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# Neural Regulatory Mechanisms of Esophageal Motility and Its Implication for GERD

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## 1. Introduction

Gastroesophageal reflux disease (GERD) is one of the representative esophageal disorders and can severely influence the quality of life in humans (Jung, 2011; Moayyedi & Talley, 2006; Salvatore & Vandenplas, 2003). In GERD patients, abnormal reflux of gastric contents to the esophagus causes chest pain and heartburn (Moayyedi & Talley, 2006; Salvatore & Vandenplas, 2003). Esophageal mucosal erosions and/or ulcers are formed by acid exposure (Moayyedi & Talley, 2006; Salvatore & Vandenplas, 2003). On the other hand, patients with nonerosive reflux disease (NERD), one phenotype of GERD, have typical reflux symptoms induced by intraesophageal reflux of gastric contents but have no visible esophageal mucosal injury (Long & Orlando, 2008; Tack, 2005; Winter & Heading, 2008). GERD is caused mainly by acid reflux due to abnormal relaxation of the lower esophageal sphincter (LES) and/or low activity of clearance in the esophageal body (DeMeester et al., 1979; Grossi et al., 1998; Grossi et al., 2006; Moayyedi & Talley, 2006; Nagahama et al., 2003). Abnormal relaxation of the LES and low activity of clearance might be associated with dysmotility of the esophagus. The motility in the esophageal body and LES is regulated by both the central and peripheral nervous systems (Clouse & Diamant, 2006; Conklin & Christensen, 1994; Cunningham & Sawchenko, 1990; Jean, 2001; Neuhuber et al., 2006; Park & Conklin, 1999; Wörl & Neuhuber, 2005). Therefore, dysfunction of neural regulation seems to cause abnormal motility in the esophagus, resulting in excessive acid reflux and then GERD (Moayyedi & Talley, 2006; Orlando, 1997; Parkman & Fisher, 1997; Salvatore & Vandenplas, 2003; Vandenplas & Hassall, 2002).

In fact, there are many reports about the involvement of esophageal dysmotility in the pathogenic mechanism of GERD (Dogan & Mittal, 2006; Moayyedi & Talley, 2006; Orlando, 1997; Parkman & Fisher, 1997; Salvatore & Vandenplas, 2003; Shiina et al., 2010; Vandenplas & Hassall, 2002). On the other hand, since neural regulatory mechanisms of esophageal motiliy, especially roles of the intrinsic nervous system in the striated muscle portion, have remained to be clarified (Clouse & Diamant, 2006; Conklin & Christensen, 1994; Goyal & Chaudhury, 2008), little attention has been paid to the relationship between intrinsic neural regulatory mechanisms for esophageal motility and pathophysiology of GERD. Discussion of this relationship is important and might indicate novel therapeutic targets for GERD. In this chapter, we describe neural regulation of the esophageal motility on the basis of results

of our studies, and we discuss the relationship between pathogenic mechanisms of GERD and esophageal dysmotility.

## 2. Neural regulation of esophageal motility

The tunica muscularis of the stomach, small intestine and large intestine is constituted entirely of smooth muscle (Makhlouf & Murthy, 2009). Gastrointestinal smooth muscle motility is regulated by the enteric nervous system (Furness, 2006; Hansen, 2003; Kunze & Furness, 1999; Olsson & Holmgren, 2001; 2011). 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 (Furness, 2006; Hansen, 2003; Kunze & Furness, 1999; Olsson & Holmgren, 2001; 2011).

In contrast to other gastrointestinal tracts, 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 (Izumi et al., 2002; Neuhuber et al., 2006; Shiina et al., 2005; Wooldridge et al., 2002; Wörl & Neuhuber, 2005) (Fig.1). In humans, horses, cats and pigs, the upper and lower portions of the 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 the esophagus consists mostly of striated muscle fibers. On the other hand, the tunica muscularis of the LES consists of smooth muscles (Neuhuber et al., 2006; Wörl & Neuhuber, 2005). Esophageal motility is controlled centrally by an extrinsic neuronal mechanism and peripherally by an intrinsic neuronal mechanism (Clouse & Diamant, 2006; Conklin & Christensen, 1994; Cunningham & Sawchenko, 1990; Goyal & Chaudhury, 2008; Jean, 2001; Neuhuber et al., 2006; Park & Conklin, 1999; Wörl & Neuhuber, 2005). Below, we describe the neuronal controls of these two muscle types in the esophageal body and smooth muscles in the LES.

