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Review

The vagus nerve, food intake and obesity

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ABSTRACT

Food interacts with sensors all along the alimentary canal to provide the brain with information regarding its composition, energy content, and beneficial effect. Vagal afferents innervating the gastrointestinal tract, pancreas, and liver provide a rapid and discrete account of digestible food in the alimentary canal, as well as circulating and stored fuels, while vagal efferents, together with the sympathetic nervous system and hormonal mechanisms, codetermine the rate of nutrient absorption, partitioning, storage, and mobilization. Although vagal sensory mechanisms play a crucial role in the neural mechanism of satiation, there is little evidence suggesting a significant role in long-term energy homeostasis. However, increasing recognition of vagal involvement in the putative mechanisms making bariatric surgeries the most effective treatment for obesity should greatly stimulate future research to uncover the many details regarding the specific transduction mechanisms in the periphery and the inter- and intra-neuronal signaling cascades disseminating vagal information across the neuraxis.

Contents

1. Introduction

There is no doubt that the prevalence of obesity and the metabolic syndrome is rapidly increasing, with abdominal obesity in more than half of the adult US population and a 60% increase of abdominal obesity from 1999–2004 in children [1,2]. The strong correlation between BMI and development of type 2 diabetes, cardiovascular disease, gall bladder disease, osteoarthritis, sleep, and mental disorders makes it the major health problem.

Current treatment of obesity targets both energy intake and expenditure, and includes dieting and physical exercise (life style changes), as well as surgery, drugs, plant extracts, and many scientifically undocumented remedies. Most of these treatments are not very effective, with a typical maximal weight loss of less than 10%, and not able to stop the

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epidemic. Obesity surgery is presently the most effective treatment with sustained weight loss of up to 50%. Obesity surgery consists of restricting the capacity of the stomach to accommodate ingested food and/or redirecting the flow of digesta to the lower gut, implicating gut–brain signaling as an important factor in the development and prevention of obesity [3]. The vagus nerve is arguably the most important link between the gut and the brain, and the present review attempts to clarify the role of this nerve in the control of food intake, energy balance, and the development of obesity. Furthermore, some of the literature exploiting stimulation of vagal components as potential obesity treatment is reviewed.

2. Ingested food interacts with sensors along the alimentary canal: importance of vagal afferents

2.1. Oral cavity: taste receptors and trigeminal mechanosensors

Gustatory input via taste receptor cells on the tongue and palate is considered most important for guiding food intake and selection (Fig. 1). Although only a minor portion of this information is mediated to the brain by the vagus nerve, the gustatory system is included here because it shares the nucleus tractus solitarius (NTS) and other central processing stations with vagal afferents from the gastrointestinal tract. The gustatory and trigeminal systems act as "gate keepers" at the entrance to the alimentary canal [4]. According to this view, the classical four taste modalities represent innate detectors for acceptable foods (sweet), dangerous or toxic foods (bitter and sour), and special needs (salt, water).

There was considerable recent progress in taste receptor physiology, with a number of receptor proteins and signaling mechanisms discovered (as reviewed by [5]). There is also some progress in deciphering the neural encoding mechanism. The observation that in the mouse, each taste bud is innervated by about 5 primary afferent geniculate ganglion cells that only innervate that bud, suggests a labeled-line system, although each taste bud can contain receptor cells of different modality [6]. In addition to receptors for sweet, bitter, sour, and salty substances, there may also be a taste for fat. The fatty acid transporter CD36 is co-expressed with α-gustducin in taste receptor cells and unlike wildtype mice, CD36-deficient mice are unable to develop a preference for fatty foods [7]. The newly discovered tastes for fat and amino acids (also known as Umami taste) suggest that the system may be capable of at least recognizing, if not metering, the macronutrient content of mixed foods.

The trigeminal somatosensory system with its mechano- and temperature sensors picks up important additional attributes of ingested foods, such as creaminess and crunchiness. These are thought to be important dimensions of overall palatability of particular food items.

Understanding the transduction mechanisms of the gustatory system may have important implications for investigation of chemosensory processes in the small intestines as discussed below.

