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Review

The neural regulation of the mammalian esophageal motility and its implication for esophageal diseases

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Abstract

In contrast to the tunica muscularis of the stomach, small intestine and large intestine, the external muscle layer of the mammalian esophagus contains not only smooth muscle but also striated muscle fibers. Although the swallowing pattern generator initiates the peristaltic movement via vagal preganglionic neurons that project to the myenteric ganglia in the smooth muscle esophagus, the progressing front of contraction is organized by a local reflex circuit composed by intrinsic neurons similarly to other gastrointestinal tracts. On the other hand, the peristalsis of the striated muscle esophagus is both initiated and organized by the swallowing pattern generator via vagal motor neurons that directly innervate the muscle fibers. The presence of a distinct ganglionated myenteric plexus in the striated muscle portion of the esophagus had been enigmatic and neglected in terms of peristaltic control for a long time. Recently, the regulatory roles of intrinsic neurons in the esophageal striated muscle have been clarified. It was reported that esophageal striated muscle receives dual innervation from both vagal motor fibers originating in the brainstem and varicose intrinsic nerve fibers originating in the myenteric plexus, which is called 'enteric co-innervation' of esophageal motor endplates. Moreover, a putative local neural reflex pathway that can control the motility of the striated muscle was identified in the rodent esophagus. This reflex circuit consists of primary afferent neurons and myenteric neurons, which can modulate the release of neurotransmitters from vagal motor neurons in the striated muscle esophagus. The pathogenesis of some esophageal disorders such as achalasia and gastroesophageal reflux disease might be involved in dysfunction of the neural networks including alterations of the myenteric neurons. These evidences indicate the physiological and pathological significance of intrinsic nervous system in the regulation of the esophageal motility. In addition, it is assumed that the components of intrinsic neurons might be therapeutic targets for several esophageal diseases.

Keywords: Esophageal disorders; Intrinsic neurons; Peristalsis; Smooth muscle; Striated muscle

Contents

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1. Neural regulation of the mammalian esophageal motility

The gastrointestinal smooth muscle motility is regulated by the enteric nervous system [1–3]. The sequence of peristaltic events does not depend on extrinsic autonomic innervation, but rather involves the activation of intrinsic sensory neurons, which are coupled via modulatory interneurons to excitatory and inhibitory motor neurons projecting into the smooth muscle layer [2,3].

In contrast to the tunica muscularis of the stomach, small intestine and large intestine that are constituted entirely of smooth muscle, the external muscle layer of the mammalian esophagus contains striated muscle fibers, which extend from the pharyngoesophageal junction to the thoracic or even abdominal portion, depending on the species [4,5]. In humans and cats, the upper and lower portions of esophagus are composed of striated and smooth muscles, respectively, with a mixed portion between them. In dogs, ruminants and rodents including mice, rats and hamsters, the muscle layer of esophagus consists mostly of striated muscle fibers.

The mechanisms of peristalsis control are different for these two muscle types. In both of these segments, esophageal peristalsis is controlled by the swallowing pattern generator (SPG) located in the brainstem [6–10]. According to the conventional view the SPG both initiates and organizes peristalsis in the striated esophageal muscle. Striated muscle fibers are innervated exclusively by excitatory vagal efferents that arise from motor neurons localized in the nucleus ambiguus and terminate on motor endplates [11–13]. We could confirm this view additionally by demonstrating that vagal nerve stimulation evokes twitch contractile responses of the striated muscle in the isolated segment of mammalian esophagus, which are abolished by D-tubocurarine but not by atropine or hexamethonium [14–17]. Peristalsis in the striated esophageal muscle is executed according to a sequence pre-programmed in the compact formation of the nucleus ambiguus [18]. The compact formation of the nucleus ambiguus receives projections from the central subnucleus of the nucleus of the solitary tract [19–21], which in turn receives vagal afferents from the esophagus [22,23], thus closing a reflex loop for esophageal motor control [10,12,19].

In contrast, motor innervation of the smooth muscle esophagus is more complex. Here, the SPG initiates peristalsis via preganglionic neurons in the dorsal motor nucleus of the vagus that project to the myenteric ganglia in the esophagus [9]. The smooth muscle is innervated by myenteric motor neurons that can release acetylcholine (ACh), tachykinins or nitric oxide (NO) [1,9]. However, the progressing front of contraction is organized by virtue of their local reflex circuits as elsewhere in the gut [1,9,24]. In fact, the smooth muscle esophagus can exhibit propulsive peristaltic contractions in response to an intraluminal bolus of food even in the vagotomy model [25,26]. Moreover, peristaltic reflexes can be elicited by distention in a segment of the smooth muscle esophagus that is removed from the opossum [27].

It has been well known for a long time that there are myenteric neurons in the striated muscle portion of the mammalian esophagus comparable to other gastrointestinal tracts [4,5]. However, in this widely accepted model for peristalsis control, the presence of a distinct ganglionated myenteric plexus in the striated muscle esophagus remained enigmatic and was therefore not included.

2. Involvement of intrinsic neurons in the motility of the esophageal striated muscle

The conventional view of peristalsis control in the striated esophageal muscle was challenged by the discovery of ‘enteric co-innervation’ of esophageal motor endplates. Originally described in the rat, esophageal striated muscle receives dual innervation from both vagal motor fibers originating in the brainstem and varicose intrinsic nerve fibers originating in the myenteric plexus [28,29]. This new paradigm of striated muscle innervation has meanwhile been confirmed in a variety of species including human, underlining its significance [5,30]. It could be demonstrated that neuronal nitric oxide synthase (nNOS) was highly colocalized with vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), galanin (GAL) and Met-enkephalin (M.ENK) in enteric nerve terminals on esophageal motor endplates [28,29,31–35]. These markers are suggestive of inhibitory modulation of vagally induced striated muscle contraction [5]. Since morphological studies revealed further that spinal afferent nerve fibers closely innervate myenteric neurons in the esophagus [5,36–38], the presence of a ‘local neural reflex’ regulating the motility of esophageal striated muscle consisting of afferent and enteric neurons in the esophagus was suggested [5,32].

These mainly morphological data could be confirmed by functional studies using the stimulants of sensory neurons such as capsaicin and piperine [14–17]. In brief, we isolated rodent esophagi and performed electrical stimulation of the vagal nerves, which evoked contractile responses of the striated esophageal muscle. Capsaicin or piperine inhibited the vagally mediated contractions of the esophageal preparations via attenuating ACh release from vagus nerve. The inhibitory effects of capsaicin and piperine on the contractile responses were blocked by a NOS inhibitor or a tachykinin NK_1 receptor antagonist. Our data suggests that the mammalian esophagus has a putative local neural reflex that regulates the motility of striated muscle by inhibiting ACh release from vagal motor neurons pre-synaptically (Fig. 1), which solidify and extend the recently raised hypothesis on the basis of morphological studies. This reflex arc consists of capsaicin-sensitive, transient receptor potential vanilloid 1 (TRPV1)-positive, tachykininergic afferent neurons and myenteric nitrergic neurons. The local neural reflex might be involved in coordinating the esophageal peristalsis in the striated muscle portion. In addition, our reports suggest the significance of myenteric nitrergic neurons in the esophageal