Changes in Differential Functional Magnetic Resonance Signals in the Rodent Brain Elicited by Mixed-Nutrient or Protein-Enriched Meals

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BACKGROUND & AIMS: The hypothalamus and brain stem have important roles in regulating food intake; the roles of other nonhomeostatic centers in detecting nutrient content of ingested food have been poorly characterized. We used blood oxygen level—dependent functional magnetic resonance imaging (BOLD fMRI) to map brain regions that are responsive to intragastric infusion of isocaloric amounts of a mixed nutrient or protein, and assessed the role of blood glucose in the observed BOLD signal changes. **METHODS:** Brain images were acquired, using a 9.4 T MRI system, from anesthetized rats during intragastric infusion of saline (n = 7), or 12 kcal of a mixed nutrient (n = 13) or protein (n = 6). Nutrient-induced changes in blood parameters and the effects of intravenous infusion of saline or glucose (n = 5/treatment) on BOLD fMRI signal changes were also evaluated. Intragastric nutrient infusion reduced the BOLD fMRI signal intensity in homeostatic (hypothalamus, nucleus tractus solitarius) and nonhomeostatic (thalamus, hippocampus, caudate putamen, cerebral cortex, cerebellum) centers; these effects were mimicked qualitatively by intravenous glucose. In contrast to a mixed meal, protein load reduced the BOLD fMRI signal in the amygdala. BOLD fMRI signal changes were inversely correlated with circulating concentrations of amylin, insulin, peptide YY, and glucagon-like peptide-1. **CONCLUSIONS: The caloric content of a meal is signaled from the gut to the brain and affects activity in homeostatic and nonhomeostatic centers; blood glucose concentrations have an important role. The satiety effects of protein are associated with activity changes specifically in the amygdala.**

Keywords: Diet; Neuroimaging; Neuroendocrine Signaling; Rodent Model; Satiety.

Understanding the central mechanisms regulating food intake is important for gaining insights into the etiology of obesity and for developing rational prevention and treatment strategies. It is well-documented that following ingestion of food, neuroendocrine signals generated from the gastrointestinal tract and other peripheral tissues are integrated within homeostatic regions such as the hypothalamus and brain stem to control meal termination.[1,2] Given that feeding behavior may be influenced by social context, emotion, palatability, and availability of different foods, it is apparent that nonhomeostatic regions such as the higher corticolimbic structures can strongly influence and even override the homeostatic control mechanisms regulating food intake.[1,2] In humans, noninvasive neuroimaging techniques such as blood oxygen level–dependent functional magnetic resonance imaging (BOLD fMRI) are increasingly applied for understand the roles of homeostatic and nonhomeostatic regions in the regulation of ingestive behavior.[3,4] The development and application of BOLD fMRI techniques in rodents could provide insights into the interactions between homeostatic and nonhomeostatic regions that regulate food intake using tools and techniques that would otherwise not be possible in humans.

Previous human studies have shown that a satiating meal decreases BOLD fMRI activity in multiple regions such as the cortex, cerebellum, insula, amygdala, and hippocampus.[5–9] Other studies have also observed decreased BOLD fMRI activity within the hypothalamus following the ingestion of glucose solution in humans,[10,11] and following oral intake or intraperitoneal injection of glucose in rats.[12–14] However, it is less clear whether the purported homeostatic and nonhomeostatic brain regions exhibit differential sensitivity to caloric content and/or macronutrients in the gut. Among the macronutrients, protein is the most potent in decreasing food intake, with whey protein diets in particular resulting in weight loss in rodents and humans.[15,16] The satiety effects of dietary protein may be due in part to enhanced secretion of the anorexigenic gut peptides, including cholecystokinin, amylin, peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and/or an imbalance of circulating amino acids.[15,17] There is some evidence that the hypothalamic-brain stem networks play a key role in the satiety effects of dietary protein[15]; however, the role of other nonhomeostatic regions is less clear. Therefore, the relative importance of metabolic, hormonal, and neural signals in mediating the effects of nutrients on BOLD fMRI activity in

Abbreviations used in this paper: BOLD fMRI, blood oxygen level—dependent functional magnetic resonance imaging; GLP-1, glucagon-like peptide-1; IG, intragastric; IV, intravenous; NTS, nucleus tractus solitarius; PYY, peptide YY; ROI, regions of interest.

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homeostatic and nonhomeostatic regions remains to be determined.

In the current study, we applied a BOLD fMRI technique in a novel rat model to map the activity changes in homeostatic (eg, hypothalamus, nucleus tractus solitarius) and nonhomeostatic (eg, hippocampus, thalamus, amygdala) brain regions in response to intragastric infusion of a mixed nutrient meal in overnight fasted rats and compared these with the response to an isocaloric protein load. We quantified circulating concentrations of the gut peptides PYY, GLP-1, amylin and insulin, as well as blood gases and glucose to assess whether these blood-borne signals play a role in influencing the nutrient-induced BOLD fMRI responses. To determine whether the BOLD responses are influenced by nutrient-induced elevations in circulating glucose concentrations, we also determined the effects of intravenous (IV) infusion of a physiological dose of glucose on BOLD fMRI signal changes.

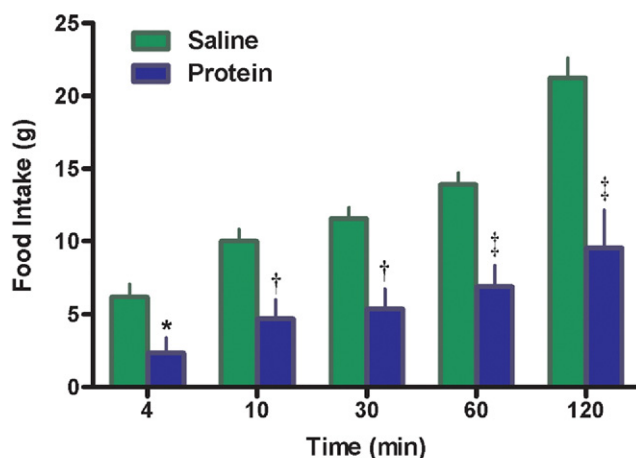

Figure 1. Effects of intragastric infusion of saline or protein (Beneprotein; 12 kcal) on intake of Ensure Plus in rats (n = 16). Values are mean ± standard error. $^{*}P < .05$, $^{\dagger}P < .01$, $^{\ddagger}P < .001$ when compared to saline.

Methods

All experiments were performed in accordance with the Canadian Council for Animal Care Guidelines under protocols approved by the University of Calgary Animal Care Committee. Male Sprague Dawley rats (430 ± 16 g; Charles River, Saint-Constant, Quebec, Canada) were used throughout. Upon arrival the animals were maintained at 19−25°C in shoebox cages under a 12-h light/dark cycle (dark period onset 1000 h) with ad libitum access to pelleted rat chow (Labdiet; Canadian Lab Diets, Inc, Leduc, Alberta, Canada) and water. The reverse light schedule ensured that subsequent behavioral tests and brain imaging occurred during the normal nocturnal feeding time of the rats. After a week of adaptation to the environmental conditions, the animals were then individually housed in hanging wire cages and provided the mixed nutrient liquid meal Ensure Plus (57%, 15%, and 28% calories from carbohydrate, protein, and fat respectively; 1.5 kcal/mL; Abbott Laboratories, Saint-Laurent, Quebec, Canada) during the dark period with ad libitum access to water.

Surgery

Three weeks prior to imaging, rats were implanted with intragastric (IG) catheters as described previously.[18] Briefly, Silastic catheters (~17 cm long, 0.040” ID, 0.085” OD; Dow Corning, Midland, MI) were implanted into the stomach at the junction between corpus and fundus along the greater curvature, and tunneled subcutaneously to exit in the dorsal aspect of the neck.

Food Intake Measurements

Overnight food-deprived rats, under our experimental conditions, typically consume 8.7 ± 0.6 mL (13.0 ± 0.9 kcal) of Ensure Plus during the first 4 minutes of access to food at dark onset.[18] Therefore, a 12-kcal IG caloric load was used in the current experiments. To assess the effects of IG infusion of an isocaloric load of protein (Resource Beneprotein, 100% whey protein isolate, Nestlé Health Care Nutrition, North York, Ontario, Canada) on food intake, rats were adapted to mild restraint (30-min) in Bollman cages for a week prior to testing. On test days, in a repeated measures design, overnight fasted rats (n = 16) received IG infusion of 8 mL either vehicle (saline) or protein (12 kcal, 1.5 kcal/mL in saline) at 2 mL/min for 4 min. The feeding tests were conducted at dark onset (~1000 h) and at 48-hour intervals. Following IG infusion of saline or protein, animals were returned to hanging metal cages, and intake of Ensure Plus was recorded (Figure 1).

Animal Preparation for BOLD fMRI

Animal preparation for imaging and physiological monitoring was as described previously.[18] In brief, following an overnight fast (~16 h), the femoral artery and vein were cannulated with polyethylene tubing (PE 50, Intramedic; Clay-Adams, Inc., Parsippany, NJ) under isoflurane anesthesia. Tracheal intubation permitted manipulation of the ventilation rate and blood gases. A circulating water blanket maintained body temperature at 37 ± 0.5°C measured with a rectal thermometer. After surgery, rats were gradually converted from isoflurane to α-chloralose anesthesia (80 mg/kg IV; Sigma, Oakville, Canada) and maintained on α-chloralose (20 mg/kg every ~45 min). The animal was placed in a plastic cradle and its head secured with an incisor bar and ear pins to minimize motion artifacts. The cradle was subsequently positioned within the center of the magnet. The muscle relaxant pancuronium bromide (0.6 mg/kg, IV; Sabex Inc., Boucherville, Canada) was administered when required to minimize motion artifacts.

BOLD fMRI Signal Acquisition

A 9.4 T/21 cm horizontal bore magnet (Magnex, Oxford, UK) equipped with an elliptical surface radiofrequency coil (24 mm × 18 mm) and Biospec console (Bruker, Rheinstetten, Germany) were used to acquire functional brain images. Scout images were used to position the animal for functional imaging such that the 10th slice transected the bregma. Functional images were acquired with a T_2-weighted multislice, single-shot rapid acquisition with relaxation enhancement sequence and the following parameters: effective echo time = 48 ms, time of repetition = 9700 ms, field of view = 30 × 30 mm, matrix size = 64 × 64, number of averages = 2, slice thickness = 1.5 mm, and number of slices = 10. Functional imaging data obtained was subsequently reconstructed enhancing resolution to 256 × 256 using zero-filling. The imaging coil was positioned to capture key corticolimbic, hypothalamic, and brain-stem structures with the most rostral image positioned at −1.3 mm from bregma; the prefron-

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