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Postprandial plasma PYY concentrations are associated with increased regional gray matter volume and rCBF declines in caudate nuclei — A combined MRI and $H_2^{15}O$ PET study

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ABSTRACT

The anorexigenic gastrointestinal hormone Peptide YY plays an important role in the communication between the gastrointestinal tract and the central nervous system. PYY has been shown to modulate brain activity in regions implicated in reward and food related behavior. Its effects on brain structure however, remain unknown. Voxel-based morphometry was used to investigate the relationship between fasting and postprandial plasma PYY concentrations and regional gray matter volume (GMV). For this analysis twenty adult, non diabetic Caucasians were included (18 F/2 M, age 31 ± 9 y, percentage of body fat [PFAT] 32 ± 8%) who had volumetric brain magnetic resonance images and underwent $H_2^{15}O$ positron emission tomographic (PET) measurements of regional cerebral blood flow (rCBF), a marker of local neuronal activity, and measurements of plasma total PYY, prior to (fasting) and following a satiating liquid meal. Voxel-wise analysis revealed a regional positive association between postprandial PYY and gray matter volume bilaterally in the caudate nuclei. These associations remained significant ($p<0.05$) after small volume correction for multiple comparisons. Based on these findings we investigated whether postprandial PYY is associated with PET measured rCBF of the caudate nucleus. We found a significant negative association between average postprandial caudate rCBF and postprandial plasma PYY concentrations ($r=-0.60$, $p<0.02$, age, sex and PFAT adjusted). Average postprandial caudate rCBF was also negatively associated with rCBF in the right medial orbitofrontal cortex and the right hippocampal formation ($p<0.05$, corrected for multiple comparisons). Total PYY is positively associated with gray matter but negatively with postprandial activity in the caudate nuclei while caudate activity is negatively associated with rCBF in prefrontal and paralimbic regions implicated in reward behavior. Thus, PYY may act centrally to modulate eating behavior via striatal networks.

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Introduction

In the past decades, obesity has become a medical and socioeconomic problem of pandemic proportions in industrialized countries. A vast number of illnesses have been associated with excessive overweight including the major causes of death in western countries, cardiovascular disease, certain types of cancer, and stroke (Guh et al., 2009). In this respect, understanding the physiological events underlying feeding behavior and the development of obesity has become a research question of major importance. Gastrointestinal hormones play a crucial role in the communication between the gastrointestinal tract and the brain, mediating signals of both hunger and satiety. The gastrointestinal hormone Peptide YY (PYY) is a member of the pancreatic peptide fold family along with neuropeptide Y (NPY) and pancreatic polypeptide (PP) and is known to decrease appetite and food intake in lean and healthy humans (Batterham et al., 2003, 2007; Degen et al., 2005; Sloth et al., 2007), inhibit stomach emptying (Witte et al., 2009) and increase gastrointestinal water and electrolyte absorption (Cox, 2007). Synthesized by L-type Endocrine cells in the distal gastrointestinal tract, PYY is secreted into the circulation in response to a meal and postprandial plasma concentrations remain elevated for approximately 6 h (Adrian et al., 1985). Two endogenous and physiologically active forms have been identified, PYY1-36 and PYY3-36. PYY3-36 is formed by the ubiquitously expressed enzyme dipeptidyl peptidase IV (DP-IV) via cleavage of the first three n-terminal amino acids of PYY1-36 (Mentlein et al., 1993). Effects of PYY are mediated by Y-receptors, a G-protein coupled receptor family (Cabrele and Beck-Sickinger, 2000), widely distributed throughout the gastrointestinal tract and the central nervous system (Parker and Herzog, 1999; Widdowson, 1993). So far four subtypes have been identified in humans (i.e. Y1, Y2, Y4, Y5) (Berglund et al., 2003; Gehlert, 1998; Michel et al., 1998). The anorectic effects of PYY have

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been mainly attributed to PYY3-36 and the Y2-receptor. Animal and human studies have shown a reduction in appetite and food intake after systemic administration of PYY 3–36 (Batterham et al., 2003, 2007; Degen et al., 2005; Sloth et al., 2007). In rodents, this effect is absent in Y2R-knockouts (Batterham et al., 2002) or after administration of Y2R antagonists (Abbott et al., 2005). While PYY3-36 exhibits a highly selective binding profile with a strong affinity for Y2-receptors, PYY1-36 has affinity for Y1, Y2 and Y5-receptors. (Batterham and Bloom, 2003; Dumont et al., 1995). Although the primary effect of PYY on appetite and eating behavior is believed to be mediated via the Y2 receptor of the arcuate nucleus within the hypothalamus, a significant decrease in high-fat food seeking in response to systemic PYY that was independent of arcuate nucleus Y2R signaling was reported in rodents (Ghitza et al., 2007). There is evidence indicating that postprandial rises of PYY are lower in obese compared to lean individuals leading to reduced satiety and relatively higher food intake, yet ratios of PYY1-36 and PYY3-36 do not seem to change with adiposity (le Roux et al., 2006). Importantly, obese individuals do not appear to develop a resistance to the anorectic effects of PYY as occurs with the adipokine leptin (Batterham et al., 2003). PYY may also play an important role in weight regain following gastric bypass surgery as attenuated postprandial PYY profiles have been found in individuals with poor weight loss (Meguid et al., 2008). Intravenous administration of PYY3-36 modulates brain regions implicated in both homeostatic (e.g. hypothalamus) and reward related feeding behavior (e.g. prefrontal cortical regions, ventral tegmental area, putamen, globus pallidus) (Batterham et al., 2007).

