

Cocaine's Appetite for Fat and the Consequences on Body Weight

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Abstract

For many individuals in treatment for cocaine dependence, weight gain is a substantial problem during recovery. This weight gain causes significant distress and seems to increase the risk of relapse. The mechanisms underlying cocaine's effects on weight remain elusive. It is widely assumed that this weight gain reflects a metabolic or behavioural compensatory response to the cessation of cocaine use. Here we challenge this assumption and outline potential mechanisms by which chronic cocaine use produces disturbances in the regulation of fat intake and storage, through its effects on the central and peripheral nervous systems, specifically the sympathetic nervous system. We hypothesise that the cocaine-induced alteration in fat regulation results in cocaine users developing a pronounced appetite for fatty food but keeps their fat mass low. This altered fat appetite subsequently leads to excessive weight gain when individuals enter treatment and stop using cocaine. Our aim is to shed light on the neurobiological mechanisms that may underlie the alterations in eating and fat regulation in cocaine-dependent individuals, to open up potential new avenues to support these individuals in recovery.

Whilst cocaine is best known for its reinforcing effects and addictive potential, its influence on appetite and body weight is less well understood. This is surprising, given that weight gain is a substantial problem during recovery from cocaine dependence and is associated with significant distress and poorer compliance with treatment. There are currently no guidelines for health care professionals on how to address weight change in cocaine-dependent individuals receiving treatment. Instead, clinical practice seems to be dominated by the view that this weight gain during recovery reflects a compensatory response to restore weight that was previously lost due to the appetite suppressant effects of cocaine (1). Another prevailing view is that individuals who give up drug-taking replace the drug with food, further increasing the risk of weight gain. Neither of these beliefs are really supported by scientific evidence. In fact, the pre-clinical evidence shows that cocaine's anorexigenic effects are acute and transient (2) and are shortly followed by a compensatory *increase* in the consumption of fat and carbohydrates (3). These pre-clinical observations are in keeping with the eating patterns that have been reported in cocaine-dependent humans (4;5), who show a preference for fat but without concomitant weight gain. The mechanisms underlying these effects of cocaine on eating behavior and weight remain elusive. Here we aim to turn the spotlight on the effects that cocaine exerts on the central and the peripheral, sympathetic nervous systems. These may not only elucidate a variety of metabolic disturbances possibly underpinning cocaine users' preferences for fatty food in spite of low body weight, but may also explain the excessive weight gain in abstinent cocaine-dependent individuals.

1. Central nervous effects of cocaine on fat regulation

1.1 Cocaine's modulatory effects on fat intake

Cocaine is a central nervous system stimulant that blocks the reuptake of monoamines. However, its addictive potential has mainly been attributed to its ability to inhibit the dopamine transporter (DAT), thereby increasing extracellular dopamine (DA) availability in the synaptic cleft and stimulating postsynaptic dopamine receptors. It is this sharp increase in extracellular dopamine that has been linked to its euphorogenic effect and the desire to take the drug again. But could cocaine's central dopaminergic effects also influence an individual's food preference? Pre-clinical work by Thanos et al. (6) supports this hypothesis. They demonstrated that the dopamine D2 receptor (D2-R) agonist bromocriptine, which increases dopaminergic neurotransmission in the midbrain, acutely suppresses overall food intake in rats. Once these acute effects fade and the animals commence eating, they express a preference for high fat food pellets over regular food, possibly reflecting an enhanced motivational drive for fat-rich food (6). Similarities between the effects of bromocriptine and cocaine on midbrain dopamine transmission have fuelled speculations about whether the compulsive use of food and drugs may have a common biochemical origin (7).

