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# Wired for Obesity?

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The central nervous system (CNS) plays an important role in the regulation of appetite, energy expenditure, and body weight. Understanding the neural pathways involved is essential to the development of mechanism-based approaches to the prevention and treatment of obesity and diabetes (Fig. 1). Recent advances in MRI of fast acquisition sequences and image-processing software now enable us to noninvasively examine patterns of brain neuronal activation in vivo using functional MRI (fMRI). Using this technique, several studies have demonstrated the complex interplay of activation in cortical and subcortical regions that control the affective/emotional responses to food that modulate feeding/eating behavior (1,2). These responses may have an important role in driving and sustaining energy intake over and above pure requirement, contributing to the obesity epidemic.

An example of this approach is the elegant work of van Bloemendaal et al. (3), which appears in this issue. The authors examined the effects of GLP-1 agonists on regional brain responses to food cues (images of food) using fMRI. Their aim was to test the hypothesis that the behavioral response (i.e., a reduction in food intake) following GLP-1 receptor activation is mediated through changes in appetite- and reward-related brain areas. In a crossover, randomized, placebo-controlled trial of 48 subjects (16 obese patients with type 2 diabetes [T2DM], 16 normoglycemic obese, and 16 lean control subjects), they used fMRI to determine the acute effects of intravenous administration of the GLP-1 receptor agonist exenatide, with or without prior GLP-1 receptor blockade (exendin 9-39), on brain responses to food pictures during a somatostatin pancreatic-pituitary clamp. They observed increased brain responses to food pictures in appetite- and reward-related brain regions (insula and amygdala) in obese subjects (with and without T2DM) versus lean subjects studied in the fasted state. Acute administration of exenatide in T2DM and normoglycemic obese subjects diminished the food-related brain responses, which was associated with decreased

food intake. These effects were largely blocked by prior GLP-1 receptor blockade using exendin 9-39 and were independent of circulating metabolic and hormonal factors (e.g., glucose). These novel findings provide valuable insights into the effects of GLP-1 analog therapy on neural pathways that could in part explain the effects of this class of drugs on appetite suppression and resultant weight loss.

The results from this interesting study clearly speak for themselves. Nevertheless, the findings merit further reflection. In clinical practice, treatment effects and responses to GLP-1 receptor agonists are not necessarily constant at different stages of the treatment pathway (i.e., the response tends to be greater earlier in the treatment pathway, at a less advanced stage of disease). Subjects with T2DM included in this study would appear to be at a relatively early stage of disease with comparatively short duration of diabetes (median 7.0 [interquartile range 4.2–10.7] years) and reasonable glycemic control ( $HbA_{1c}$   $51.6 \pm 2.4$  mmol/mol) on either one or two oral hypoglycemic agents. Further studies investigating the effects of GLP-1 agonists on CNS food-related responses in responders versus nonresponders may offer insights about which patients are more or less likely to respond to treatment and whether there is a relationship with duration of disease. Interestingly, as noted by van Bloemendaal et al., the inhibitor exendin 9-39 used in this study has low uptake in the brain, suggesting that the central effects of GLP-1 analogs are possibly mediated by its action on peripheral receptors. This is relevant with the arrival of long-acting GLP-1 receptor agonist molecules that are larger and have lower CNS permeability. Understanding the connection between appetite, weight gain, and reward from food is essential to developing effective weight maintenance strategies. The knowledge that fMRI responses in reward-related brain areas to food images are significantly different between lean and obese people also raises a question: Does reward generate obesity, or is it a consequence of obesity?

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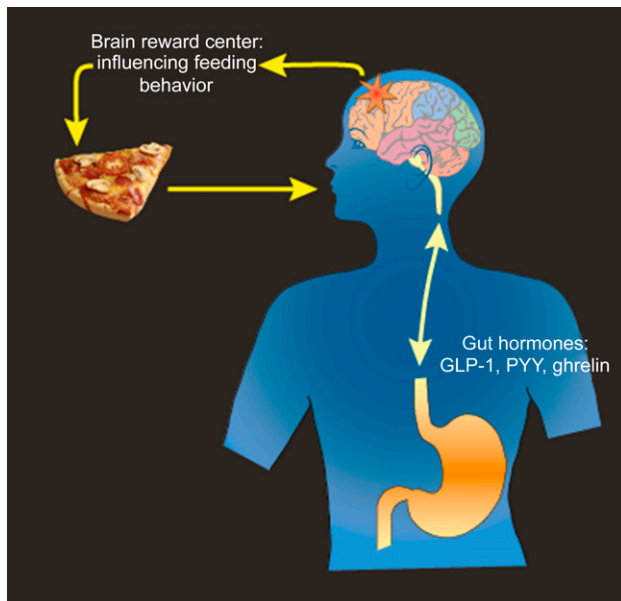
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See accompanying article, p. 4186.



**Figure 1**—Neurohormonal regulation of appetite and reward (modified from <http://gut-brain-axis.org/>). PYY, peptide tyrosine tyrosine.

Finally, this well-designed study by van Bloemendaal et al. (3) is a good example of the integration of recent advances in MRI with careful physiological studies in well-phenotyped subgroups of individuals to address clinically relevant questions. This study adds to a growing body of work where fMRI has been used to study the brain response to physiological stimuli such as fasting/refeeding (4); to specific hormones such as leptin (5), ghrelin (6), peptide tyrosine tyrosine (7), and GLP-1 (8); to therapeutic interventions such as caloric restriction (9), weight loss maintenance (10), sibutramine (11), and Roux-en-Y bypass surgery (12,13); and to the effects of common (14) and rare obesity-associated genetic variants (15,16).

Such studies can drive the selection and validation (and indeed rejection) of potential drug targets (17), thereby increasing the probability of success of drug development programs. At present, most imaging methods do not meet biomarker status. However, if the techniques used in the study by van Bloemendaal et al. (3) are demonstrated to be robust and reproducible, then they could be applied in future proof of concept studies for the clinical evaluation of new drug candidates for the management of obesity and T2DM.

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**Duality of Interest.** P.C. has served on advisory boards for Sanofi and Lilly, which are manufacturers of GLP-1 receptor agonists. No other potential conflicts of interest relevant to this article were reported.

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