Peripheral PYY clearly has important effects on brain function and has sustained postprandial elevations. Furthermore, other peripherally circulating hormones have been shown to influence brain morphology (Bourdeau et al., 2002; Matochik et al., 2005; Pannacciulli et al., 2007; Starkman et al., 1999). Thus, we sought to investigate the effects of total PYY concentrations in the fasting state and in response to a satiating liquid meal on gray and white matter volume using voxel-based morphometry (VBM). After demonstrating associations with bilateral caudate gray matter, we investigated associations with Oxygen-15 water positron emission tomographic (PET) measurements of regional cerebral blood flow in a caudate nucleus region-of-interest (ROI). Associations between caudate nucleus rCBF and other brain regions were furthermore investigated in a voxel-based analysis, hypothesizing a modulation of prefrontal and limbic/paralimbic neuronal activity.

Subject and methods

Subjects

All subjects in this study had previously participated in brain imaging studies of hunger, satiation, and the predisposition to obesity. Twenty adult, non-diabetic, right-handed Caucasians with a wide range of adiposity (18 F/2 M; age 31 ± 9 y; percentage of body fat [PFAT] 32.2 ± 8.4%; BMI 31.2 ± 9.6) were included who had available MRI and PET scans and measurements of PYY. All subjects were recruited from the Phoenix, AZ metropolitan area by newspaper advertisements. All subjects were free of medical disorders, not taking any medications, as determined by medical history, physical examination, and screening laboratory tests. Female subjects were studied while in the follicular phase of the menstrual cycle. Subjects with a history of substance or alcohol abuse or addiction; endocrine disorders (including abnormal thyroid function and type 2 diabetes); hypertension, pulmonary, cardiovascular, gastrointestinal, hepatic, renal or central nervous system disorders were excluded from the study at screening. The Structured Clinical Interview for DSM-III-R (Spitzer et al., 1990) was used to screen for behavioral and psychiatric conditions (claustrophobia, major depression, the presence of psychotic symptoms, anorexia nervosa, or bulimia nervosa) incompatible with safe and successful participation in the study. All subjects were admitted for one week to the metabolic unit of the Obesity and Diabetes Clinical Research Section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Phoenix, AZ. Subjects were restricted to the research ward and were limited to sedentary activity for the duration of the study. The protocol was approved by the Institutional Review Boards of the NIDDK and the Banner Good Samaritan Regional Medical Center. All subjects provided a written informed consent prior to participation. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Experimental protocol

The experimental procedures have been described previously (Tataranni et al., 1999). In brief, upon admission, subjects received a weight maintaining diet (50% of calories from carbohydrate, 30% fat and 20% protein). Body composition was assessed by dual energy x-ray absorptiomery (DPX-1; Lunar Corp, Madison, WI); resting energy expenditure (REE) was measured for 45 min using a ventilated-hood system (DeltaTrac, SensorMedics, Yorba Linda, CA). Prior to the brain imaging session, subjects fasted for 36 h. Study subjects had free access to water and non-caloric, non-caffeinated beverages during the fast.

Metabolite analysis

Plasma concentrations of fasting and postprandial total PYY (including PYY1-36 and PYY3-36) were measured by a commercially available radioimmunoassay kit (Phoenix Pharmaceuticals, Belmont, California, USA) with a 100% crossreactivity between PYY1-36 and PYY3-36. Plasma glucose concentrations were measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin concentrations were determined by an automated radioimmunoassay (Concept 4; ICN, Costa Mesa, CA).

Imaging procedures

Magnetic Resonance Imaging (MRI) and positron emission tomography (PET) procedures were carried out at the Banner Good Samaritan Regional Medical Center (Phoenix, AZ). MRI scans were performed on a 1.5 Tesla Signa system (General Electric, Milwaukee, WI, USA). A set of high-resolution T1-weighted images was acquired with a fast spoiled gradient echo (FSPGR) 3d sequence (repetition time [TR]/echo time [TE] = 12/5.2; inversion time (TI) = 300 ms, number of excitations (NEX) = 1; field-of-view [FOV] = 24 × 24 cm; 256 × 256 matrix); the whole brain data were acquired in an axial plane yielding 120 contiguous slices with slice thickness of 1 mm. Each subject's MRI scans were evaluated by an experienced neuroradiologist in order to exclude individuals with anatomic abnormalities.

O-15 water positron emission tomographic measurement of regional cerebral blood flow (counts/voxel/min) was performed on an ECAT-951/31 scanner (Siemens, Knoxville, TN). To adjust for attenuation of γ-radiation by the brain and skull, a 10 min transmission scan was performed using a retractable external ring source of 68 Ga/68Ge. For each 1-min PET scan, subjects remained motionless in the supine position and were requested to keep their eyes closed and pointing forward. Subjects received a 50-mCi intravenous bolus of ^{15}O-water during each scan. Each individual underwent two scans at baseline (fasting, premeal condition) and two after oral administration of a satiating amount of a liquid formula meal (Ensure Plus, 1.5 kcal/ml, Ross-Abbott Laboratories, Columbus, OH) providing 50% of the subject's measured REE, with intervals of 10 min between scans. Formula flavor (strawberry, vanilla or chocolate) was chosen by the subject and the meal was administered continuously over