Effect of exenatide (a weight loss drug) on fMRI response to food-cues in lean and obese

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TARGET AUDIENCE: Neuroscientists, obesity researchers, phfMRI, physiologists.

PURPOSE Glucagon-like peptide-1 (GLP-1) plays an important role in regulating satiety. GLP-1 enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. Exenatide, synthetic form of glucagon-like peptide-1, is known to promote satiety and weight loss. Most people who use exenatide lose weight. However, the neural circuitry on which Exenatide acts remains unknown. This study investigated the neural effects of exenatide on fMRI responses to visual food cues in lean and obese subjects.

METHODS BOLD fMRI at 3T was performed on ten lean (5 M and 5 F, body mass index = 23.9±2.9 kg/m^2) and ten obese subjects (5 M and 5 F, body mass index = 31.2±1.3 kg/m^2). The fMRI paradigm consists of participants viewing pictures of high-caloric content food versus non-food . A fMRI trial contained 31 blocks lasting 15 mins. Each block contained 10 pictures of food followed by 10 pictures of non-food items, with each image shown for 3s. The first fMRI data set of visual food cues was performed in the morning in the fasted state. Exenatide was infused intravenously with 0.3µg over 1min, followed by 0.05 µg over 15mins, while the second fMRI data set was acquired. Glucose was clamped after Exenatide injection by at fasting level by insulin infusion.

RESULTS In the lean group, Exenatide evoked *increased* fMRI responses to food cues compared to pre-Exenatide condition (**Figure 1**) in: **a)** the cognitive control and decision-making areas: medial frontal gyrus (BA 6 and 9 and 10), superior temporal gyrus (BA 39 and 40), and **b)** the motivation areas: precuneus and orbitofrontal cortex (BA 47), cingulate cortex (BA 24 and 31), lentiform nucleus, thalamus, insula (BA 13) and parahippocampus. Exenatide did not evoked *decreased* fMRI responses to food cues

In the obese group, Exenatide evoked *increased* fMRI responses to food cues compared to pre-Exenatide condition (**Figure 2**) in the lingual gyrus and cingulate cortex (BA 32), which are part of motivation circuitries. Exenatide evoked *decreased* fMRI responses to food cues in the inferior frontal gyrus (BA 11).

By comparison, the overall number of activated pixels in the obese was much smaller compared to lean. There were also substantial differences and non-overlapping activation patterns between the two subject groups.

DISCUSSION In the lean group, all the activated structures were involved in reward process and appetitive regulation (cognitive control and decision making)[1-9]. These findings suggest that Exenatide increases satiety by acting on brain structures responsive to hedonic characteristics of food, down regulating food craving, and/or by acting on cognitive circuitries producing an inhibitory effect.

By contrast, in the obese group, activations were categorized as motivation circuitry. A possible explanation for the differences between leans and obese is that obese subjects may have reduced number of GLP-1 receptors or reduced sensitivity to GLP-1 peptide.

Previous neuroimaging studies of similar gut peptides such as PYY (which it regulates inter-meals intervals) and ghrelin (which helps to initiate food intake) have reported activations in the hypothalamus, anterior cingulate cortex and orbitofrontal cortex activation[10-11]. While these peptides activated some common as well as different brain structures as Exenatide and the experimental paradigms were different, together they provide evidence that these peptides act on the brain's satiety and reward/craving circuitries.

An alternative paradigm is to investigate the effects of Exenatide on the BOLD fMRI signals per se without using food cues. However, this approach appears susceptible to signal drift because it is a single epoch (one dose of Exenatide) and the direct effects of Exenatide appeared weak. It may be possible to inject Exenatide at multiple time points to create a multiepoch stimulation paradigm to improve detectability.

CONCLUSION Lean showed an increased response in motivation, cognitive control and decision-making components of food intake regulation after Exenatide administration, whereas obese subjects showed increased neural response following Exenatide infusion only in a few structures involved in motivation circuitry. fMRI of visual food cues offers a reliable methods to map the neural correlates of drugs regulating satiety. Improved understanding of the neural correlates of these peptides could help to better understand eating disorders.

REFERENCES (1) Rothermund et al. 2007. (2) Small et al. 2010. (3) Fuhrer et al. 2008. (4) Labar et al. 2001 (6) Santel et al. 2006. (7) Mohanty et al. 2008. (8) van der Laan et al. 2011. (9) Kroemer et al. 2012. (10) Malik et al. 2008. (11) Batterham et al. 2007.

Figure 1. fMRI response to visual food cues between post and pre exenatide infusion in lean subjects.

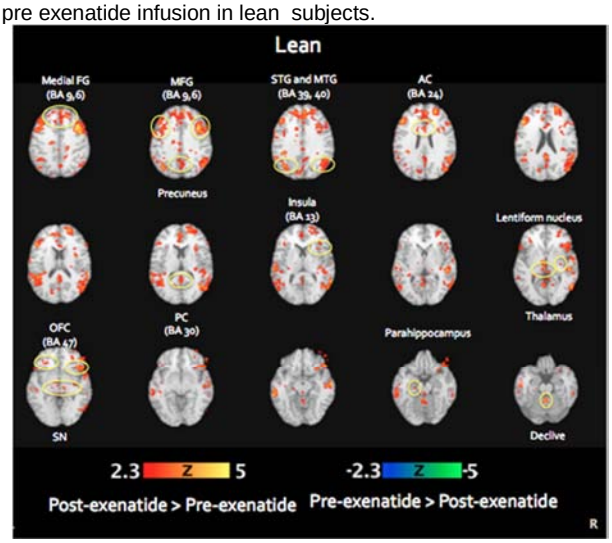

Figure 2. Comparison of neural response to visual food cues post and pre exenatide infusion in obese subjects.