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Resting state hypothalamic response to glucose predicts glucose-induced attenuation in the ventral striatal response to food cues

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ABSTRACT

Feeding behavior is regulated by a complex interaction of central nervous system responses to metabolic signals that reflect nutrient availability and to food cues that trigger appetitive responses. Prior work has shown that the hypothalamus is a key brain area that senses and responds to changes in metabolic signals, and exposure to food cues induces the activation of brain areas involved in reward processing. However, it is not known how the hypothalamic responses to changes in metabolic state are related to reward responses to food cues. This study aimed to understand whether changes in hypothalamic activity in response to glucose-induced metabolic signals are linked to food-cue reactivity within brain areas involved in reward processing. We combined two neuroimaging modalities (Arterial Spin Labeling and Blood Oxygen Level Dependent) to measure glucose-induced changes in hypothalamic cerebral blood flow (CBF) and food-cue task induced changes in brain activity within reward-related regions. Twenty-five participants underwent a MRI session following glucose ingestion and a subset of twenty individuals underwent an additional water session on a separate day as a control condition (drink order randomized). Hunger was assessed before and after drink consumption. We observed that individuals who had a greater reduction in hypothalamic CBF exhibited a greater reduction in left ventral striatum food cue reactivity (Spearman's rho = 0.46, P = 0.048) following glucose vs. water ingestion. These results are the first to use multimodal imaging to demonstrate a link between hypothalamic metabolic signaling and ventral striatal food cue reactivity.

1. Introduction

Eating behavior requires that changes in metabolic state are recognized by the central nervous system (CNS) which regulates brain responses to sensory information associated with food availability. The hypothalamus is the primary appetite control center in the brain and plays a key role in sensing and responding to changes in circulating levels of hormones and nutrients, including glucose (Morton, Cummings, Baskin, Barsh, & Schwartz, 2006). Because of its critical role in glucose sensing and energy homeostasis, investigators have used neuroimaging methods to determine how the hypothalamus responds to ingestion of a standardized glucose load (Flanagan et al., 2012; Liu, Gao, Liu, & Fox, 2000; Matsuda et al., 1999; Smeets, de Graaf, Stafleu, van Osch, & van der Grond, 2005a, 2005b; Vidarsdottir et al., 2007; van Opstal et al., 2015). Most prior studies used Blood Oxygen Level Dependent (BOLD)- functional magnetic resonance imaging (fMRI) single-slice methods to focus specifically on the hypothalamic region and found a significant reduction in hypothalamic activity following glucose ingestion in normal-weight adults (Flanagan et al., 2012; Liu, Gao, Liu, & Fox, 2000; Matsuda et al., 1999; Smeets et al, 2005a, 2005b; Vidarsdottir et al., 2007; van Opstal et al., 2015). Similar findings were reported in a study that used arterial spin labeling (ASL) methods and found a significant reduction in hypothalamic cerebral blood flow (CBF), a marker of neuronal activity, in response to glucose ingestion (Page et al., 2013). These findings are also in line with earlier work using positron emission tomography

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(PET) showing that the ingestion of a liquid meal resulted in a decrease in hypothalamus CBF (Gautier et al., 2000, 2001; Tataranni et al., 1999).

In our current environment with abundant exposure to highly palatable foods, hedonic processes mediated by dopaminergic brain pathways play a key role in promoting feeding behavior (Alonso-Alonso et al., 2015). fMRI task based food-cue paradigms are commonly used to target hedonic aspects of feeding behavior, and prior studies have implemented these procedures to identify how hunger modulates neural food-cue reactivity (see meta-analysis (van der Laan, de Ridder, Viergever, & Smeets, 2011)). Results indicate that when compared to a fasted state, a satiated state is associated with diminished brain responses to food cues in regions previously implicated in processing sensory food cues including the ventral striatum (VS), orbital frontal cortex (OFC), amygdala, insula, and hypothalamus (Cornier et al., 2009; Farooqi, Bullmore, Keogh, Gillard, O'Rahilly, & Leptin , 2007; Fletcher et al., 2010; Frank et al., 2010; Führer, Zysset, & Stumvoll, 2008; Goldstone et al., 2009; LaBar et al., 2001; Martens et al., 2013; Siep et al., 2009; Stice, Burger, & Yokum, 2013; Uher, Treasure, Heining, Brammer, & Campbell, 2006). More recently, fMRI studies have also reported that brain reactivity to food cues in areas involved in appetite and reward processing is modulated by glucose ingestion (Kroemer et al., 2013, Heni et al., 2014). Together, prior work has suggested that changes in metabolic state can modulate brain reward sensitivity to food cues.

However, fMRI has not previously been used to investigate the interaction between metabolic state-dependent shifts in hypothalamus activity and task-induced brain activation to food cues within brain areas implicated in food reward. We combined two neuroimaging modalities, ASL and BOLD-fMRI, and leveraged the unique advantages of both techniques to study how glucose-induced changes in hypothalamic activity are related to changes in food-cue reactivity within brain reward areas.