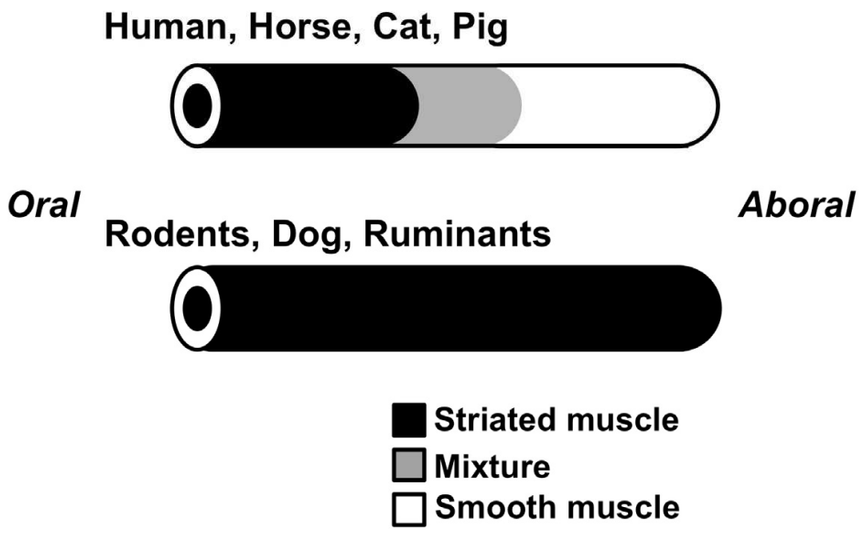



Fig. 1. Tunica muscularis of the esophageal body in mammals. Left is oral side and right is aboral side.

### 2.1 Esophageal body

The mechanisms of peristalsis control are different between striated muscle and smooth muscle in the esophageal body. However, in both portions, esophageal peristalsis is controlled by the swallowing pattern generator (SPG) located in the brainstem (Bieger, 1993; Bieger & Neuhuber, 2006; Conklin & Christensen, 1994; Jean, 2001; Jean & Dallaporta, 2006), depending on extrinsic neurons unlike other gastrointestinal tracts.

#### 2.1.1 Neural control of peristalsis in the esophageal striated muscle portion

According to the conventional view, the SPG both initiates and organizes peristalsis in the striated esophageal muscle, i.e., both primary and secondary peristaltic contractions are centrally mediated in the striated muscle portion (Bieger, 1993; Bieger & Neuhuber, 2006; Conklin & Christensen, 1994; Goyal & Chaudhury, 2008; Jean & Dallaporta, 2006). 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 (Bieger & Hopkins, 1987; Cunningham & Sawchenko, 1990; Neuhuber et al., 1998). We could confirm this view additionally by demonstrating that vagal nerve stimulation evokes twitch contractile responses of the striated muscle in an isolated segment of mammalian esophagus, which are abolished by d-tubocurarine, an antagonist of nicotinic acetylcholine receptors on the striated muscle, but not by atropine, an antagonist of muscarinic acetylcholine receptors on the smooth muscle, or hexamethonium, a blocker of ganglionic acetylcholine receptors (Boudaka et al., 2007a; Boudaka et al., 2007b; Izumi et al., 2003; Shiina et al., 2006). Peristalsis in the striated esophageal muscle is executed according to a sequence pre-programmed in the compact formation of the nucleus ambiguus (Andrew, 1956). The compact formation of the nucleus ambiguus receives projections from the central subnucleus of the nucleus of the solitary tract (Barrett et al., 1994; Cunningham & Sawchenko, 1989; Lu & Bieger, 1998), which in turn receives vagal afferents from the esophagus (Altschuler et al., 1989; Ross et al., 1985), thus closing a reflex loop for esophageal motor control (Bieger, 1993; Cunningham & Sawchenko, 1990; Lu & Bieger, 1998). Neural controls of motility in the striated muscle esophagus are illustrated in Fig. 2.

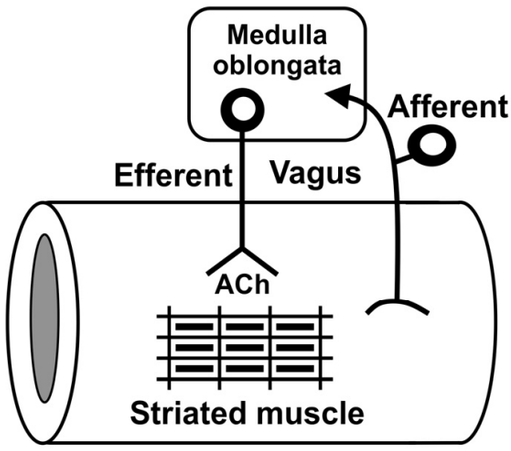



Fig. 2. Neural control of peristalsis in the striated muscle portion of the esophagus by vago-vagal reflex. ACh; acetylcholine.

