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Research report

Effect of the dopamine D_3 receptor antagonist GSK598809 on brain responses to rewarding food images in overweight and obese binge eaters

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ABSTRACT

The dopamine D_3 receptor is thought to be a potential target for treating compulsive disorders such as drug addiction and obesity. Here, we used functional Magnetic Resonance Imaging (fMRI) to investigate the effects the selective dopamine D_3 receptor antagonist GSK598809 on brain activation to food images in a sample of overweight and obese binge-eating subjects. Consistent with previous studies, processing of food images was associated with activation of a network of reward areas including the amygdala, striatum and insula. However, brain activation to food images was not modulated by GSK598809. The results demonstrate that D_3 receptor manipulation does not modulate brain responses to food images in overweight and obese subjects.

Introduction

Obesity is increasingly viewed as a disorder of compulsive overeating which shares many characteristics with drug addiction, including compulsive consumption, cravings, tolerance, withdrawal and abnormalities in the dopaminergic mesocorticolimbic neural circuitry underlying the processing of rewarding stimuli (Stice, Spoor, Bohon, & Small, 2008; Wang et al., 2001). Like drugs of abuse, the rewarding effects of food are linked to activity in the dopaminergic system. Consumption of natural rewards such as food and exposure to food reward-related stimuli leads to increases in mesolimbic dopamine (DA) release (Bassareo & Di Chiara, 1997, 1999a, 1999b; Hajnal, Smith, & Norgren, 2004; Hernandez & Hoebel, 1988; Martel & Fantino, 1996a, 1996b) whilst in animals and humans, DA regulates the motivation for food intake (Swanson, Heath, Stratford, & Kelley, 1997; Szczypka et al., 2001; Taber & Fibiger, 1997; Volkow et al., 2002).

Components of the dopaminergic system are potential targets for treating disorders of compulsive consumption including drug addiction and obesity, and the DA D_3 receptor has recently been suggested as a promising candidate (Heidbreder et al., 2005). In animals, D_3 antagonists reduce drug seeking (Di Ciano, Underwood, Hagan, & Everitt, 2003; Heidbreder et al., 2005; Pilla et al., 1999) and reduce food intake and responses for food in an operant task (Thanos et al., 2008) whilst D_3 receptor deficient mice have been shown to become obese when fed a high fat diet (McQuade, Benoit, Xu, Woods, & Seeley, 2004). In humans, mixed D_2/D_3 antagonists attenuate cue-induced craving (Gawin, Allen, & Humblestone, 1989) and reduce attentional biases to drug-relevant stimuli (Franken, Hendriks, Stam, & Van den, 2004). PET studies employing radioligands for the dopamine D_2 receptor, which also have affinity for the D_3 receptor, have shown reduced availability of striatal D_2/D_3 receptors in obese individuals (Wang et al., 2001) which has been associated with reduced prefrontal metabolism (Volkow et al., 2008). These results suggest that low striatal D_2/D_3 receptor availability, perhaps secondary to enhanced dopamine release, may contribute to a lack of inhibitory control involved in compulsive overeating.

As in drug addiction, individual differences in personality and patterns of behaviour play an important role in the development of dysregulated consumption. High levels of impulsivity (Galanti, Gluck, & Geliebter, 2007; Nasser, Gluck, & Geliebter, 2004; Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006) and reward responsiveness (Davis & Fox, 2008; Franken & Muris, 2005) are

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associated with the development and maintenance of obesity and such factors have also been shown to modulate reward-related neural circuitry when viewing appetitive stimuli (Beaver et al., 2006). A high level of dietary restraint, that is, the extent to which individuals attempt to control their weight by dieting and by resisting the foods and behaviours that lead to weight gain, is also associated with abnormal eating behaviour (Herman & Mack, 1975) and individual differences in restraint modulate brain responses to food in normal, healthy subjects (Coletta et al., 2009). Furthermore, effects of dopaminergic drugs on brain activation have been shown to be modulated by differences in personality characteristics such as impulsivity (Cools, Sheridan, Jacobs, & D'Esposito, 2007).

In the present study, we investigated the effects of the selective DA D_3 receptor antagonist GSK598809 on brain activation to food images in a sample of binge and emotional eating obese and overweight subjects. This stratified sample was selected to ensure the obese population had characteristic overeating behaviours. Binge eating has been linked to overconsumption of food and compulsive behaviour (Bryant, King, & Blundell, 2008; de Zwaan, 2001; de Zwaan & Mitchell, 1992). Given the strong association between dopamine and addiction, we reasoned that brain responses to appetitive stimuli would be most sensitive to modulation of the dopaminergic system in this subset of obese and overweight people.

