Commentary

MOLECULAR METABOLISM

Vagal leptin signalling: A double agent in energy homeostasis?

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In this issue of Molecular Metabolism, de Lartigue et al. reveal the effect of leptin receptor depletion in vagal afferents on food intake and weight regulation. de Lartigue et al. showed deletion of leptin receptor in Nav1.8 expressing sensory neurons resulted in increased food intake (specifically in the dark phase), reduced sensitivity to the satiety hormone cholecystokinin (CCK), which ultimately led to increased adiposity and a modest increase in weight. Curiously, feeding this knockout line a high fat diet led to no further weight gain, compared to the chow fed knockout animals, and, in fact, they were substantially lighter than high fat diet fed wildtype mice. This landmark paper provides direct evidence for the physiological importance of leptin—vagal afferent interactions in satiety signalling and long term weight regulation.

Currently, the long term regulation of energy homeostasis is largely attributed to homeostatic pathways within the central nervous system. The satiety hormone, leptin, secreted primarily from white adipose tissue, provides a signal to the hypothalamus reflecting the size of fat stores [1,2] and serves as a long-term regulator of nutrient intake, adiposity and body weight [3]. However, although the levels of circulating leptin reflect the degree of adiposity [1], in obesity, where leptin levels are high, there is an inability for leptin to suitably regulate body weight, a phenomenon dubbed 'leptin resistance'.

In the periphery, it is well recognised that signals generated in the gastrointestinal tract are involved in the short term regulation of food intake influencing meal size and duration [4]. This involves integration of both gastric and small intestine feedback. In the small intestine this signalling is thought to be an enteroendocrine response to nutrients, and the data of de Lartigue et al. indicate that leptin receptor disruption, specifically in vagal afferents, decreases vagal afferent sensitivity to the anorexigenic hormone CCK, thus presumably reducing the satiety signal arising from the small intestine. On the other hand, CCK also activates gastric afferents [5] and, as there were no means to actually determine the location of the afferent ending involved this may be somewhat premature. Additionally, the authors fail to consider satiety signals from the stomach. In the stomach, vagal afferent satiety signals are generated largely in response to mechanical stimuli. Gastric vagal afferents can also be acted on by a number of appetite regulating peptides, including leptin, to regulate food intake [6], suggesting the results of de Lartigue et al. likely have intestinal and gastric contributions. Although gastrointestinal vagal afferents are an important link between the periphery and the central nervous system the influence of vagal afferent satiety signals on long term regulation of energy homeostasis has been under debate for many years. This is largely due to the multiple central and peripheral sites of action of appetite regulating hormones (Figure 1). By specifically manipulating

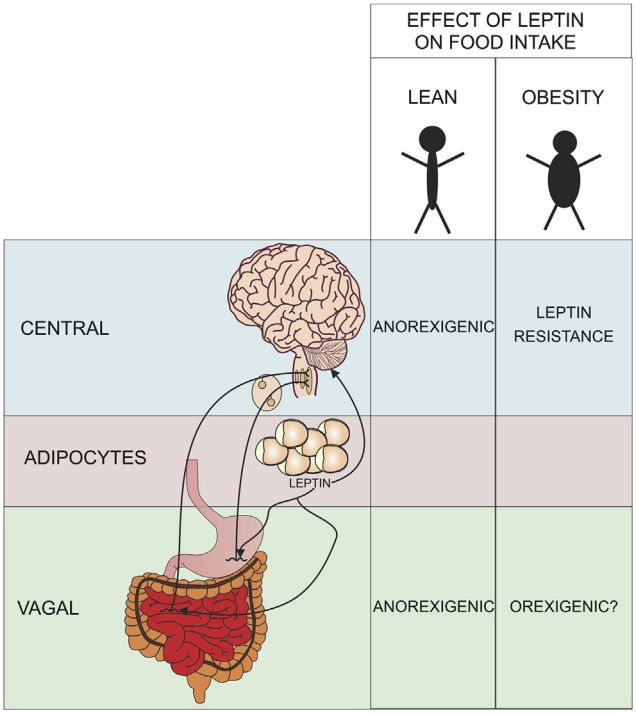

Figure 1: Illustration of the effect of leptin on appetite regulation within the central nervous system and on peripheral vagal afferents under standard and high fat diet induced obese conditions.

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leptin signalling in vagal afferents de Lartigue et al. have established conclusively that vagal afferents are an important component to regulate satiety and influence long term food intake and weight gain. An interesting observation in the data of de Lartigue et al. is that in high fat diet conditions weight gain is reduced in vagal afferent leptin receptor knockout mice. This implies that in high fat diet conditions leptin has 'orexigenic' effects possibly increasing food intake. Unfortunately, the authors fail to provide food intake data on this group of mice and therefore at this stage this cannot be confirmed. However, a previous report [7] indicating a 'switch' in the effect of leptin on gastric vagal afferents in high fat diet conditions supports the data of de Lartigue et al. Thus this data introduces the intriguing possibility that leptin is a 'double agent' normally having anorexigenic effects but under certain physiological/nutritional states switching to an orexigenic agent.

As a whole de Lartigue et al. demonstrate the importance of vagal afferents in regulation of long term food intake and weight with vagal leptin signalling required to maintain a healthy weight, but in contrast, are also required to develop high fat diet induced obesity. It is apparent that a better understanding of the underlying mechanisms in vagal afferent satiety signalling under varying states of nutrition is essential before any pharmacotherapy for the treatment of obesity can be established.

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