Neural and Behavioral Effects of a Novel Mu Opioid Receptor Antagonist in Binge-Eating Obese People

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Background: Binge eating is associated with obesity and has been conceptualized as "food addiction." However, this view has received only inconsistent support in humans, and limited evidence relates key neurocircuitry to the disorder. Moreover, relatively few studies have used pharmacologic functional magnetic resonance imaging to probe the underlying basis of altered eating behaviors.

Methods: In a double-blind, placebo-controlled, parallel group study, we explored the effects of a potent mu-opioid receptor antagonist, GSK1521498, in obese individuals with moderate binge eating. Subjects were tested during a baseline placebo run-in period and retested after 28-days of drug ($n = 21$) or placebo ($n = 21$) treatment. Using functional magnetic resonance imaging and behavioral measures, we determined the drug's effects on brain responses to food images and, separately, on motivation to expend energy to view comparable images.

Results: Compared with placebo, GSK1521498 was associated with a significant reduction in pallidum/putamen responses to pictures of high-calorie food and a reduction in motivation to view images of high-calorie food. Intriguingly, although motivational responding was reduced, subjective liking for the same images actually increased following drug treatment.

Conclusions: Stimulus-specific putamen/pallidal responses in obese people with binge eating are sensitive to altered mu-opioid function. This neuromodulation was accompanied by reductions in motivational responding, as measured by grip force, although subjective liking responses to the same stimuli actually increased. As well as providing evidence for a link between the opioid system and food-related behavior in binge-eating obese individuals, these results support a dissociation across measures of motivation and liking associated with food-related stimuli in these individuals.

Key Words: Binge eating, fMRI, hedonics, motivation, obesity, opioid

Human and animal studies of reward processing demonstrate that motivation towards obtaining, and the hedonic value of a reward, though highly related, are dissociable. This has been framed as a dissociation between "wanting" and "liking," subserved by dopaminergic and opioidergic systems respectively (1). Although this perspective has generated debate and it has been pointed out that the dopamine-wanting perspective resonates strongly with a previously expressed view of dopamine's role in the "activation" of behaviors (2), there is a broad consensus that behaviors may be highly motivated toward the acquisition of outcomes even when those outcomes have limited hedonic value, as in habitual responding (3). This important observation is a cornerstone of models of addiction (4,5), in which a critical element of the addictive process is the transition to habitual behavior that is relatively insensitive to the current hedonic value of the outcome.

A key mediator in the hedonic valuation process is the mu-opioid receptor (MOR) system (6–12). In humans, mu-opioid antagonists reduce the hedonic responses to, and consumption of, palatable foods. The system also has a role in the motivational aspects of food-related behaviors (13), mediated by interactions with dopaminergic systems (14). MORs localized on inhibitory gamma-aminobutyric acid-ergic interneurons in the ventral tegmental area (VTA) and hypothalamus can modulate dopamine release in the nucleus accumbens and other dopaminergic target areas (15–17). Furthermore, MOR knockout mice demonstrate decreased firing frequency (including reduced bursting activity) of midbrain dopamine neurons (18) and decreased dopamine reuptake in the nucleus accumbens (19). The system has also been implicated in animal models of binge eating, with MOR antagonism reducing such behaviour (13,20,21). Although the effects are less clear in humans, there is some genetic evidence that implicates the gain of function 118G polymorphism of *OPRM1*, the MOR gene, in binge eating disorder (22).

It has been argued that a food addiction process is relevant to the development of obesity, particularly in those who binge (23,24). However the evidence supporting this in humans has been questioned on clinical/behavioral (25) and neuroscientific (26) grounds. A critical challenge in furthering the neuroscientific exploration of this issue is establishing the functional neuroanatomy and neurochemistry of the systems that subserve motivation toward and enjoyment of foods and how they may be perturbed in conditions such as binge eating. Pharmacologic imaging studies offer a powerful way of characterizing these systems and may offer insights that

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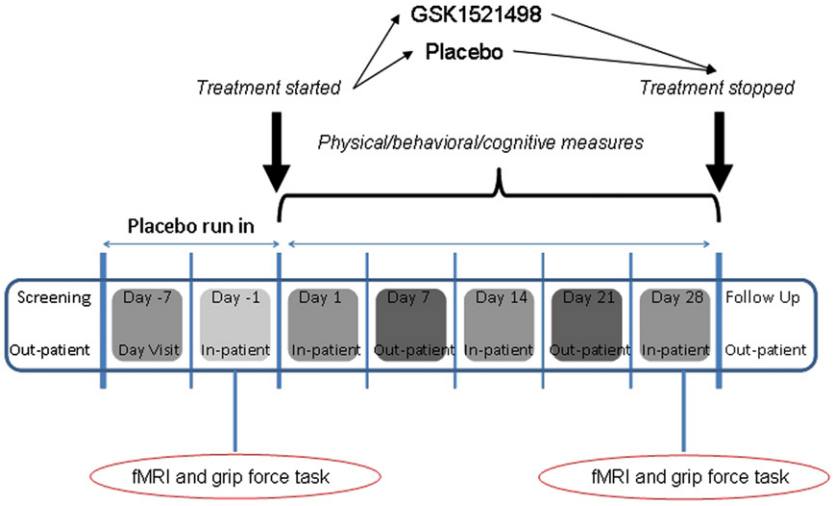

