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Treating Diet - Induced Obesity: A New Role for Vagal Afferents?

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TREATING DIET - INDUCED OBESITY:

A NEW ROLE FOR VAGAL AFFERENTS?

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As of the 2007-2008 National Health and Nutrition Examination Survey, 34 percent of adults – or over 72 million people - were obese, having a BMI greater than 30. And childhood obesity has been catching up, strongly implying that this epidemic will only continue to grow for the foreseeable future. The current “obesogenic” environment is often cited as the major cause of the obesity epidemic. However, the fact that a large percentage of the population has not become obese could imply that a gene-environment interaction contributes. For instance, this differential response to the obesogenic environment suggests one’s inherited physiological makeup (which itself is modulated by environment) either resists or favors obesity. Given the powerful influence of the current environment, if one’s physiology favors obesity it takes tremendous discipline to avoid excessive caloric intake and weight gain.

Having obesity might not be so unfortunate if weight gain and increased fat mass were the only consequences. However, as has been clear for some time now, obesity is associated with numerous sequelae such as diabetes, cardiovascular disease, and cancer [1]. Further, individuals that develop proportionately large visceral abdominal fat stores are more likely to experience the morbidity and mortality associated with these obesity-related diseases [2]. Regrettably, despite the fact that these consequences have been known for a long time, no satisfactory non-invasive treatment for obesity has been developed. As a consequence, large numbers of people with obesity have been driven to undergo expensive and risky bariatric surgical procedures. One of these surgeries, gastric bypass, has been fairly effective at reducing body weight, and it has also turned out to be useful for treating type 2 diabetes [3]. The mechanism underlying these effects is not fully understood, but appears to involve many factors, including

decreases in consumption of high calorie foods, meal size and nutrient absorption as well as changes in anorexigenic and orexigenic hormone levels, increased energy expenditure, and altered vagal gastrointestinal (GI) innervation [4]. It may be that the multifactorial nature of the effects of gastric bypass is a key to its success at reducing body weight.

Before bariatric procedures became popular, truncal vagotomy, involving division of the right and left vagal trunks below the diaphragm was employed to treat morbid obesity [5]. However, the interruption of vagal pre- motor axons as part of the vagotomy procedure caused gastric stasis and “dumping” of food from the stomach to the intestine, which resulted in unpleasant sensations, including nausea. One way to overcome the adverse side effects of vagotomy and retain some of the benefits would be to reduce or avoid damage to the vagal pre-motor axons. Indeed, selective sensory vagotomy appears to retain some of the benefits as it has been shown to reduce food intake, body weight and fat accumulation in rodent obesity models [6-7]. Moreover, in one of these studies sensory vagotomy reduced the excess abdominal visceral fat found in aging rats [7]. Stearns et al. took this approach further by distinguishing the effects of sensory vagotomy on different fat depots in rats subjected to diet-induced obesity (DIO) [8]. They produced sensory vagotomy by applying capsaicin to the abdominal vagal branches and compared the effect of this treatment on DIO in rats fed a high-energy “Western diet” for 11 months with the effects of truncal vagotomy and sham surgery. Interestingly, although sensory vagotomy produced only a small, non-significant reduction in body weight, it also led to a modest, but significant and selective 18% reduction in visceral abdominal fat compared to controls. Given the association of

this fat depot with several causes of morbidity and mortality that can result from obesity this is an important finding. Moreover, as the authors pointed out, even this fairly small effect of sensory vagotomy on visceral fat could produce significant decreases in morbidity and mortality. For instance, in patients with a large visceral fat depot, small changes in its size can have a big influence on overall mortality risk [9]. Stearns et al. [8] further suggested that sensory vagotomy could provide a valuable adjunct to bariatric surgery by enhancing its ability to reduce body fat, and in particular visceral fat. Consistent with this possibility, truncal vagotomy has been used successfully as an adjunct to gastroplasty to augment weight loss [10].

Another important implication of the findings of Stearns et al. [8] is that vagal GI afferents may contribute to DIO. However, this interpretation goes against traditional views of vagal GI sensory function in two ways. First, the main roles of vagal afferents are thought to be inhibition of food intake [11] and regulation of vago-vagal digestive reflexes [12] - not facilitation of food intake or weight gain. Secondly, the influences of vagal afferents on food intake and body weight are thought to act on a short-term, or meal-by-meal basis - not to accrue over the long-term [11].

