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Early postnatal overnutrition: Potential roles of gastrointestinal vagal afferents and brain-derived neurotrophic factor

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ABSTRACT

Abnormal perinatal nutrition (APN) results in a predisposition to develop obesity and the metabolic syndrome and thus may contribute to the prevalence of these disorders. Obesity, including that which develops in organisms exposed to APN, has been associated with increased meal size. Vagal afferents of the gastrointestinal (GI) tract contribute to regulation of meal size by transmitting satiation signals from gut-to-brain. Consequently, APN could increase meal size by altering this signaling, possibly through changes in expression of factors that control vagal afferent development or function. Here two studies that addressed these possibilities are reviewed. First, meal patterns, meal microstructure, and the structure and density of vagal afferents that innervate the intestine were examined in mice that experienced early postnatal overnutrition (EPO). These studies provided little evidence for EPO effects on vagal afferents as it did not alter meal size or vagal afferent density or structure. However, these mice exhibited modest hyperphagia due to a satiety deficit. In parallel, the possibility that brain-derived neurotrophic factor (BDNF) could mediate APN effects on vagal afferent development was investigated. Brain-derived neurotrophic factor was a strong candidate because APN alters BDNF levels in some tissues and BDNF knockout disrupts development of vagal sensory innervation of the GI tract. Surprisingly, smooth muscle-specific BDNF knockout resulted in early-onset obesity and hyperphagia due to increases in meal size and frequency. Microstructure analysis revealed decreased decay of intake rate during a meal in knockouts, suggesting that the loss of vagal negative feedback contributed to their increase in meal size. However, meal-induced c-Fos activation within the dorsal vagal complex suggested this effect could be due to augmentation of vago-vagal reflexes. A model is proposed to explain how high-fat diet consumption produces increased obesity in organisms exposed to APN, and may be required to reveal effects of EPO on vagal function.

1. Introduction

1.1. General introduction and organization of review

Overeating and obesity have reached not only epidemic, but also pandemic proportions [1]. A potential cause of obesity that has attracted recent interest involves exposure of an organism to abnormal nutrition in utero or shortly after birth [2,3]. Such exposure is thought to disrupt development of tissues involved in the regulation of food intake and body weight, resulting in a predisposition to develop obesity. One change in feeding behavior that accompanies this obesity of developmental origin, as well as obesity in general, is the consumption of large meals [4–6]. A neural system that could play a role in this increase in meal size is the sensory component of the vagus nerve that innervates the gastrointestinal (GI) tract. This system reports to the brain on the status of food in the upper GI tract during a meal and this information contributes to meal termination, or satiation [7,8]. One mechanism that could mediate the effects of abnormal perinatal nutrition (APN) on vagal sensory neurons would be altered expression of genes that control their development or function. A gene that is a strong candidate for this role is brain-derived neurotrophic factor (BDNF). Brain-derived neurotrophic factor expression is altered in both central and peripheral tissues by APN and related perinatal manipulations [9,10]. Also, vagal afferents that innervate the GI tract are dependent on BDNF for normal development [11]. In the remainder of Section 1 (Sections 1.2–1.4), the anatomical and functional organizations of the vagal sensory system and its integration with central nervous system (CNS) structures are described. Sections 2 and 3 review two sets of experiments presented at the 2011 SSIB meeting. The first set examined the effects of APN on patterns of food intake and development of vagal afferents that innervate the GI tract. The second set of experiments explored the ability of BDNF produced by the GI tract to regulate vagal afferent signaling and feeding behavior. Additionally, several implications of the findings of this study are considered.

