaine > control
Fox et al. [53]	• 28 cocaine-dependent individuals (abstinent) • 27 social drinking controls	Plasma TNFα, IL10, IL1ra Serial sampling: pre and post mental imagery (2 conditions: stress, neutral) Additional measurements: drug craving	IL10 baseline: cocaine < control TNFα following stress imagery: cocaine > control
Loftis et al. [54]	• 20 methamphetamine-dependent (abstinent) • 20 healthy controls	Plasma IL1β, IL2, IL6, IL10, TNFα, MCP-1, MIP-1α, MIP-1β, ICAM-1	No significant group differences.
Irwin et al. [34•]	• 19 cocaine-dependent men (abstinent) • 19 healthy male controls	Plasma TNFα, IL6 *In vivo*: 40 mg cocaine IV and placebo IV Serial sampling: pre and every 4 hours post treatment *In vitro*: LPS stimulation Additional measurements: heart rate variability	TNF-α baseline: cocaine < control TNFα and IL6 post treatment: cocaine < placebo LPS-stimulated TNFα: cocaine < placebo
Rios-Olivares et al. [33]	• 30 cocaine and heroin-dependent individuals with hepatitis C (not abstinent) • 30 healthy controls without hepatitis C	Plasma + supernatants TNFα, IFNγ, IL1β, IL2, IL4, IL6, IL10 *In vitro*: PHA and PAI stimulation	TNFα, IFNγ, IL2,IL4, IL6, IL10 (unstimulated): cocaine > control
Halpern et al. [35•]	• 2 × 15 cocaine users (not dependent, abstinent)	Plasma IL6, cortisol, ACTH, DHEA, cocaine levels *In vivo*: either IV 0.4 mg/kg cocaine or placebo Serial sampling: pre/2 hours post treatment Additional measurements: endocrine responses	IL6 baseline: no group differences IL6 post treatment: cocaine < placebo
Gan et al. [22]	• 15 cocaine-dependent individuals (not abstinent) • 4 healthy blood donors	Plasma INFγ, TNFα,IL1β, IL2, IL6 IL10, IL12 Lymphocytes profile: CD4+, CD8+, NK-cells *In vivo*: 40 mg cocaine IV, pre/post cocaine *In vitro*: cocaine stimulation in four healthy controls	INFγ: cocaine > baseline IL10: cocaine < baseline *In vitro* stimulation: cocaine suppressed INFγ and IL10 synthesis
Ruiz et al. [25]	• 63 cocaine users (not dependent, not abstinent) • 20 healthy controls	Lymphocytes profile *In vitro*: PHA, AntiCD3, PMA, IL2 – stimulations	No significant group differences in lymphocyte profile
Ruiz et al. [23]	• 34 cocaine users (not dependent, not abstinent) • 22 healthy controls	Lymphocytes profile	CD4+ and NK-cells: cocaine > controls CD8+ T-cells: cocaine < controls
Chen et al. [32]	• 47 polydrug users with a history of cocaine use (mainly abstinent) • No controls	Plasma IL1, IL2, IFN, SIL-2R	No relationships between cytokine expression and severity of drug use.
Van Dyke et al. [24]	• 8 occasional cocaine users (abstinent) • No controls	Lymphocytes profile and activity *In vivo*: 0.6 mg cocaine or placebo IV Serial sampling: pre/post intervention	NK-cell activity: cocaine > placebo

of the infection and promoting the development of the HIV-associated neurocognitive disorder.

Possible clinical implications

The most obvious clinical consequences resulting from compromised immunity are an increased susceptibility to, and accelerated progression of, infectious diseases, as well as other medical complications, including cardiovascular and cerebrovascular disorders [41]. The combination of risky behaviour patterns, insufficient avoidance of adversity and drug-induced changes to immunity may render chronic cocaine users particularly prone to developing medical complications with a chronic trajectory. Interventions that aim to achieve greater success should therefore not solely rely on users' insight into the health risks associated with their drug use, but rather actively protect them from potential threats to their health that they will likely fail to avoid and that their immune system will struggle to fight.

Not only may cocaine's immunomodulatory effects diminish the users' ability to fight infections, but it is also plausible that these immunomodulatory effects could play a part in the development of addiction itself. Just as the neuroendocrine effects of cocaine have been linked with processes such as sensitization, which enhance cocaine's reinforcing properties [42], cocaine's anti-inflammatory effects might also perpetuate its regular use through mechanisms of negative reinforcement in individuals with systemic inflammation. Any activation of the peripheral immune system leads to increased peripheral concentrations of pro-inflammatory cytokines, which induce a syndrome of sickness behaviour characterized by fatigue, anhedonia, anorexia, and depressed mood [43]. The short-term anti-inflammatory effects of cocaine may thus alleviate such inflammation-related or stress-induced discomfort, thereby motivating further use of cocaine.

A further line of enquiry may be to consider what could lie at the roots of an individual's proneness to systemic inflammation. One possible factor might be psychological stress, which can trigger acute inflammatory responses [44]. Childhood trauma and adversity have been linked with enhanced inflammatory responsiveness to psychosocial stress [45], and both of these have been linked with later life depression [46]. Such histories are also common in cocaine-dependent individuals, which raises the question as to whether early-life stress mediates the vulnerability to both depression and addiction in these individuals via immunological mechanisms. These individuals, having faced significant adversity early in life [47,48] and thus developed a propensity to increased inflammatory responses, may then be more likely both to suffer from depression and to self-medicate with cocaine [49]. Although the idea of self-medication in the development of cocaine addiction is not new, the anti-inflammatory

effects of the drug have, to the best of our knowledge, not yet been considered within this context.

Possible implications for research

It is indisputable that the need to improve treatment for cocaine addiction is highly pressing. A better understanding of cocaine's effects on immunity may shed light on new pathways for progress towards meeting this need by revealing mechanisms underpinning the development and chronicity of cocaine addiction, which may serve as targets for future interventions. Although this review only focuses on research conducted in humans, there is also a wealth of animal literature in this field. The present ambiguity of findings thus far in humans highlights the need for further animal research, as well as translational studies in order to apply the knowledge that has been acquired in animals to humans. It is also important that research in humans expands on the animal work by addressing clinically relevant issues such as potential variations in the immunomodulatory effects of cocaine at different stages of the addiction cycle, and how these might determine treatment outcomes.

As cocaine is most commonly used concurrently with other drugs, in particular with alcohol and opiates, it would also be critical to investigate its immunomodulatory effects in combination with other drugs that affect the immune system in their own way [6,50]. As we know from research on the central nervous system, poly-drug use relative to mono-drug use is associated with an amplification of adverse effects on brain structure and function (see Meyerhoff in this issue), and a similar effect may conceivably be mirrored in the changes observed in the immune system. The prolonged use of drugs is another clinically important aspect that requires investigation. Many patients who are seeking treatment have been using cocaine for many years, but the majority of studies only investigate the acute effects of the drug. However, the effects in chronic users are likely to differ and should be considered in research. Furthermore, studies addressing the long-term use of cocaine would be greatly enhanced by assuming a holistic approach, taking into account the multiple interacting systems, including the immune system, which cocaine may exert an influence on.

Turning towards broader considerations, it is worth highlighting the effects of ageing on immune function. Like older people, cocaine users show increased susceptibility to inflammatory diseases and microbial infections [51]. On this basis, an improved understanding of cocaine-related immune adaptations may help to elucidate the relationship between cocaine use, accelerated brain ageing [52] and altered immunity [5]. In a similar vein, it is also possible that cocaine's immunological effects may relate to other notable effects associated with cocaine addiction, such as low body weight and poor sleep quality.

Future research should therefore not be restricted to the classical psychotropic actions of addictive drugs, but should also take into consideration the effects at multiple levels in both the brain and the periphery.

No doubt, the growing interdisciplinary field of neuropsychoimmunology offers much potential for progress in our understanding of brain-immune system interactions, and the implications for psychiatric disorders. This is an exciting new field that is opening up to addiction researchers, bringing opportunities to deepen our understanding and broaden our conceptualization of addiction as a disorder that goes beyond the bounds of the brain as a discrete entity, and thereby potentially paving the way for identifying new targets for the treatment of cocaine addiction.

Conflict of interest
Nothing declared.

Acknowledgement

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