2.2. Stomach: stretch, tension, leptin, and ghrelin

Far from being a passive reservoir for ingested food, the stomach is a highly regulated organ with elaborate neural and hormonal control mechanisms. The presence of ingested food is detected by vagal afferent fibers in the mucosa sensitive to mechanical touch [8], and the volume of ingested food is detected by vagal afferents in the external muscle layers sensitive to stretch and tension [9] (Fig. 2). Intraganglionic laminar vagal afferent endings are located in the connective tissue capsule of myenteric plexus ganglia, between the longitudinal (outer) and circular (inner) muscle layers [10]. They thus respond to muscle tension generated by both passive stretch and active contraction of the muscle layers [11]. This type of vagal afferent ending is found in large numbers throughout the esophagus and gastrointestinal tract [12,13]. Intramuscular arrays are distinctly different from intraganglionic laminar endings and are almost exclusively located in the stomach longitudinal and circular muscle layers [14] (Fig. 2). Although IMAs were thought to represent in-series tension receptors long before the functional proof of mechanosensitivity for IGLEs [11], it is now unclear how they are functionally different from IGLEs.

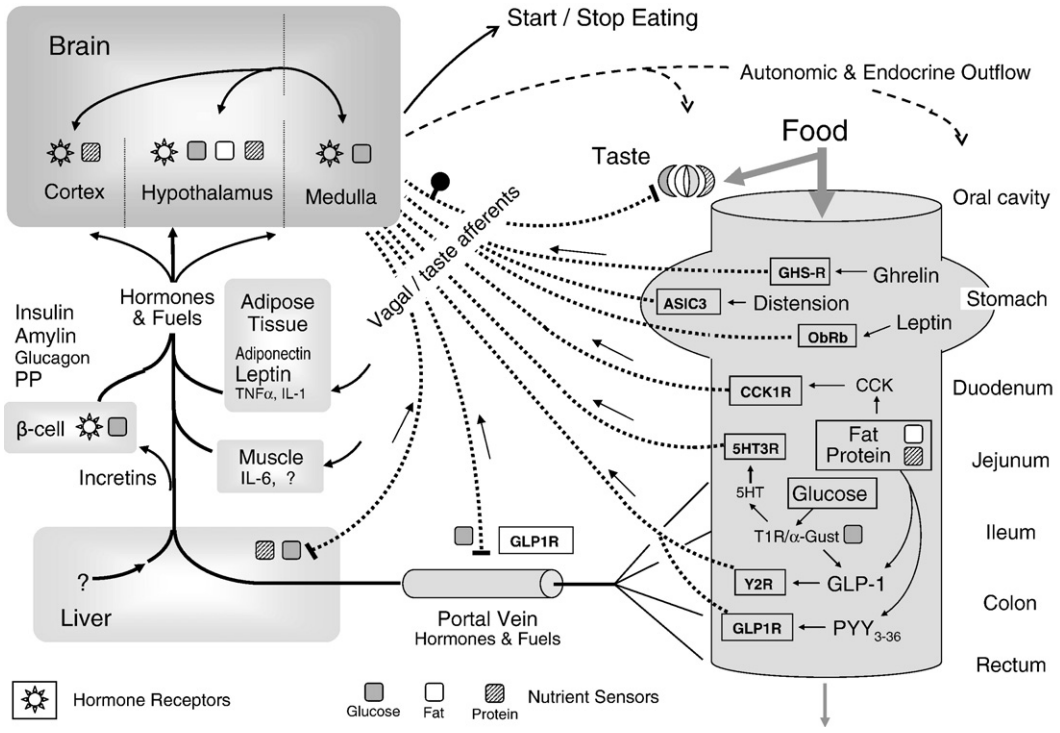

Fig. 1. Nutrient sensing in the alimentary canal and the control of food intake. Simplified schematic diagram showing the major pre- and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy dotted lines) or through the blood circulation (full lines). Specific receptors expressed by vagal afferent neurons are shown in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids/proteins, and lipids/fatty acids are shown by gray, striped, and white squares, respectively.