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Relationship between craving and plasma leptin concentrations in patients with cocaine addiction

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ABSTRACT

Background: There is robust evidence indicating an overlap between neurobiological circuitry and pathways that regulate addictions and those that regulate appetite and food intake. Rodent work suggests a role of the appetitive peptide leptin in cocaine-seeking behaviours. The goal of this study was to investigate the possible relationship between plasma leptin concentrations and cocaine craving and use in patients seeking treatment for cocaine dependence.

Methods: Patients ($N = 43$) with a DSM-IV diagnosis of cocaine dependence were studied before starting detoxification (baseline; T0) and then again 14 days after (T1; only those patients who abstained from cocaine during the study). Blood samples for plasma leptin concentrations were collected and cocaine craving was assessed using the Brief Cocaine Craving Questionnaire (Brief-CCQ). Food craving was also assessed using a food Visual Analogue Scale (f-VAS). Barratt Impulsiveness Scale (BIS) was used to evaluate impulsivity.

Results: Plasma leptin concentrations at T0 significantly correlated with baseline Brief-CCQ scores ($r = 0.34$, $p < 0.05$). Furthermore, plasma leptin concentrations at T1 significantly correlated with the baseline amount of cocaine used ($r = 0.5$, $p < 0.05$). There were no significant correlations between plasma leptin concentrations and f-VAS scores either at T0 or T1 (p's > 0.05).

Conclusions: The present study suggests a potential relationship between plasma leptin concentrations and cocaine craving and use. Future mechanistic studies are needed to determine whether manipulations of leptin signalling may lead to novel pharmacological approaches to treat cocaine addiction.

1. Introduction

Cocaine dependence represents a chronic relapsing disorder associated with significant disability and several health, social and economic consequences (Karila et al., 2012). Cocaine is one of the most commonly used illicit drugs and about 20% of cocaine users develop a cocaine use disorder (United Nations Office of Drugs and Crime and World Health Organization, 2015).

Craving for cocaine represents an important predictor of relapse and treatment failure in cocaine-dependent patients (Kozlowski and Wilkinson, 1987; Orford, 2001). However, craving is difficult to operationalize as its assessment in clinical and research settings primarily relies on self-reported measures. Therefore, investigating objective biological surrogates that correlate with craving has the potential to guide the identification of novel biomarkers for craving, which in turn may lead to the development of new pharmacological approaches to treat cocaine-dependent patients.

There is an overlap between neurobiological pathways that regulate cocaine-related reward processing and cocaine-seeking behaviours (*e.g.*, cocaine craving and use), and those that regulate appetite, food intake and reward (Carpenter et al., 2013; Garavan et al., 2000). Key brain regions like the nucleus accumbens and striatum play important roles in reward processing related to both food and cocaine (Grant et al., 1996), and cocaine and food cues activate similar brain pathways (Tomasi et al., 2015). In particular, the hedonic and rewarding aspects of appetitive and consummatory behaviours are linked to behavioural and

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neurochemical alterations very similar to those seen in drug addiction, such as dopamine release and striatal structure activity (Brownell and Gold, 2014; Cansell and Luquet, 2016; Wiss et al., 2017). Furthermore, consistent with the shared neural pathways, it is common that alterations in feeding behaviours, hyperphagia and weight gain may follow the cessation of taking drugs of abuse, as shown in humans (Edge and Gold, 2011) and animals (Orsini et al., 2014).

In vivo imaging studies report similar deficits in dopamine D2/D3 receptor availability in individuals with obesity and those with cocaine dependence (Wang et al., 2004), in non-human primates exposed to cocaine (Nader et al., 2008) and in rat models of obesity (Thanos et al., 2008). Furthermore, dopamine receptor binding availability predicts both future body weight and cocaine preference in rats (Michaelides et al., 2012). Consistent with this body of literature, there is increasing evidence suggesting that neuroendocrine pathways involved in appetite, food intake and reward processing may also be involved in the neurobiological processes that regulate craving and other behaviours related to cocaine addiction (Kenna et al., 2012). Leptin signalling may be one of such feeding-related neuroendocrine pathways.

Leptin, a 167 amino acid peptide secreted by white adipocytes, plays an important role in the regulation of food intake, energy expenditure and whole-body energy balance (Friedman, 2014; Guyenet and Schwartz, 2012; Schwartz et al., 2000). Furthermore, leptin seems to play an important role in brain reward processing (Fulton et al., 2000) via its receptor, which is highly expressed in dopaminergic neurons of the VTA (Krügel et al., 2003). More recently, a potential relationship between leptin signalling and addictive behaviours has been suggested. For example, in rats, manipulations of leptin signalling via infusion of exogenous leptin suppresses dopaminergic activity in the VTA, and attenuates both food intake and the rewarding effects of cocaine (Figlewicz et al., 2003; Shen et al., 2016). In humans, a few studies indicate that blood leptin concentrations correlate with sexual behaviours (Govic et al., 2008), and with craving for alcohol (Berridge, 1996; Hillemacher et al., 2007; Kiefer et al., 2001a, 2001b; Pelleymounter et al., 1995) and for nicotine (al'Absi et al., 2011). Furthermore, a human study reported significantly reduced blood leptin concentrations in individuals with heroin dependence compared to healthy controls (Housova et al., 2005). More recently, You et al. (2016) reported that both cocaine administration and cocaine expectancy reduced plasma leptin concentrations. In addition, exogenous leptin, administered intraperitoneally or centrally in the VTA, attenuated: a) cocaine-induced increase in accumbens dopamine levels; b) cocaine-induced establishment of conditioned place preference; and c) the ability of cocaine-predictive stimuli to prolong responding in extinction of cocaine-seeking (You et al., 2016).

