Aberrant Disgust Responses and Immune Reactivity in Cocaine-Dependent Men

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Background: Infectious diseases are the most common and cost-intensive health complications associated with drug addiction. There is wide belief that drug-dependent individuals expose themselves more regularly to disease-related pathogens through risky behaviors such as sharing pipes and needles, thereby increasing their risk for contracting an infectious disease. However, evidence is emerging indicating that not only lifestyle but also the immunomodulatory effects of addictive drugs, such as cocaine, may account for their high infection risk. As feelings of disgust are thought to be an important psychological mechanism in avoiding the exposure to pathogens, we sought to investigate behavioral, physiological, and immune responses to disgust-evoking cues in both cocaine-dependent and healthy men.

Methods: All participants ($N = 61$) were exposed to neutral and disgust-evoking photographs depicting food and nonfood images while response accuracy, latency, and skin conductivity were recorded. Saliva samples were collected before and after exposure to neutral and disgusting images, respectively. Attitudes toward disgust and hygiene behaviors were assessed using questionnaire measures.

Results: Response times to disgust-evoking photographs were prolonged in all participants, and specifically in cocaine-dependent individuals. While viewing the disgusting images, cocaine-dependent individuals exhibited aberrant skin conductivity and increased the secretion of the salivary cytokine interleukin-6 relative to control participants.

Conclusion: Our data provide evidence of a hypersensitivity to disgusting stimuli in cocaine-dependent individuals, possibly reflecting conditioned responses to noningestive sources of infection. Coupled with a lack of interoception of bodily signals, aberrant disgust responses might lead to increased infection susceptibility in affected individuals.

Key Words: Conditioned immunoactivation, cytokines, drug addiction, interleukin (IL)-6, infection susceptibility, interoception

One of the most serious and costly health complications associated with drug addiction is the risk of contracting or transmitting infectious diseases (1–5). Reducing the disproportionately high rate of infection in chronic drug users has long been a priority target of harm-reduction policies (6). Although the introduction of needle-exchange schemes has been successful for intravenous cocaine users, harm reduction remains a challenge for users who snort cocaine or inhale crack-cocaine (7–9). For instance, hepatitis C rates of up to 80% have been estimated in crack-cocaine smokers (6). Risky behaviors such as sharing unsterile straws or pipes, engaging in unprotected sex, or personal hygiene inadequacies have been considered to account for the increased prevalence of infections in noninjecting users (10–12). Yet several studies have failed to find relationships between these risky behaviors and infection rates in this population (10,13), suggesting that factors other than lifestyle may account for their high infection risk.

Emerging evidence indicates that addictive drugs have immunomodulatory effects that may decrease drug users' ability to fight infections (14–17). Cocaine has been shown to alter immune cell activity and cytokine production (18,19), leading to the suppression of innate immune responses (20,21). Conversely, cocaine has also been shown to prolong inflammation, possibly through neuroendocrine interactions (22), which could facilitate the development of systemic low-grade inflammation (23,24). Current strategies to tackle the high infection rates in chronic drug users focus primarily on remediating harm, although proactive approaches strengthening protective mechanisms might be more desirable.

Self-care behaviors are one vital means through which infectious diseases can be prevented. A critical mechanism underlying the development of avoidant and protective self-care strategies are learned relationships between cues signaling sickness, feelings of disgust, and unconditioned immune responses (25–27). Stimuli evoking feelings of disgust can induce bodily sensations of revulsion and nausea, eliciting a desire to withdraw from disgust-evoking cues (28,29). Stimuli that typically convey the so-called "core" or "pathogen disgust" are rotten food, decomposing organic matter, poor hygiene, and body products (30,31). Repeated encounters with disgusting stimuli, and the feelings of sickness they elicit, may be necessary to associate these evocative memory traces with avoidance or hygienic behaviors (27,32). As the central nervous system actively communicates with the immune system, Pavlovian conditioning to disgust-evoking cues can be observed in both behavioral and immune responses (26,33,34). For example, Schaller and colleagues examined blood samples of healthy volunteers who were exposed to either infection- or gun-related photographs (35). Subsequent in vitro stimulation of these blood samples with bacterial lipopolysaccharide (LPS) showed that samples provided by volunteers who were exposed to the disease-related photographs had a significantly greater increase in the cytokine interleukin-6 (IL-6) compared with those in the control condition.

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The pro-inflammatory cytokine IL-6 is a key regulator of inflammatory processes in response to acute infection (36;37). The authors suggested that participants' prior experience with pathogens associated with the infectious diseases shown in the photographs may have triggered an anticipatory response that facilitated the release of IL-6 (35).

Several studies have shown that cocaine directly suppresses production of IL-6 in the blood during acute infection (20,21), but little is known of how cocaine-dependent individuals (CDIs) respond to cues signaling infection. Salivary immune responses are of particular interest because the mouth is a major gateway of microbial infection and mucosal immunity, which is independent from the rest of the peripheral lymphoid immunity (38). In the current study, we measured disgust-induced behavioral, physiological, and immune responses in CDIs and healthy volunteers to investigate two contrasting hypotheses of infection risk in CDIs. It is possible that CDIs are insensitive to disgust-evoking cues, thereby failing to anticipate risks of infection and exposing themselves to pathogens. If this hypothesis were correct, we would predict blunted disgust processing in the cocaine group, along with self-reports showing little reflection on disgusting experiences and poor hygienic practices. Alternatively, CDIs could show conditioned hypersensitive responses to disgust-evoking stimuli because of their frequent history of infection, but they fail to use this information appropriately to guide their behavior. If this hypothesis were correct, we would predict increased responses to stimuli predictive of infection in the cocaine group but no difference from the control group in terms of cognitive and behavioral strategies relating to risks of infection.