In addition, we investigated whether individual differences in personality characteristics and patterns of eating behaviour would modulate the effects of GSK598809 on brain activation to food images. fMRI has revealed a network of brain areas that is modulated by satiety during the viewing of high calorie food images, with greater activation in a fasted than in a fed state, including the insula, striatum, amygdala and hypothalamus (Cornier, Von Kaenel, Bessesen, & Tregellas, 2007; Cornier et al., 2009; Fuhrer, Zysset, & Stumvoll, 2008; Goldstone et al., 2009; Holsen et al., 2005, 2006; LaBar et al., 2001; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Piech et al., 2009; Porubska, Veit, Preissl, Fritsche, & Birbaumer, 2006; Smeets et al., 2006; Uher, Treasure, Heining, Brammer, & Campbell, 2006). We hypothesised that in a fasted state, GSK598809 would reduce activation across a network of brain regions responsive to food images and that brain activation changes would correlate with individual differences in factors such as impulsivity, reward sensitivity and restraint. Specifically, we hypothesised that GSK598809 would have a stronger effect in subjects with higher levels of impulsivity and reward sensitivity and lower levels of restraint.

Methods

Participants

Twenty-six otherwise healthy, overweight and obese participants (15 males, 11 females) aged between 18 and 45 years (mean age = 35.1 ± 7.1 years) were recruited for this study. All participants had a body mass index (BMI) of greater than or equal to 27 kg/m^2 (mean = 32.7 ± 3.7; range 27–40 kg/m^2). Participants were recruited from the general population of the Cambridgeshire area through local newspaper and radio advertisements and were considered for inclusion if they had no personal or family history of psychiatric disorders, had no history of substance abuse, had no history of eating disorders, had reported no significant weight loss (or gain) (defined as a change of $\geqslant$5% in the 3 months prior to screening or those who had lost >5% of their body weight in the preceding 30 days), had no history of head injury or neurological disorders and reported they were omnivorous (vegetarians were excluded to ensure a homogeneous sample, as they may show atypical negative responses to stimuli depicting meat) based on screening investigations, physical examination and a clinical interview by a medical physician. Additionally, participants were only included if they reported binge eating behaviour (minimum one episode per week as assessed by the Y-BOCS-BE questionnaire (Q6) (Goodman et al., 1989; McElroy et al., 2007) and emotional eating behaviour (by attaining a score of at least 3 in at least one of questions of the emotional eating scale (Q3, Q6 and Q10) of the TFEQ-R18 (Stunkard & Messick, 1985). All participants gave written informed consent for participation in the study, which was approved by the Hounslow and Hillingdon Research Ethics Committee, UK.

Procedure

The study was conducted at GlaxoSmithKline, Clinical Unit Cambridge (CUC), Addenbrookes Centre for Clinical Investigation, Cambridge, UK and at the GSK Clinical Imaging Centre in Hammersmith, London, UK (ClinicalTrials.gov Identifier: NCT01039454). The study utilised a randomized, double-blind, placebo-controlled, two-way cross over design, where each participant was tested under two acute treatment conditions separated by a at least a 7-day washout period. The two treatment conditions were; GSK598809 (175 mg capsule) (GlaxoSmithKline R&D, UK) and placebo. Individual assignment to the order of treatment conditions was randomized and counterbalanced to control for order effects that might arise. The dose of GSK598809 was based on internal pre-clinical data, clinical investigations in healthy participants indicating that it was well tolerated (unpublished observations) and PET receptor occupancy data indicating >90% occupancy in substantia nigra (Searle et al., 2010). Subjects reported to the CUC on the morning of Day −1 and remained in the unit for two overnight stays. Dosing and functional Magnetic Resonance Imaging (fMRI) assessments were conducted on Day 1. Subjects were required to fast for approximately 15 h prior to scanning. Scanning was performed approximately 3 h post dose (chosen to coincide with the approximate time of peak concentration (T_{max}) of GSK598809). Subjects were discharged from the unit on Day 2 following all assessments at the discretion of the investigator.

Imaging task and technical details

The task performed in the scanner has been used in previous fMRI studies of food processing (Farooqi et al., 2007; Fletcher et al., 2010). Participants were scanned while watching a series of images of high-calorie food items (e.g., chocolate), low-calorie foods (e.g., broccoli), or nonfood items [everyday objects (watches, jewelry, clothing) and scenes], matched across categories for colour and other visual properties. Four sets of 75 images (25 high-calorie food, 25 low-calorie food, 25 nonfood) were selected. Images from each category were presented in counterbalanced order in blocks of five (each image appearing for 5 s) interspersed with periods of fixation, each block lasting 25 s. Participants were instructed to think about how much they liked each image. Participants pressed a button with their index finger when each image was presented to prove that they were attending to the task.

Personality and eating behaviour scales

We used four questionnaire scales to measure individual differences in personality characteristics: the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995), a 30 item scale measuring impulsivity; the BAS reward sensitivity subscale, a subset of five questions from the BIS/BAS scale (Carver & White, 1994) which measures an individual's responsivity to reward; the Three Factors Eating Questionnaire (TFEQ) (Stunkard & Messick, 1985),