

# Glucagon-like peptide-1 Modulates Functional Magnetic Resonance Imaging Signal Activity in the Rodent Brain

Prasanth K Chelikani<sup>1</sup>, Ursula I Tuor<sup>2</sup>, and David K Min<sup>1</sup>

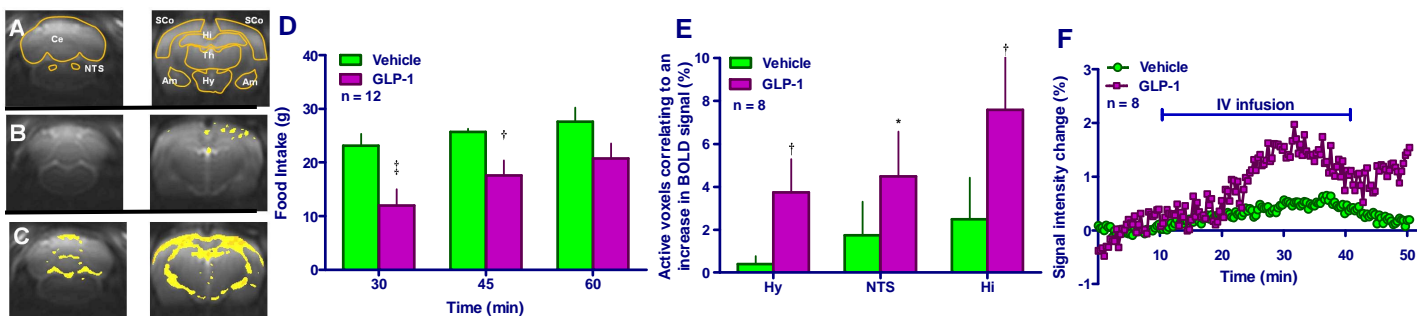
<sup>1</sup>Gastrointestinal Research Group, Production Animal Health, Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta, Canada, <sup>2</sup>Clinical Neurosciences, Radiology, and Physiology and Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

**Target Audience:** Basic scientists and clinicians interested in obesity and neuronal control of appetite.

**Purpose:** The lower gut peptide- glucagon-like-peptide-1 (7-36) amide (GLP-1), and its analogues, are currently used for treating diabetes and hold considerable anti-obesity potential<sup>1</sup>. The hypothalamus and brain stem networks are hypothesized to play a role in mediating the anorexic effects of GLP-1<sup>1</sup>; however, little is known of other brain regions. Therefore, we used a novel rat model to characterize the effects of IV infusion of GLP-1 on BOLD fMRI activity changes in homeostatic (e.g. hypothalamus, nucleus tractus solitarius) and non-homeostatic (e.g. hippocampus, thalamus, amygdala) brain regions that are purported to regulate food intake.

**Methods:** In a repeated measures design, overnight fasted rats (n = 12) received IV infusion of vehicle or GLP-1(7-36) (20 pmol/kg/min) at 3.2 ml/hr for 30-min and intake of Ensure Plus® was recorded. Following ingestive behavioural testing, animals were subjected to fMRI imaging and physiological monitoring as described previously<sup>2,3</sup>. A 9.4 T/21 cm horizontal bore magnet (Magnex, UK) equipped with a surface RF coil and Biospec console (Bruker, Germany) were used to acquire functional brain images. The fMRI experiment consisted of 31 images during baseline (10 min), 93 images during a 30-min IV infusion of vehicle (n = 6) or GLP-1 (n = 8; 20 pmol/kg/min, 3.2 ml/hr), and 31 images following the cessation of infusions (10 min). BOLD data was analyzed using fuzzy cluster followed by correlation analyses using the program Evident<sup>TM</sup>, as described previously<sup>2,3</sup>. The numbers of active voxels were analyzed in specific regions of interest (ROI), and the ROI's were selected based on their purported role in regulation of food intake. Arterial blood samples were collected before and after each IV treatment infusion for analyses of partial pressure of carbon dioxide (P<sub>a</sub>CO<sub>2</sub>), oxygen (P<sub>a</sub>O<sub>2</sub>), and glucose concentrations.

**Results:** Compared to vehicle infusion, a 30-min IV infusion of GLP-1 produced a significant reduction of food intake of 16-30% by 30-45 min (Figure 1D). GLP-1 infusion resulted in an increase in the number of voxels in the whole brain that correlated to an increase in BOLD signal (6.55 ± 3.1% vs 2.53 ± 1.5%) (Figure 1 B, C). ROI analyses demonstrated that GLP-1 infusions produced a significant increase in fMRI activity with 4% of the total voxels in the hypothalamus and nucleus tractus solitarius (NTS), and 7% of the voxels in the hippocampus, correlating to an increase in the fMRI signal intensity when compared to vehicle (Figure 1 B, C, E). The percentage of active voxels which correlated to an increase in BOLD signal within the caudate putamen, cerebral cortex, thalamus, cerebellum and medulla oblongata, as well as voxels correlating to a decrease in BOLD signal, did not differ among treatments. Time course of the BOLD signal revealed that relative to vehicle, a 30-min IV GLP-1 infusion exhibited a significant increase beginning 10-min after onset of infusion and lasting for ~20-min (Figure 1 F). GLP-1 infusion did not alter blood levels of P<sub>a</sub>O<sub>2</sub> (100.1 mm Hg), P<sub>a</sub>CO<sub>2</sub> (38.4 mm Hg), pH (7.38 ± 0.01) or glucose (4.78 mmol/L).



**Figure 1.** (A) Coronal sections depict regions of interest including: Amygdala (Am), Cerebellum (Ce), Sensory motor cortex (SCo), Caudate Putamen (Cp), Hippocampus (Hi), Hypothalamus (Hy), Nucleus Tractus Solitarius (NTS), and Thalamus (Th). Voxels with significant increases in signal intensity during IV infusion of vehicle (B) or GLP-1 (C; 20 pmol/kg/min for 30 min) are shown. (D) Effects of vehicle or GLP-1 on intake of Ensure Plus®. (E) Effects of vehicle or GLP-1 on percentages of active voxels correlating to increase in fMRI signal intensity in various regions of interest. (F) Time course of average BOLD signal intensity change in a representative NTS section. Values are mean ± SE. \* P < 0.05, † P < 0.01, ‡ P < 0.001 vs vehicle.

**Discussion:** The results demonstrate that IV infusion of an anorexic dose of GLP-1 increased BOLD fMRI signal intensity in both homeostatic (hypothalamus, NTS) and non homeostatic (hippocampus) regions. To our knowledge, this is the first study to map the whole brain BOLD fMRI signal responses to systemic infusion of GLP-1 in a novel rodent model.

**Conclusion:** These data support that hypothalamus, NTS and hippocampus may play an important role in mediating the satiety effects of GLP-1. The relative importance of endocrine, neurocrine and paracrine mechanisms in mediating peripheral GLP-1 induced BOLD fMRI signal changes in the brain remains to be determined.

**References:** <sup>1</sup> Holst JJ 2007 *Physiol Rev*:1409-1439; <sup>2,3</sup> Min DK, *et al.*, 2011, *Neuroscience*:151-158; *Gastroenterology*:1832-1841.