Figure 1. Study design. Following screening and a 7-day single-blind, placebo run-in, a baseline assessment was performed during a 2-day stay on the clinical research unit. This included the functional magnetic resonance imaging (fMRI) and grip force tasks that are the focus of this article. Thereafter, participants were randomised to receive oral GSK1521498 (5 mg) or placebo for 28 days. Further inpatient assessments were performed on Day 14 and Day 28. fMRI and grip force task were repeated on Day 28. Several other physical, cognitive, and eating measures were performed over the course of the visits (see Ziauddeen *et al.* [26] for details).

suggest ways of identifying, developing, and refining therapeutic strategies (13,27,28).

Previous pharmacologic imaging studies in obesity (29–35) have focused largely on serotonergic and dopaminergic mechanisms; opioid mechanisms have received little investigation. Given their critical role in food reward processing and potentially in binge eating, as well as their implication in substance addictions (36), further investigation of the MOR is warranted, both as a potential pharmacologic target and as a neural system relevant to the understanding of normal and aberrant eating behavior. This study sought to examine this system using GSK1521498, a potent antagonist with 14- to 20-fold selectivity for MORs, in otherwise healthy, obese volunteers who were moderate binge eaters. The aim was to determine, in the context of a clinical trial of this drug's effects on weight and eating behavior, the concurrent changes in behavioral and neural responses to food images in obese individuals with a target behavior potentially sensitive to this receptor modulation.

In both preclinical models of obesity and binge eating (21,37) and a Phase 1 study in healthy overweight humans (38), GSK1521498 has been shown to reduce food intake, particularly of high fat/sugar foods. These findings were supported in this 28-day treatment trial (39) in which treatment with GSK1521498 5 mg/day led to a significant reduction in hedonic responses to high fat and high sugar foods and a reduction in ad libitum consumption, particularly of high fat foods. However, no overall weight loss was found. Furthermore, in animal models, GSK1521498 has been shown to reduce food seeking (21).

The tasks reported here were chosen to explore drug-related changes in motivation and pleasure associated with food stimuli. During functional magnetic resonance imaging (fMRI), subjects viewed images of high and low calorie foods and high and low reward nonfoods, making liking responses for each. In a novel, complementary behavioral task outside the scanner, we measured the effort volunteers were willing to expend (on a grip force transducer) to view images of different types and whether drug treatment affected this effort measure and subjectively rated "liking" responses.

Methods and Materials

Sixty-three volunteers (28 [44%] males) aged 18 to 60 years (mean ± SD, 41.5 ± 10.0 years) endorsing moderate-severe binge eating (Binge Eating Scale [BES] scores ≥19) (40,41) (mean 26.4 ± 6.7), and with body mass index ≥30 kg/m^2 (mean 37.3 ± 4.76 kg/m^2), were enrolled in this study. The study (identification number EudraCT 2009-016663-11, ClinicalTrials.gov identifier NCT01195792) was approved by Berkshire Research Ethics Committee (United Kingdom), and all participants provided signed informed consent.

Study Design

In a double-blind, placebo-controlled, parallel-group design, subjects received 1-week single-blind placebo run-in, followed by 4-week treatment with either placebo (n = 21), GSK1521498 2 mg/day (n = 21) or GSK1521498 5 mg/day (n = 21). Full details of the study are reported elsewhere (39) and summarized in Figure 1. On Day 1 (predrug), each participant underwent fMRI scanning and the behavioral and eating measures described subsequently. Following 28 days of treatment, subjects returned for full evaluation and repeated all measures. Here we consider only data from the placebo and GSK1521498 5 mg/day groups. The 5-mg dose achieved 82% to 92% 24-hour MOR occupancy compared with 64% to 80% with the 2-mg dose, which showed no effect on eating behavior (39). Thus, data from the 2-mg group were not analyzed here to minimize multiple comparisons conducted in investigating drug effects at a dose unlikely to have a pharmacodynamic effect.

fMRI Task. Participants fasted for 10 to 12 hours and performed a simple task adapted from one reported previously (34,42). The task entailed viewing and reporting subjective liking for images from four categories: high-calorie foods (e.g., chocolate), low-calorie foods (e.g., broccoli), rewarding nonfood items (e.g., watches, jewelry) and less rewarding nonfood items (e.g., staplers). Images were matched across categories for color, size, and background. Thirty images from each category were presented in blocks of 5, resulting in a total of 120 images over 24 blocks. Each image was presented for 4 sec with a 1-sec intertrial interval (block length = 22 sec). Image blocks were randomly interspersed with fixation periods. Participants were instructed to press a button to indicate their liking for each image with duration of button press indicating their rating. A mixed-effects analysis of variance (ANOVA) model was used for the behavioral analysis.

Image Acquisition and Analysis. Because of an initial problem with task randomization, imaging data were unreliable