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1.2. Vagal afferents that innervate the GI tract

The vagus nerve innervates the viscera, including the GI tract, and therefore has a critical role in the regulation of food intake. Vagal afferents that innervate the wall of the GI tract transduce both chemical and mechanical stimulation produced by food as it is processed within the gut. For example, they increase their firing rate in response to nutrients such as glucose and lipids, and to distension of the gut wall [12–17]. The signals generated by these vagal afferents are transmitted directly to the brain, informing it about the amount, quality and location of food within the GI tract. This is possible because vagal sensory neurons project directly from peripheral organs to the brain [18–20]. The signals generated by vagal afferents provide the majority of the negative-feedback from the gut to the brain that lead to satiation or the end of a meal [7,8]. Vagal sensory signals also contribute to satiety, which influences the length of the delay from one meal to the next, and they regulate digestive reflexes that can indirectly influence feeding [7,8,21].

Vagal afferents have different functional specializations, achieved in part through innervation of specific tissue layers of the wall of the GI tract (Fig. 1). From the outermost serosal layer to the lumen, the layers of the GI wall include longitudinal smooth muscle, neurons and axons of the myenteric plexus, circular smooth muscle, submucosa, and the mucosa, which consists of lamina propria and epithelium. Four different classes of vagal afferents have been described, including villus afferents and crypt afferents that innervate the mucosa, intramuscular arrays (IMAs) that innervate the circular and longitudinal smooth muscle layers, and intraganglionic laminar endings (IGLEs) that innervate the myenteric plexus (Fig. 1). In the mucosa, villus afferents ramify within the lamina propria inside villi (a variant of this receptor, the antral gland afferent, terminates in the analogous tissue of the stomach antrum), and crypt afferents form rings around the crypts [22,23]. Electrophysiological studies of GI mucosal innervation suggest it consists of both mechanoreceptive and chemoreceptive elements [15]. However, the relationship between these elements and the morphological classes of crypt and villus (or antral gland) afferents are unknown.

The two classes of vagal afferents that innervate the outer muscle wall of the GI tract are mechanoreceptors (Figs. 1 and 2). Intramuscular arrays are thought to function as stretch receptors and IGLEs as tension receptors [24–27]. The long rectilinear terminals of IMAs are

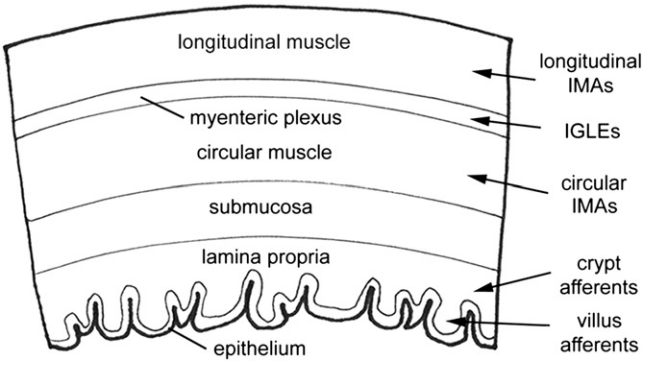

Fig. 1. This is a schematic drawing that illustrates the specific tissue layers of the GI tract wall and the types of vagal afferent receptors that innervate them. A wedge of a cross-section through the GI tract wall oriented with the outer serosal surface at the top and the inner lumen below is depicted here. This drawing represents a generalized set of tissue layers of the GI tract wall. Each tissue layer varies in thickness and structure from one GI organ compartment to another. The name of each tissue layer is indicated on the drawing. The different classes of vagal sensory receptors that innervate the GI tract are listed to the right of the drawing. Arrows point from each receptor type to the tissue layer(s) they innervate. Intramuscular arrays are only present in the longitudinal and circular muscle layers of the forestomach and the circular layer of the lower esophageal and pyloric sphincters. Crypt and villus afferents innervate the mucosa of the small intestine and antral gland afferents (not shown) supply a similar tissue as villus afferents, but within the mucosa of the stomach antrum.

