MOLECULAR METABOLISM

Correspondence

Vagal plasticity the key to obesity

In their commentary on our article in Molecular Metabolism [1], Page et al. [2] propose the concept that leptin can act as a "double agent" — inhibiting food intake in lean animals, but promoting food intake in obese animals. This hypothesis stems from our finding that knocking out leptin receptor in vagal afferent neurons increases food intake and weight gain in low fat fed mice, while preventing weight gain in high fat fed animals. The development of hyperphagia and obesity in *Nav1.8/LepR*$^{fl/fl}$ mice is consistent with the predicted role of leptin, acting at the level of vagal afferent neurons, to induce satiation. However, the absence of weight gain in high fat fed *Nav1.8/LepR*$^{fl/fl}$ mice led Page et al. to suggest that leptin may promote food intake in high-fat fed, obese animals. They propose that knocking out leptin receptors removes leptin-induced reduction in gastric vagal afferent mechanosensitivity in diet-induced obese mice [3]. Thus, the loss of leptin signaling in this population of vagal afferent neurons will restore sensitivity to gastric distention, preventing overconsumption of the high calorie diet.

This double agent hypothesis is intriguing, but is unlikely to account for the almost complete absence of weight gain in *Nav1.8/LepR*$^{fl/fl}$ mice fed a high fat diet. Reducing the sensitivity of gastric vagal afferent mechanoreceptors has not been demonstrated to promote food intake. In addition, leptin reduces mechanosensitivity in gastric vagal afferent neurons of diet-induced obese mice by only 25—30% [3]. Any increased accommodation as a result of the loss leptin signaling in high fat diet *Nav1.8/LepR*$^{fl/fl}$ mice may be mitigated by the loss of gastric relaxation provided by small intestinal feedback. Under normal conditions, CCK will synergistically interact with vagal afferent neurons responsible for sensing gastric distention to promote gastric relaxation [4]; therefore, reduced sensitivity of VAN to CCK in *Nav1.8/LepR*$^{fl/fl}$ mice will decrease gastric accommodation, and balance the increased gastric accommodation caused by the loss of leptin signaling. Another reason that loss of leptin receptor in this mechanosensitive population of vagal afferent neurons is unlikely to account for the full difference in body weight between wildtype and *Nav1.8/LepR*$^{fl/fl}$ mice fed high fat diet, is that *Nav1.8/LepR*$^{fl/fl}$ mice become hyperphagic and gain weight on a low fat diet. Following a meal, mechanosensitivity of gastric vagal afferent fibers of lean mice are insensitive to leptin [3], yet low fat fed *Nav1.8/LepRfl/fl* mice gain weight; since high fat fed *Nav1.8/LepRfl/fl* mice should have similar gastric accommodation to low fat fed mice it is unclear how this could explain the absence of weight gain. Instead, we hypothesize that *Nav1.8/LepR*$^{fl/fl}$ mice have developed compensatory downstream mechanisms allowing energy homeostasis to occur in the absence of gastrointestinal signals and that this is the most likely cause of the absence of weight gain of *Nav1.8/LepR*$^{fl/fl}$ mice on a high fat diet.

Leptin-induced reduction in gastric mechanoreceptor sensitivity does not exclusively occur in response to chronic high fat feeding; an identical response also occurs in fasted lean mice [3]. There is strong evidence that vagal afferent neurons lose plasticity in chronic high fat feeding, resulting in the neurons of obese animals remaining in a fasted phenotype irrespective of the feeding status of the animal. Protein expression of vagal afferent neurons in lean animals switches from proteins associated with stimulating food intake in fasted animals, to proteins associated with stimulating food intake in fed animals [5]. In diet-induced obesity, vagal afferent neurons constitutively express orexigenic proteins similar to that observed in a lean fasted animal. Furthermore, the sensitivity of vagal afferent neurons to gastrointestinal hormones such as cholecystokinin, serotonin, or leptin are blunted in high fat fed animals [5—7], that is, vagal afferent neurons are not responsive to meal-related stimuli. There are also changes in the electrophysiological properties of vagal afferent neurons in diet-induced obesity [4]. Membrane conductance of vagal afferent neurons is reduced, with input resistance reduced, nearly twice the amount of current required to induce a single action potential, and supra-threshold stimulus elicit a 3—4 fold reduction in the number of action potentials in vagal afferent neurons of high fat fed mice compared to low fat fed mice [6]. Importantly, there is evidence that vagal afferent sensitivity is not lost to all stimuli in chronically high fat fed animals. Cannabinoid, melanin-concentrating hormone [5], and ghrelin receptors [8] are all up-regulated in vagal afferent neurons in response to a high fat diet, indicating a possible increase in sensitivity to these orexigenic hormones. Kentish et al. also demonstrated that sensitivity to leptin increases in gastric mechanosensitive vagal afferent neurons [3]. Crucially, all of these changes are identical to the responses seen in vagal afferent neurons of fasted lean mice. These data support the concept that vagal afferent neurons of high fat fed animals, lose plasticity, and become stuck in a fasted phenotype.

An interesting unanswered question is: why does leptin reduce mechanoreceptor sensitivity to tension in vagal afferent neurons of fasted lean mice? We hypothesize that in response to the first meal after a prolonged fast, the role of the stomach would be to accommodate a large volume of food. Distention-induced satiation would be inappropriate, as it would cause premature termination of a meal. Under these conditions, gastric leptin release in response to initial nutrient ingestion could reduce the sensitivity of mechanosensitive vagal afferents innervating the stomach, thereby prolonging nutrient ingestion. We predict that the inability of vagal afferent neurons of obese animals to switch between a fed and fasted phenotype may increase the reservoir function of the stomach in fed conditions. Restoring the loss of plasticity in vagal afferent neurons could therefore reinstate not only appropriate mechanosensitivity, but also firing, signaling, and gene expression of vagal afferent neurons to meal cues, and result in appropriate meal termination. Since *Nav1.8/LepR*$^{fl/fl}$ mice show similar loss of vagal afferent neuron plasticity seen in diet-induced obesity [1], we suggest that leptin plays a key role in enabling appropriate vagal afferent neuron plasticity in fed and fasted conditions. Restoring leptin sensitivity could therefore reinstate plasticity in vagal afferent neurons and enable appropriate meal-termination signals in response to a meal.

Although the absence of weight gain in high fat fed *Nav1.8/LepR*$^{fl/fl}$ mice is interesting, and suggests that leptin resistance may be necessary for the onset of obesity; the real significance of this research is that we have found that vagal afferent neurons are involved in long-term regulation of food intake. Chronic increases in meal size and duration, caused by loss of leptin signaling in vagal afferent neurons, result in hyperphagia and obesity. Clearly, further work will be needed

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to distinguish the relative importance of different subpopulations of vagal afferent neurons; however, the Nav1.8 cre mice can be a useful tool to provide further insight into the role of individual proteins of the gut-brain pathway in the treatment of obesity.

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