Methods and Materials

Participants

Sixty-five men were recruited within the local community upon referral from probation officers, health care professionals, advertisements, or word-of-mouth. For inclusion, participants had to be male, 20 to 60 years of age, and able to read and write in English. Drug-dependent volunteers had to satisfy the DSM-IV-TR (39) criteria for cocaine dependence, whereas healthy control volunteers were required to have no personal or family history of substance misuse disorders. Exclusion criteria for all volunteers included a lifetime history of a psychotic disorder, neurological illness or traumatic head injury, an autoimmune or metabolic disorder, or HIV infection. All volunteers consented in writing and were screened for current psychiatric disorders using the Mini-International Neuropsychiatric Inventory (40). Psychopathology in drug users was further evaluated using the Structured Clinical Interview for DSM-IV (41). Current negative emotional states were measured using the Depression Anxiety Stress Scale (DASS-21) (42); verbal IQ was estimated using the National Adult Reading Test (NART) (43). The protocol was approved by the National Research Ethics Committee (NREC10/H0306/69, Principal Investigator: K.D. Ersche) (44).

The 35 CDIs met the DSM-IV-TR criteria for cocaine dependence, but none were actively seeking treatment for cocaine use. Urine samples tested positive for stimulants in all but four users, indicating they had consumed cocaine or amphetamines within the past 72 hours (45). To avoid potentially confounding effects of drug abstinence, we restricted subsequent analysis to those with a stimulant-positive urine screen, leaving 31 CDIs in the sample. Participants reported using cocaine for an average of 15 years (±7.9 SD), mainly intranasally or by inhalation; approximately one quarter of users (23%) injected cocaine intravenously (Supplement 1). The majority of CDIs also met criteria for dependence on another substance (93% nicotine, 45% opiates, 29% alcohol, 23% cannabis, 3% amphetamines) and used other drugs sporadically (51% cannabis, 19% sedatives, 16% ecstasy, 6% opiates, 3% hallucinogens; see Supplement 1 for details on sporadic and prescription drug use).

Thirty healthy control participants were screened for drug and alcohol misuse, and none met criteria for abuse or dependence. Urine samples were negative for illicit substances in all individuals. Seventy percent were either past or current tobacco smokers, and 57% reported having social experiences with cannabis; none reported taking prescribed or illicit drugs on a regular basis.

Procedures

Participants were assessed at the Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital, Cambridge, United Kingdom. Biological samples and fitness assessments were taken on arrival to establish health status. Urine samples were tested for current infection with cytomegalovirus (CMV) and Epstein-Barr virus, persistent viruses that affect the immune system (46). Blood samples were drawn to measure serum levels of C-reactive protein (CRP) as a marker of inflammation (47). We used saliva sampling as a noninvasive method to measure changes in cytokine levels before and after exposure to neutral and disgust-evoking photographs; a method that has been used successfully in previous studies (48,49). At three time points during their visit, participants were asked to rinse their mouth with water to provide a 2-mL sample of saliva by passive drool through a straw into a cryovial (http://www.salimetrics.com). Samples were provided on arrival (t_1), immediately after exposure to neutral photographs (t_2), and immediately after exposure to disgust-evoking photographs (t_3); the samples were frozen at −80°C before being analyzed for the following cytokines: IL-6, IL-1beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), which are typically induced together during an infectious challenge (36,37). We also examined interferon-gamma (IFN-γ) and IL-12, two TH1-cytokines with important roles in both cellular and innate immunity (50); the anti-inflammatory cytokine IL-10; and IL-8, a pro-inflammatory neutrophil chemotactic factor (51).

Before the exposure procedures, participants completed two questionnaires to assess interindividual differences in disgust reactions. The Disgust Propensity-Sensitivity Scale—Revised (52) is a trait measure of disgust, in which participants rated on a 5-point Likert scale the frequency of affective experiences of disgust and the cognitive evaluation of these experiences. The Hygiene Inventory (HI-23) (53) is a measure to assess various aspects of hygiene-related behaviors, including hand-washing, personal grooming, food handling, and household cleanliness.

Evocative Task

Participants were shown 120 colored photographs, half depicting images of neutral valence (neutral foods, household items) and the other half showing disgusting images (rotten/moldy foods, dirty objects, dead bodies/animals, disease/injury, body products). The photographs were selected from a pool of 180 pictures either downloaded from the Internet or selected from the International Affective Picture Series (54). To ensure the correct valence classification, all pictures were rated for pleasantness, arousal, disgust, and nausea on a Likert scale (1 = not, 7 = very) by 15 healthy men before experimental testing (Table S1 in Supplement 1). The Wilcoxon signed-rank test confirmed that