Less is known on the potential relationship between blood leptin concentrations and cocaine craving and use in individuals with cocaine dependence. Therefore, the primary aim of this preliminary study was to investigate the potential relationship between plasma leptin concentrations and cocaine craving in a clinically-relevant population of patients seeking treatment for cocaine dependence. The relationship between plasma leptin concentrations and cocaine use was also investigated. Furthermore, given the role of impulsivity in cocaine craving and use (Rodriguez-Cintas et al., 2016), a secondary aim of the study was to investigate the relationship between plasma leptin concentrations and impulsivity. Finally, to explore possible relationships between leptin concentrations and severity of cocaine use, we conducted additional exploratory analyses to investigate leptin concentrations in subgroups of patients within our sample.

2. Subjects and methods

2.1. Setting

This study was conducted at the *Day Hospital of Psychiatry and Drug Dependence* of the 'Agostino Gemelli' Hospital, Catholic University, Rome (Italy). The study was approved by the local Ethics Committee and conducted according to the national and local regulatory requirements, Good Clinical Practice guidelines and the Declaration of Helsinki of 1975, as revised in 1983. All participants signed a written informed consent before starting any research procedure. As part of the informed consent process, all participants received information on the study procedures and on the possibility to withdraw from the study at any time.

2.2. Subjects. screening and enrollment

A total of 102 patients seeking treatment for current cocaine use were evaluated by attending psychiatrists during screening for this study. Inclusion criteria were: age range 18–60 years (inclusive); current diagnosis of cocaine dependence according to the Structured Clinical Interview for DSM-IV (First et al., 1996); desire to achieve total abstinence from cocaine; Body Mass Index (BMI) range 18.5–29.9 kg/m^2 (inclusive); and the ability to understand and sign written informed consent. Exclusion criteria were: lifetime diagnosis of abuse/dependence on alcohol and/or substance of abuse (except cocaine and nicotine); current (*i.e.*, last three months) use of neuroleptics, antidepressants, other psychotropic medications, antihypertensive or hypoglycaemic medications; clinically significant medical and/or psychiatric disorders; urine drug screen positive for a substance of abuse; individuals requiring inpatient treatment for cocaine dependence; participation in any clinical trial within the last 60 days; court-mandated participation in cocaine treatment or pending incarceration. Reasons for not being eligible for the study were: the desire to reduce cocaine use but not achieving total abstinence (n = 4), alcohol abuse/dependence (n = 26), other substance abuse/dependence (n = 11), concurrent psychiatric disorders (n = 6), current use of psychotropic medications (n = 15), BMI > 29.9 kg/m^2 (n = 6) (Fig. 1).

A total of 44 individuals were eligible; 43 of them signed a written consent form and enrolled in the study (baseline: T0). There were no significant differences between the demographic and baseline characteristics of the patients enrolled in the study and those who did not. Regardless of their eligibility and participation in this study, all screened individuals received patient care and treatment for their cocaine addiction *via* a rehabilitation program based on the Minnesota Model (McElrath, 1997) (Martinotti et al., 2007). Enrolled participants were scheduled to come back to our Day Hospital for a follow-up visit after 14 days (T1). Participants did not receive any compensation or reimbursement.

2.3. Methods

2.3.1. Study procedures

2.3.1.1. Leptin assay. All samples were obtained at approximately 08:00 am after an overnight food fasting both at T0 and T1. Plasma leptin concentrations were measured by an enzyme-linked immunosorbent assay [ELISA; DRG® Leptin (Sandwich) Enzyme Immunoassay Kit]. Normal leptin concentrations in the general healthy population are 3.84 ± 1.79 ng/mL in males and 7.36 ± 3.73 ng/mL in females.

2.3.1.2. Clinical assessments. Weight, height, BMI, blood pressure, heart rate, electrocardiogram and routine laboratory blood work (cell blood count, triglycerides, cholesterol, liver and renal tests) were assessed both at T0 and T1 for clinical monitoring.

2.3.1.3. Urine drug test and alcohol breathalyzer. These tests were performed at T0, T1 and during a brief interim visit on Day 7, to assure participants' safety and compliance to the study procedures in terms of abstinence to cocaine and other drugs of abuse. A positive urine drug test (cocaine, opioids, amphetamines, methamphetamines, THC) or a positive alcohol breathalyzer test resulted in withdrawal from