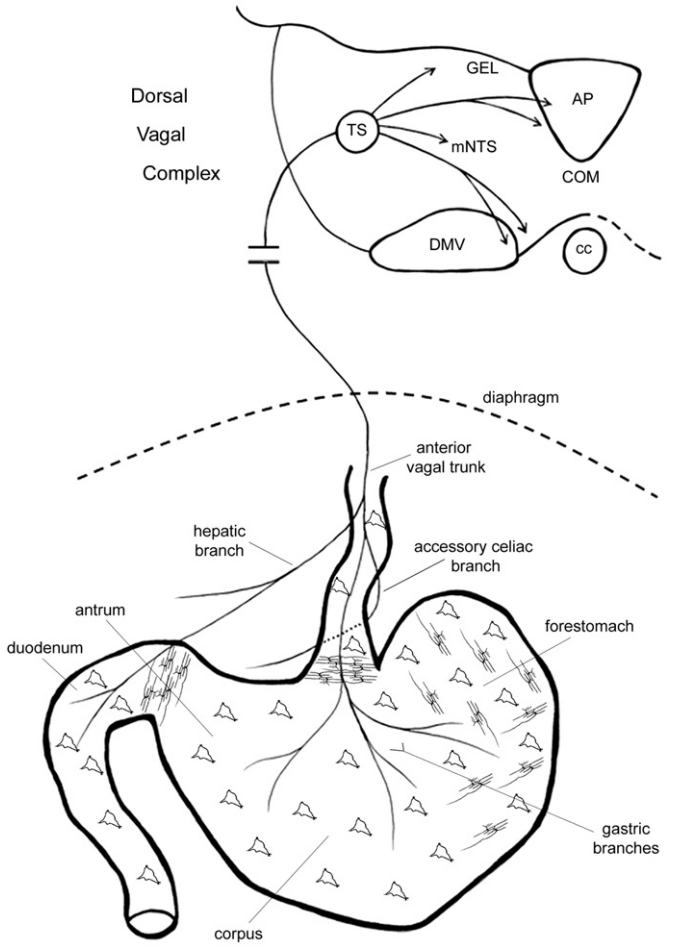

Fig. 2. This is a schematic drawing that illustrates the peripheral connections of vagal sensory neurons in the upper GI tract (bottom portion of schematic) as well as their central connections in left dorsal vagal complex of the brainstem (top part of schematic). For clarity, only the anterior vagal trunk and its branches are drawn, which arise mainly from the left cervical vagus nerve. From this ventral view the posterior trunk, which is not shown would lie behind the esophagus and give off gastric and celiac branches that innervate the dorsal stomach wall and intestine, respectively. The nodose ganglion, which houses the vagal sensory neurons and lies just outside the skull adjacent to the brainstem, is not shown. Also, the approximate distributions of the two main smooth muscle mechanoreceptor classes, IMAs and IGLEs, are indicated by parallel interconnected lines and amorphous shapes, respectively. See text for details. Abbreviations: AP, area postrema; cc, central canal; COM, commissural subnucleus; DMV, dorsal motor nucleus of the vagus; GEL, gelatinous subnucleus; mNTS, medial NTS; TS, solitary tract.

interconnected by cross-bridge fibers and run parallel to one-another and to smooth muscle fibers [24–27]. They also run parallel to, and in close apposition with the processes of intramuscular–interstitial cells of Cajal and form contacts with them [24–27]. Intramuscular arrays innervate the circular and longitudinal smooth muscle layers of the forestomach and the circular layer of the lower esophageal and pyloric sphincters (Figs. 1 and 2). These regions of the GI tract expand as food collects during a meal (forestomach), or as it passes from one compartment to the next (sphincters). Expansion of these regions would stretch IMAs, and thus may activate them [26–28]. In contrast, the terminals of an IGLE form numerous puncta that aggregate densely within a plane that covers a portion of a ganglion within the myenteric plexus [27,29]. This plexus lies between the longitudinal and circular smooth muscle layers of the wall of the GI tract (Fig. 1). Intraganglionic laminar endings are distributed throughout the esophagus, stomach and intestines, but are not present in sphincters associated with these organs (Fig. 2) [26,27,30]. In addition to reporting on local muscle tension, IGLEs may be involved in coordinating motor patterns of the gut such as peristaltic contractions [27,31].