To determine the hypothalamic response to glucose-induced metabolic signals, we used ASL, which provides a semi-quantitative CBF measurement expressed in physiological units (mL/100 g brain tissue/min) and can capture low frequency changes in brain activity (Aguirre, Detre, & Wang, 2005; Detre, Wang, Wang, & Rao, 2009). We used BOLD-fMRI (Aguirre, Detre, Zarahn, & Alsop, 2002) to detect task-dependent neural changes to pictures of food and non-food items (as a control). BOLD effects are measured using rapid volumetric acquisition of T_2^* weighted images (Petcharunpaisan, Ramalho, & Castillo, 2010). Neuronal activation (in response to seeing a picture of chocolate cake, for example) leads to an increase in local CBF and a reduction in local deoxyhemoglobin, which causes an increase in BOLD T_2^* signal. While BOLD has advantages over ASL for examining task-induced neural activation and has better spatial resolution, this method assesses only relative changes in BOLD signal in specific brain regions, and does not measure baseline differences in metabolic state. In this study, we combined ASL to measure state-dependent changes in hypothalamus CBF and BOLD-fMRI to assess food cue reactivity within reward-related brain regions to investigate the link between glucose-induced changes in hypothalamic CBF and food cue reactivity in reward-related regions.

Given prior evidence suggesting that changes in metabolic state can modulate brain reward sensitivity to food cues (Cornier et al., 2009; Farooqi et al., 2007; Fletcher et al., 2010; Frank et al., 2010; Führer et al., 2008; Goldstone et al., 2009; LaBar et al., 2001; Martens et al., 2013; Siep et al., 2009; Stice et al., 2013; Uher et al., 2006), we predicted that glucose-induced reductions in hypothalamic activity would correlate with reductions in food-cue reactivity within brain areas implicated in reward processing.

2. Methods

2.1. Participants

Twenty-five healthy individuals (12 male, 13 female) between the ages of 19–25 years old with a body mass index (BMI) between 19 and 45 kg/m^2 participated in this study. Participants gave written informed consent, and all experimental procedures were approved by the Institutional Review Board of the University of Southern California (USC). Participants did not have any history of eating disorders, diabetes or other medical illnesses. Also they were nonsmokers and were not on weight-loss diets or taking medications (with the exception of oral contraceptives). Participants were all right-handed and had normal or corrected to normal vision. Participants were asked to maintain their typical diet and physical activity levels throughout this study, and female participants were studied during the follicular phase of their menstrual cycle.

2.2. Overview of study design (Fig. 1)

Anthropometric data were collected during a screening visit. Magnetic resonance imaging (MRI) visits were performed in the morning between 9:00 to 11:00 a.m. after a 12-h overnight fast at the Dana & David Dornsife Cognitive Neuroscience Imaging Center at USC. Pulsed ASL (PASL) was performed to determine hypothalamic CBF in the fasted state and again between 10 and 20 min and 30 and 40 min after the ingestion of glucose (75 g in 300 mL water). Participants were required to finish drinking within 2 min. The food cue task (details below) was performed between 20 and 30 min after ingestion of the study drink. Hunger ratings were collected in the fasted state and again at ~10 min and ~30 min after drink. A water (300 mL) drink session was conducted as a control in a subset of twenty participants on a separate day, and drink order was randomized and blinded. Non-sweetened cherry flavoring was added to both the glucose and water study drinks to improve palatability. The timing for PASL, food cue task and appetite ratings during a water drink session were consistent with the glucose session. Participants' body weight and 24-h dietary data were collected at each study session. This study is part of a larger ongoing project examining brain responses to different types of sugar.

2.3. Anthropometric and dietary data measurements

Height was measured to the nearest 0.1 cm using a portable stadiometer and weight to the nearest 0.1 kg using a portable scale. 24-hour dietary recalls were collected using the multi-pass interview technique (Johnson, Driscoll, & Goran, 1996) by trained study

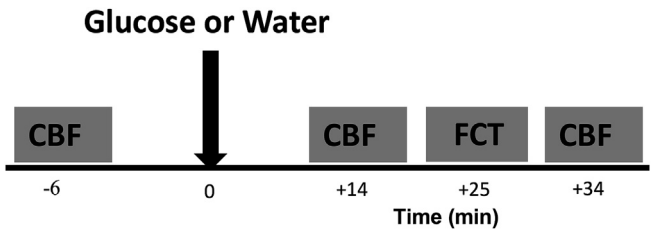

Fig. 1. Overview of Study Sessions. Pulsed arterial spin labeling was performed to determine hypothalamic cerebral blood flow (CBF) in the fasted state and again between 10 and 20 min and 30 and 40 min after the ingestion of glucose or water. The food cue task (FCT) was performed between 20 and 30 min after ingestion of the study drink. Time points after drink reflect the middle of CBF measurements, which started after the completion of drinking and at the start of the MRI acquisitions (which continued for approximately 8–9 min). Participants were required to finish drinking within 2 min.