One possible route by which vagal afferents could facilitate food intake and weight gain involves alterations to their control of vago-vagal GI reflexes. For example, accommodation is activated by food-induced stretch of the esophagus and forestomach [13]. It relaxes the stomach wall, which is contracted between meals. This allows the stomach to accept a meal without significantly increasing intragastric pressure. If this relaxation were exaggerated, it could permit consumption of larger-than-normal meals

before intragastric pressure increased sufficiently to activate vagal satiation signals, or to propel food into the intestine, which also activates these signals. Consistent with this possibility, loss of vagal afferents that innervate the forestomach in *steel* and W^v mutant mice led to reduced meal size, which could imply that this reduced innervation resulted in weaker activation of accommodation and thus reduced the stomach volume available to accept food (e.g., [14]). Also, increased meal size caused by knockout (KO) of *brain-derived neurotrophic factor* (*BDNF*) in GI smooth muscle was associated with increased activation of gastric vagal pre-motor neurons, an effect consistent with augmentation of accommodation or gastric motility [15-16]. However, these suspected changes in vago-vagal reflexes in *steel*, W^v and *BDNF* mutants need to be verified. As noted by Stearns et al. [8], a more direct pathway vagal afferents could utilize to promote abdominal obesity was identified in pilot experiments that suggested intestinal mucosal nerves were necessary for accumulation of visceral fat [17]. However, it remains to be determined whether vagal afferents are involved.

Regarding the implication of the results of Stearns et al. [8] that vagal afferents contribute to the long-term accumulation of the visceral fat component of body weight, there are only a handful studies that have provided supporting evidence. Interestingly, the vagal manipulations in these studies have typically occurred in conjunction with alterations to the CNS feeding regulatory circuit, suggesting these alterations are needed to reveal a long-term vagal afferent role. These studies involved reductions in central and peripheral CCK receptors that resulted in obesity [18], intracerebroventricular leptin injection paired with subthreshold peripheral CCK infusion that reduced body weight [19], and partial reduction of central BDNF levels combined

with KO of *BDNF* in GI smooth muscle that caused obesity [16]. These peripheral CCK and BDNF effects presumably involved altered vagal afferent signaling, but this needs to be verified. Additionally, consumption of a high-energy diet by *neurotrophin-4* KO mice, which lack most of the vagal afferents that innervate the smooth muscle of the small intestine, revealed an increased hyperphagia compared to controls [20]. A possibility to consider is that the long-term effects associated with the loss of vagal afferents in *neurotrophin-4* mutants and in the DIO rats of Strearns et al. [8] involved changes to the CNS feeding regulatory circuit. High-energy diets can reduce the levels of anorexigens, including BDNF, in CNS nuclei that regulate feeding and body weight [21], and in some instances these reductions have been demonstrated to contribute to hyperphagia and obesity [22]. Thus, if the high-energy diets fed to the *neurotrophin-4* mutants or the DIO rats of Stearns et al. [8] reduced anorexigen levels in key CNS nuclei, then these reductions may have combined with the effects of the missing vagal GI afferents in these animals to produce long-term effects on body weight. Finally, as noted by Stearns et al. [8], clinical studies using chronic electrical stimulation of the cervical vagus observed weight loss in depressed patients with obesity, which is consistent with a long-term role for vagal afferents in body weight regulation.

Future studies will make valuable progress by building on the results and experimental design of Stearns et al. For example, to better understand the contributions of changes in feeding behavior and energy expenditure to the effects of vagotomy, it would be valuable to characterize them early in the dynamic phase of weight gain. Obesity can have its own effects on food intake and energy expenditure that become confounded with the effects of vagotomy on these variables. Therefore,

measuring them prior to development of obesity will help establish whether changes in these variables are a cause or a consequence of obesity. Another valuable addition would be to have two reference groups that are fed a balanced diet with its components matched as closely as possible to those of the high-energy diet: one group that receives no treatment and another that receives vagotomy. These groups provide baselines that permit one to distinguish, for example, the actual degree of obesity in each group, rather than just the relative degree. Also, the proportions of the obesity and excess visceral fat due to aging [7] vs. diet [8] could be distinguished, both with and without vagotomy. Further, since capsaicin produces only a partial loss of vagal GI afferents, it will be informative to assess residual vagal function in vagotomized animals before they are exposed to a high-energy diet, for example, by examining CCK suppression of meal size. In addition to confirming the success of the vagotomy procedure, these types of experiments could help identify the vagal sensory pathways that contribute to DIO. Finally, when lengthy postvagotomy survival times are involved, vagal afferents regenerate [23], and therefore, this should be examined because it could actually mask some of the beneficial effects of vagotomy on DIO.

Studies that build on the findings of Stearns et al. [8] by considering these and possibly additional useful variations of the experimental design will bring us closer to knowing whether vagal GI afferents contribute to long-term regulation of food intake and body weight, and if so how they do this. Such progress will provide novel targets for gaining control over the excessive overeating and weight gain that has become so pervasive.

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