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PERSPECTIVES

Vagal afferent dysfunction in obesity: cause or effect

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The gastrointestinal (GI) tract plays a vital role in the initiation of processes that regulate food intake and blood glucose levels. The advances in our understanding of the signalling mechanisms within the GI tract over the past few decades have been extensive. We now know that nutrients within the lumen of the intestine activate specific 'taste' or 'nutrient' receptors that subsequently initiate the release of neuroendocrine hormones or molecules that regulate gut function either via entering the blood circulation or acting on vagal afferent endings within the GI tract (Page *et al.* 2012). For example, luminal glucose induces the release of 5-hydroxytryptamine (5-HT) from enterochromaffin cells, which in turn either (1) acts on 5-HT_3 receptors on peripheral vagal afferent endings within the GI tract that subsequently relay signals to the central nervous system (CNS), or (2) enters the circulation where it has relatively free access to vagal afferent cell bodies in the nodose and jugular ganglia.

Therefore, vagal afferent nerves are an important link between the GI tract and the CNS. They comprise as much as 90% of fibres within the vagus. The vagal afferents convey a vast array of sensory information to the CNS where it is processed and regulates numerous functions. Centrally the vagal afferents terminate within the nucleus tractus solitarii (NTS). From the NTS multiple synapses can be made within local regions of the brainstem such as the area postrema and the dorsal motor nucleus of the vagus (DMV). The connections between the NTS and the DMV are particularly important for vago-vagal reflex control of gastric function (Browning & Travagli, 2011).

Within the GI tract the effect of neuroendocrine hormones on vagal afferents can be split into two basic subgroups. In the stomach the vast majority of vagal afferents are mechanosensitive and in general the neuroendocrine hormones released from the endocrine cells within the stomach mucosa modulate the response to mechanical stimuli. In contrast, in the small intestine, although there are mechanosensitive vagal afferents, the majority of neuroendocrine hormones released directly activate vagal afferent endings (Kentish & Page, 2014).

There is abundant information available to suggest that vagal afferent nerves display incredible plasticity, being modulated not only by specific nutrients, peptides and gut microbiota, but also by nutritional status. However, in high fat diet-induced obesity things go awry and the problems associated with obesity are possibly initiated and certainly acerbated by changes in GI vagal afferent nerve function. It has been demonstrated by numerous laboratories that the response to mechanical stretch within both the stomach and the mall intestine is dampened in response to high fat diet-induced obesity (Daly *et al.* 2011; Kentish *et al.* 2014). In addition, the direct response of jejunal vagal afferents to the neuroendocrine hormones cholecystokinin and 5-HT is also reduced in high fat diet-induced obesity (Daly *et al.* 2011). This situation is then aggravated by certain GI hormones that modulate afferent function. For example, the appetite regulating hormone leptin, released from the stomach mucosa as well as adipose tissue, has an 'anorexigenic' effect on gastric mechanosensitive vagal afferents in lean conditions, but this is completely switched to an 'orexigenic' effect in high fat diet-induced obesity (Kentish *et al.* 2014). A concerning factor is that the effects observed in high fat diet-induced obesity appear to be irreversible, which may partially explain the difficulty in achieving and maintaining weight loss (Kentish *et al.* 2014). On a positive note, this makes GI vagal afferents a very attractive target for the peripheral pharmacotherapy of obesity.

The majority of the studies investigating the function of GI vagal afferents in high fat diet-induced obesity are restricted to one time point, namely when obesity has been achieved, with few studies investigating vagal afferent function prior to the development of obesity. The question that is repeatedly asked is whether the dampened response is the result of the diet or the obese state. The study by Troy *et al.* (2016) in this issue of *The Journal of Physiology* investigated the effect of a high fat diet on vagal afferent neuron sensitivity to CCK, 5-HT and glucose before the development of obesity. The study raises the possibility that some of the effects observed in high fat diet-induced obesity, for example the dampened response to CCK, are actually due to the diet as they occur earlier than the onset of obesity. However, some effects observed in high fat diet-induced obesity, for example the dampened response to 5-HT, do not occur in the pre-obese state (Troy *et al.* 2016) suggesting the obese state rather than the diet is responsible for these effects. It is therefore evident that there is a cascade of events initiated early in the chronic consumption of a high fat diet that make it increasingly more difficult to regulate GI motility, food intake and glycaemic control. Troy *et al.* (2016) also reported a reduction in the percentage of vagal afferent neurones in which glucose modulates vagal afferent responses to 5-HT, an effect that occurs only 3 days after consumption of a high fat diet. This raises the possibility that changes in vagal afferent function as a result of high fat diet may precede and actually play a role in the development of not only obesity but also glycaemic dysregulation.

Clearly, given worldwide obesity is reaching epidemic levels, it is vital that our understanding of the mechanisms linking diet and metabolic control are better understood. This study by Troy *et al.* (2016) suggests that altered meal-related vagal sensory signalling is an early event that may actually contribute to glycaemic dysregulation and obesity. If observations in animal models translate to humans then this study has an impact on our understanding of the development of diet-induced obesity suggesting that even short-term exposure to a high fat diet can have metabolic

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consequences. A critical question that remains to be addressed is the extent to which these changes in neural signalling can be reversed, and as such whether this could provide a therapeutic strategy for treating obese patients.

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Additional information

Competing interests

None declared.