Cocaine also inhibits the re-uptake of serotonin (5-HT) via presynaptic serotonin transporters (SERT), increasing serotonin availability in the synaptic cleft (8). Serotonergic neurons in the brainstem are known to project to hypothalamic regions including the arcuate nucleus, increasing appetite by activating postsynaptic 5-HT receptors (e.g. Htr1a) of arcuate nucleus neurons (Yadav et al., 2009). Additionally, a number of knockout studies in mice found that the inhibition of these 5-HT producing brainstem neurons induced leptin-dependent anorexic effects (9). Chronic cocaine exposure may therefore enhance food consumption by modulating

5-HT neurotransmission in the arcuate nucleus both directly, via the inhibition of SERT, and indirectly by reducing leptin production through its peripheral effects (see section 2).

The specific appetite for fat may however be modulated by cocaine's excitatory effects on the hypothalamic-pituitary-adrenal axis (HPA) through the release of hypothalamic corticotropin-releasing factor (CRF). Raised levels of circulating glucocorticoids have been linked to both an increase in the consumption of calorific food and impaired memory of the calorific ingestion, resulting in an overall increase in food intake (10). A more nuanced view on glucocorticoid hormones' influences on diet, however, differentiates the involvement of *homeostatic factors* such as hormones and neuroendocrine signals (i.e. insulin and neuropeptide Y) and *non-homeostatic* factors such as changes in motivation on both drug-taking behaviors and eating (11;12). Glucocorticoids have been shown to promote the release of neuropeptide Y (NPY) whilst inhibiting the anorexigenic modulatory effects of factors like leptin (13), possibly driving the increase in appetite. Glucocorticoids also enhance insulin release and higher circulating insulin levels are associated with fatty food consumption (14). There is pre-clinical evidence suggesting that insulin may enhance the behavioral effects of cocaine (15). It is conceivable that a glucocorticoid-stimulated increase in insulin levels may also underlie cocaine users' preference for a fatty diet. Moreover, the fat-induced increase in insulin levels in cocaine users might further be reinforced by insulin's modulatory effects on dopaminergic neurotransmission (16), thereby facilitating the overeating of foods that are specifically high in fat.

Satiety signals, modulated by leptin and insulin, typically regulate the intake of fatty foods. Both of these hormones inhibit the activities of appetite-promoting orexin and NPY/AgRP neurons in the arcuate nucleus, whilst also promoting the activity of appetite-inhibiting POMC neurons. Not only do these two satiety factors converge on the same molecular signaling

pathways, including the phosphoinositide 3-kinase (PI-3K) pathway, there also seems to be cross-talk between the biochemical responses to leptin and insulin in neurons of the arcuate nucleus (17). Thus, chronic cocaine use is likely to interfere with these two satiety signals, further facilitating an increase in the consumption of fatty foods.

1.2 Cocaine's modulatory effects on fat storage

Despite their high intake of foods rich in fat, cocaine-dependent individuals do not exhibit a concomitant increase in body weight. This somewhat paradoxical effect may be because of a variety of cocaine-induced metabolic disturbances that could interfere with the regulation of fat intake and storage. As outlined in **Figure 1**, cocaine promotes the production and the release of the neuropeptide cocaine and amphetamine regulated transcript (CART) (18), which is implicated in the regulation of feeding, satiety and body weight (19). Pre-clinical studies have shown that CART, when centrally administered, reduces food intake in the short-term, whilst changing lipid metabolism in the long-term (20). This CART-induced shift in the management of circulating lipids from deposition to mobilization and oxidation is likely to decrease the storage of body fat (20). The direct effects of cocaine on CART may thus explain cocaine users' relatively low body fat in spite of their high fat intake.

