Editorial Focus: What Happens In The Vagus, …?

Editorial Focus for NT-4 Deficient Mice Lack Sensitivity to Meal-associated Pre-absorptive Feedback from Lipids. Chi MM and Powley TL.

What Happens In The Vagus, …?

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The vagal afferents that innervate the gastrointestinal (GI) tract play a major role in conveying meal-related signals to the CNS. Functional alterations of these sensory neurons have been implicated in obesity (17) and eating disorders (9). In the past, chemical or surgical deafferentation methods have been used to examine the specific contribution of these GI afferents to the negative control of food intake. The findings from these -loss of function- experiments, although somewhat contingent on the method of deafferentation, have yielded insight into the roles of this heterogeneous population of afferent fibers. The excitotoxin capsaicin, for example, which selectively destroys unmyelinated afferent fibers (12), has been shown to increase the initial consumption of an unfamiliar high-fat diet, an effect that attenuates with repeated diet exposure (4). In contrast, surgical subdiaphragmatic vagal deafferentation has been demonstrated to increase both meal size and decrease meal number, an effect was not dependent on the novelty of the diet (18).

To further examine how signals conveyed by vagal afferents contribute to meal-related feeding controls, Chi and Powley (6) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology have employed a genetic method that results in a reduction of GI afferent innervation - the neurotrophin-4 (NT-4) knockout mouse. NT-4 is a neurotrophic factor closely related to brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which have been shown to be critical for neuronal development and regulation of neuronal plasticity (14, 16). In addition to being a specific chemoattractant for dorsal root ganglions neurons (14), NT-4 has been
demonstrated to a potent stimulator of neurite outgrowth of adult mouse nodose ganglion \textit{in vitro}, suggesting it may be involved in trophic support following regeneration or synaptic reorganization \cite{19}. NT-4 knockout mice have significant reductions in the number of nodose ganglion neurons (to 45\% of levels in wild type mice) and reductions in afferent vagal terminals both in the duodenum (10\% of wild type) and ileum (9\% of wildtype) without any alteration in motor neurons \cite{10}. Previously, it has been shown NT-4 knockout mice fed a standard diet exhibit disruptions in short-term meal-related feedback controls (i.e., increases in meal duration and size) while the long-term maintenance of body weight and calories remains intact (i.e., no differences from wild-type controls) \cite{10}.

The current study by Chi and Powley examined the contribution of vagal afferent information to the negative feedback actions of two representative macronutrients, fat and carbohydrates, using the NT-4 knockout mice. To temporally relate food consumption with the gastric presence of the nutrient, the mice were exposed to yoked infusion paradigms in which Intralipid (10\% or 20\%) or glucose (12.5\% or 25\%) was infused into the stomach coincidentally with the spontaneous intake of pelleted chow (~1 kcal infused/1 kcal ingested). By examining the pattern of pelleted chow consumption, they were able to determine if the infusions modified the pre-absorptive (i.e., within meals) and/or the post-absorptive (i.e., between meals) controls of food intake. In response to the infusion of fat, the NT-4 knockout mice had smaller reductions in meal size and duration, and smaller increases in the satiety ratio and inter-meal interval than
did control mice, indicative of reduced negative feedback signaling. The NT-4 knockout mice also failed to compensate their total daily calories intake in response to the extra calories received from the infusion of fat, which led to an overconsumption on the fat infusion days. The glucose infusions in the NT-4 knockout mice, however, did not result in any alterations in the meal patterns or in the number of total daily calories consumed. The results suggest that NT-4 knockout mice are less sensitive to the negative feedback conveyed by gastric fat in both the pre-absorptive and the post-absorptive phases of a meal. Taken together with the observation that NT-4 knockout mice demonstrate an alternating increase in caloric intake with intermittent high fat feeding (3), NT-4 dependent vagal afferents are likely to convey intestinal information related to the fat composition of ingested food.

A possible factor contributing to the diminished meal suppressive effects of gastric fat in the NT-4 knockout mice is reduced cholecystokinin (CCK) signaling. CCK is an intestinal peptide released in response to the luminal presence of fat, proteins, or their digested products. Increased CCK levels lead to a reduction of both meal size and meal duration, an effect that is primarily dependent upon vagal afferent signaling (13, 15). A role for CCK in the modulation of vagal sensory information related to GI fat is supported by the observation that CCK antagonists block the suppressive effects of intraduodenal infusions of long chain free fatty acids (LCFFA) on food intake in rats and humans (11, 20). In contrast to NT-4 knockout mice, NT-4 \textit{knockin} mice, which have a greater number of GI vagal nerve intraganglionic laminar endings and
likewise have smaller meal sizes, display an increased sensitivity (i.e., larger
meal suppression with smaller doses) to exogenously administered CCK (5).

Other intestinal peptides that derive from lower intestinal sites such as
glucagon like peptide – 1 (GLP-1) and PYY (3-36) can also signal the intralumial
presence of nutrients and reduce food intake (2). Their actions also depend upon
intact vagal afferent signaling (1). The nutrient specificity of the current Chi and
Powley findings suggest that the NT-4 knockout model would also be useful in
assessing the contributions of these peptides in the ability of lower intestinal
nutrients to inhibit food intake.

The finding of increased overall caloric intake on the fat infusion days in
the NT-4 knockout is particularly intriguing. Vagal afferent feedback has
traditionally been viewed as important for controlling the patterning rather than
the overall amount of food intake. In the present work increases in intake on fat
infusion days did not resulting significant increases in the NT-4 knockout mice.
Since, the fat infusions did not occur on consecutive days but every 2-3 days, the
lack of weight gain is likely due to adjustments in caloric intake by the NT-4
knockout mice on the non-infusion days. Data from experiments examining the
ability of jejunal fat infusions to affect food intake suggest the possibility that
vagal afferent feedback can, in fact, play a role in longer term controls of food
intake and body weight. Jejunal infusion of linoleic acid, a LCFFA, produces
suppressions of food intake beyond their caloric value resulting in decreases in
body weight (7). This suppressive effects of jejunal infused linoleic acid on food
intake has been shown to be attenuated by deafferentation of the celiac branch
of the vagus (8), suggesting that alteration in vagal afferent signaling can result in longer term changes in food intake sufficient for affecting body weight. Future investigation into whether consecutive days of gastric fat infusions would lead to long-term body weight changes in NT-4 mice would be helpful in addressing if short-term meal alterations, as a result of decreased GI vagal innervation, can translate into long-term body weight changes, a finding that would have important implication for the current obesity epidemic.

References:


