GLP-1 analogs: satiety without malaise?

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ALTHOUGH IT HAS BEEN WIDELY ACCEPTED for more than a decade that central or peripheral administration of glucagon-like peptide-1 (GLP-1) causes reduced food intake, it has also been debated whether the reductions were due to engagement of distinct physiological pathways of food intake regulation or, alternatively, if the subjects felt so ill that they reduced food intake. In the current issue of *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, Scott and Moran (13) report a physiological role of GLP-1 and GLP-1 analogs in the regulation of food intake in nonhuman primates. Their findings show that GLP-1 and GLP-1 analogs are regulators of food intake through decreased meal size. If the subjects were feeling ill, we could anticipate that they would have reduced meal frequency, too, and only the highest dose caused reduced meal frequency in these studies. Therefore, this work adds to the growing body of evidence that GLP-1 and GLP-1 analogs can reduce food intake without inducing malaise.

In 1983, Bell et al. (1) discovered GLP-1 as a tissue-specific posttranslational product of preproglucagon primarily located in the L cells of the gut but also in the alpha cells of the pancreas and in brain stem neurons (7). In subsequent years, GLP-1 was found to be an important incretin hormone that stimulated insulin release, suppressed glucagon secretion, and inhibited gastric emptying (4, 5). Further research was triggered by the discovery of the GLP-1 receptor, which was found to be distributed in many peripheral tissues, as well as the brain, including the hypothalamus and brain stem, leading to the hypothesis that GLP-1 might also play a role in the regulation of food intake (2, 9). In the mid to late nineties, a number of independent groups demonstrated that central and peripheral administration of native GLP-1 resulted in robust but transient change in food intake, and it was hypothesized that in addition to the acute food intake-lowering effect, GLP-1 might also play a role in the long-term regulation of food intake and, hence, body weight homeostasis (6, 14, 16). This role for GLP-1 as an endogenous regulator of food intake was challenged by a series of articles implicating GLP-1 and the GLP-1 neurocircuitry in mediating gastric discomfort, and it was argued that the reduced food intake was simply a reaction to malaise because high concentrations of GLP-1 triggered a conditioned taste aversion and pica behavior (kaolin intake) (11, 12, 15, 17). It was also argued, although never demonstrated, that the inhibition of food intake and the nausea/malaise could be a continuum where malaise was preceded by normal satiety and fullness (17), a proposition that many of us can relate to personal experience.

Irrespective of this mechanistic dispute, pharmaceutical companies embraced GLP-1 as a target for diabetes drug development (8, 18), and currently one GLP-1 analog, Byetta (Amylin-Lilly), is marketed, and soon other GLP-1 analogs such a Liraglutide (NovoNordisk) will also seek FDA approval (3). Native GLP-1 is rapidly cleaved and degraded; both these therapies are injectible GLP-1 analogs that possess much longer plasma half-lives than GLP-1. There are also several orally available therapies that target the GLP-1-degrading enzyme dipeptidyl-peptidase IV (DPP4), for example, Januvia (sitagliptin) and Galvus (vildagliptin) (10). In addition to the remarkable effects on glucose homeostasis, it has been reported from several clinical trials that patients undergoing GLP-1 analog treatment also experience decreases in food intake and body weight. The most often reported adverse effect is nausea, which appears in a substantial proportion of users and also appears transient. Regardless of the role of nausea in GLP-1 effects, the dramatic uptake of Byetta leads us to question the dogmas that injectible therapies will have limited use in obesity (there is rumored to be substantial off-label use of Byetta for obesity) and that patients will not tolerate nausea; they clearly do to remain on Byetta. The clinical experience validates that GLP-1 can cause nausea, but the conundrum remains, must GLP-1 cause nausea to inhibit food intake?

The article by Scott and Moran in part answers this question. The authors demonstrate dose-related anorectic responses to low doses of the GLP-1 analog exendin-4 (Ex4) in rhesus macaques. The inhibition lasted throughout the 6-h feeding test period with no inhibitory or compensatory overeating in the following 6-h feeding period. The discovery of lower food intake after Ex-4 is in itself not novel, because anorectic effects following GLP-1 or GLP-1 analogs have been demonstrated in a variety of species ranging from mice, rats, and chickens to humans. Where this paper distances itself from previous papers is by demonstrating that the lowered food intake is due to an overall reduction in meal size, and not meal number, and that the reduction in meal size is also dose related. Furthermore, behavioral observations did not demonstrate any overt signs of malaise such as decreased alertness, drooling, or vomiting, but as the authors report, “they simply seem to be uninterested in further food intake.” From experience we know that this is a species that is easily nauseated, readily develops aversions, and has distinctive behaviors as they become nauseated.

Another important aspect of the article is that the authors show that even within a subchronic setting (5 days of consecutive administration), there was a daily sustained reduction in food intake as well as a dose-related reduction in meal size, with no signs of tachyphylaxis. With the relatively short treatment period (5 days), the authors were not able to demonstrate any changes in body weight, but as the authors rightly argue, the sustained reduction in food intake over the course of...
5 days is clearly indicative of a role for Ex4 and other GLP-1 analogs in the regulation of body weight.

Given localization of GLP-1 receptors in key peripheral sites involved in the regulation of food (vagal afferent and the nodose ganglion) as well as key central hypothalamic (the arcuate, dorsomedial, and paraventricular nucleus) and brain stem (nucleus of the solitary tract and the area postrema) nuclei, it is hard to determine the site of action of Ex4. Scott and Moran argue that the effect of Ex4 more than likely is mediated via peripheral receptors on vagal afferents and the nodose ganglia, but given the high lipid solubility of Ex4, it is likely that Ex4 also interacts with GLP-1 receptors located in the hypothalamus and/or brain stem.

With this article, Scott and Moran have added an important piece to the puzzle regarding the mechanism underlying the anorectic effect of GLP-1 and GLP-1 analogs and have demonstrated how a well-thought study design combined with the right animal model can lead us to a closer understanding of the basal mechanism regulating physiological processes. Enjoy.

GRANTS

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REFERENCES

13. Scott KA, Moran TH. The GLP-1 agonist exendin-4 reduces food intake in nonhuman primates through changes in meal size. Am J Physiol Regul Integr Comp Physiol (June 20, 2007); doi:10.1152/ajpregu.00323.2007.