2. The effects of cocaine through the periphery

One of the most notable effects of cocaine use is the concomitant increase in heart rate and blood pressure, caused by increased sympathetic nerve activity through the inhibition of the noradrenaline transporter (NAT). As a potent sympathomimetic, cocaine increases the mobilization of stored lipids, metabolic rate and thermogenesis, subsequently reducing adiposity. Importantly, up-regulation of sympathetic nervous system activity has also been

linked to a reduction in the production of leptin and increased appetite(21). Cocaine's sympathomimetic effects may therefore explain prior observations in cocaine-dependent men with low plasma leptin levels, who reported uncontrolled intake of food high in fat and carbohydrates (4). Furthermore, the appetite enhancing effects of reduced leptin production coupled with the long-term metabolic effects of cocaine-induced up-regulation of CART represent a disconnection between leptin and CART signaling in the negative feedback cycle controlling body fat accumulation (20), which might result in a reduction in body weight despite increased food consumption in cocaine-dependent individuals.

3. Possible Clinical Implications

This article aims to challenge prevailing beliefs regarding weight gain in recovering cocaine-dependent individuals. Specifically, it challenges the widely-held ideas that weight gain represents a compensatory metabolic response to a previous appetite-suppressant effect and/or, a compensatory behavioral response to the loss of a substance that was compulsively consumed. Here, we outline hypotheses about how chronic cocaine use may alter the regulation of fat intake and storage. In our view, overeating in chronic cocaine users does not start during recovery as widely assumed, but may actually develop during active cocaine use, with the drug specifically affecting the choice for the consumption of highly calorific fatty foods. This may however, go unnoticed because the consumption of fatty food does not coincide with the acute pharmacological actions of the drug, but occurs after a few hours delay, and more importantly, it is not accompanied by weight gain. Excessive weight gain only occurs upon the discontinuation of cocaine use, as the dietary preference for fat-rich food persists but the effects on fat mobilization and oxidation wane. The sudden and excessive weight gain may then come

as a surprise to cocaine-dependent individuals, as they may not have noticed any change in their dietary food intake to which they could attribute the increase in body weight.

We believe an important clinical implication of the above is the need to incorporate these phenomena into our clinical conceptualization of cocaine dependence, and to anticipate them during abstinence and recovery. A better understanding of the exact molecular mechanisms underlying these metabolic disturbances would be vital to the development of pharmacological strategies to address these changes in eating behavior and fat metabolism in these individuals. However it is most important for both cocaine dependent individuals and the clinicians who treat them, to be aware of these metabolic effects of cocaine or enable them to address these early during the recovery process.

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5. Declaration of Interest

The authors declare to have no conflicts of interest.

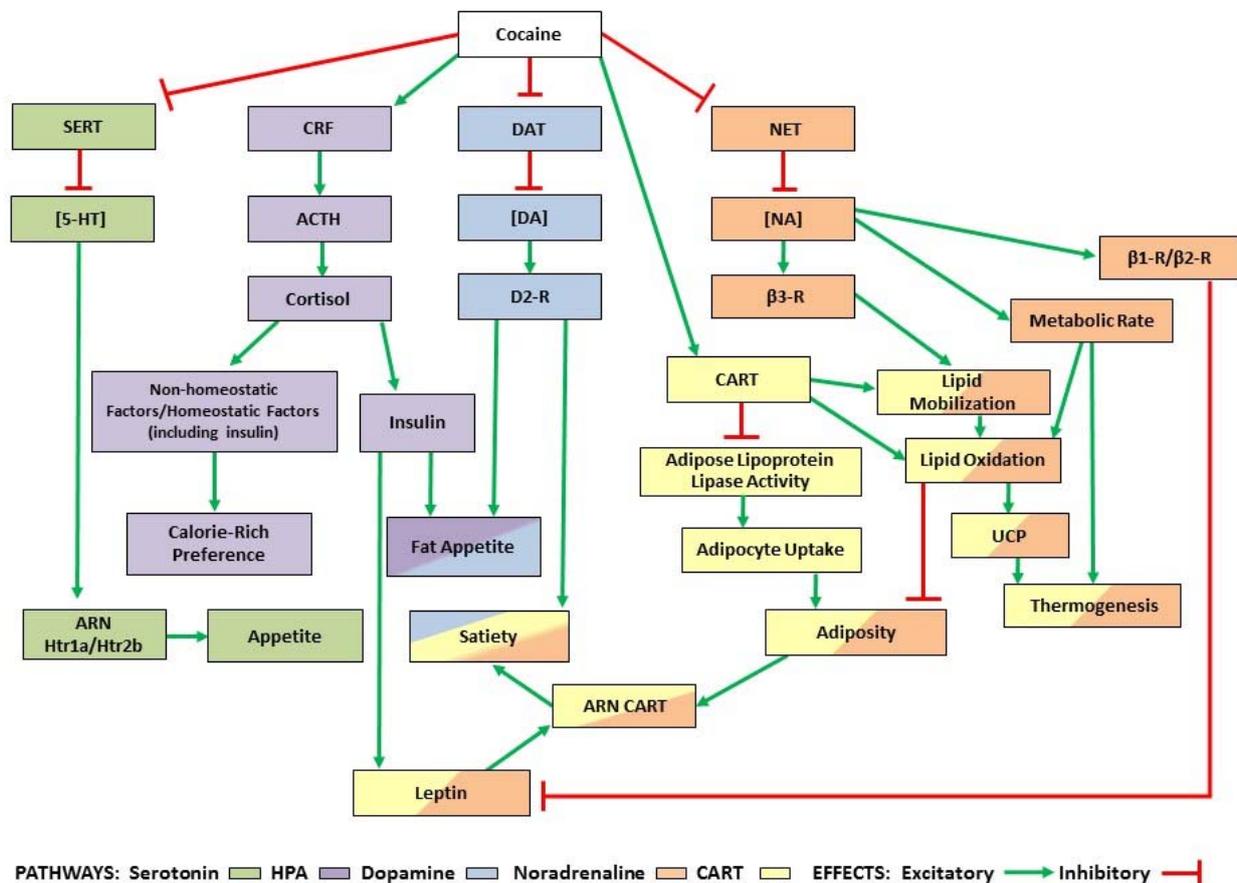


Figure 1: Possible biochemical and physiological effects of cocaine on monoaminergic neurotransmitter systems by inhibiting the reuptake of serotonin (5-HT), dopamine (DA), noradrenaline (NA), as indicated by red bar-headed lines. Blockade of the re-uptake increases the availability of monoamines in the synaptic cleft, as indicated by squared brackets. The excitatory effects of cocaine on the hypothalamic-pituitary-adrenal axis (HPA) and cocaine and amphetamine regulated transcript (CART) pathways are indicated by green arrows. Cocaine promotes **serotonergic signaling** resulting in an increase in appetite via increased activation of Htr1a/2b receptors of arcuate nucleus (ARN) neurons. **Dopaminergic signaling** is enhanced by cocaine, i.e. activation of dopamine D2 receptors (D2-Rs) leads acutely to satiety, but has been suggested to increase fat intake in chronic cocaine users. Cocaine also stimulates **CART** release, which drives short-lived anorexigenic effects. CART, in turn, initiates increased lipid mobilization and oxidation; this involves a decrease in adipose lipoprotein lipase activity (involved in fat deposition) and uncoupling proteins (UCP) up-regulation. Leptin can also stimulate CART release within selective parts of the brain e.g. ARN. Cocaine modulates the **HPA pathway**, increasing corticotrophin-releasing factor (CRF) release, resulting in increased adrenocorticotrophic hormone (ACTH) release and circulating glucocorticoids. Glucocorticoids alter homeostatic and non-homeostatic factors increasing calorie/fat dietary intake in chronic cocaine users. Cocaine enhances **noradrenergic signaling** resulting in increased metabolic rate and thermogenesis. Stimulation of beta-3 adrenergic receptors (β_3 -Rs) and beta-1 and beta-2 adrenergic receptors (β_1 -R and β_2 -R), increases thermogenesis and reduces leptin production respectively.

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