### 2.1.2 Neural control of peristalsis in the esophageal smooth muscle portion

In contrast to striated muscle, 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, i.e., the primary peristalsis involves both central and peripheral mechanisms (Conklin & Christensen, 1994). The smooth muscle is innervated by myenteric motor neurons that can release acetylcholine, tachykinins or nitric oxide (NO) (Conklin & Christensen, 1994; Furness, 2006). However, the progressing front of contraction is organized by virtue of their local reflex circuits that are composed of sensory neurons, interneurons and motor neurons as elsewhere in the gut, i.e., the secondary peristalsis is entirely due to peripheral mechanisms in the smooth muscle esophagus (Clouse & Diamant, 2006; Conklin & Christensen, 1994; Goyal & Chaudhury, 2008). In fact, the smooth muscle esophagus can exhibit propulsive peristaltic contractions in response to an intraluminal bolus of food even in a vagotomy model (Cannon, 1907; Tieffenbach & Roman, 1972). Moreover, peristaltic reflexes can be elicited by distention in an isolated segment of the smooth muscle esophagus from the opossum (Christensen & Lund, 1969). Neural controls of motility in the smooth muscle esophagus are illustrated in Fig. 3.

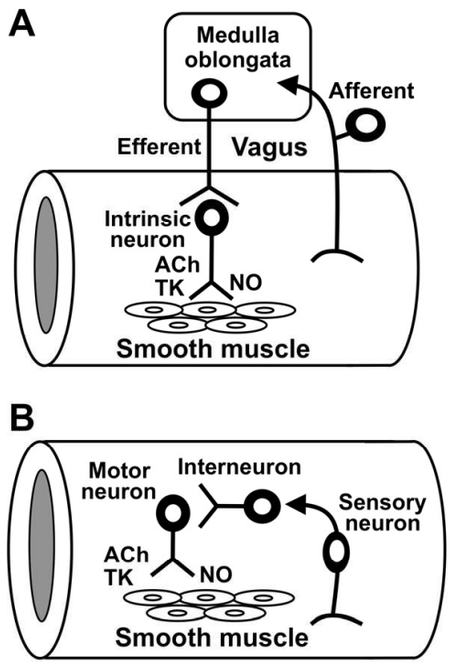



Fig. 3. Neural control of peristalsis in the smooth muscle portion of the esophagus. (A) Vagal innervation for primary peristalsis. (B) Local reflex circuit by enteric neurons for secondary peristalsis. ACh; acetylcholine. TK; tachykinin. NO; nitric oxide.

### 2.2 Involvement of intrinsic neurons in motility of the esophageal striated muscle

The striated muscle fibers in the esophagus were hitherto considered as 'classical' skeletal muscle fibers, innervated exclusively by excitatory vagal motor neurons, which terminate on motor endplates (Bieger & Hopkins, 1987; Cunningham & Sawchenko, 1990; Neuhuber et al., 1998). It is believed that peristalsis in the striated esophageal muscle is executed

according to a sequence pre-programmed in a medullary swallowing network and modulated via vago-vagal reflexes as described above (Clouse & Diamant, 2006; Conklin & Christensen, 1994; Jean, 2001; Mukhopadhyay & Weisbrodt, 1975; Park & Conklin, 1999; Roman & Gonella, 1987). On the other hand, the presence of a distinct ganglionated myenteric plexus in the striated muscle portion of the mammalian esophagus, comparable to other gastrointestinal tracts, has been well known for a long time (Gruber, 1968; Stefanelli, 1938). However, functional roles of the intrinsic nervous system in peristalsis of the striated muscle in the esophagus have remained enigmatic and have been neglected in concepts of peristaltic control (Clouse & Diamant, 2006; Conklin & Christensen, 1994; Diamant, 1989; Wörl & Neuhuber, 2005). To clarify roles of the intrinsic nervous system in motility of the esophageal striated muscle, morphological and then functional studies have been performed.

### 2.2.1 Morphological investigation

Investigation of the regulatory role of intrinsic neurons in the esophagus was advanced by the discovery of 'enteric co-innervation' of esophageal motor endplates (Neuhuber et al., 1994; Wörl et al., 1994). The enteric co-innervation challenged the conventional view of peristalsis control in the striated esophageal muscle. 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 (Neuhuber et al., 1994; Wörl et al., 1994). This new paradigm of striated muscle innervation has meanwhile been confirmed in a variety of species including humans, underlining its significance (Kallmunzer et al., 2008; Wörl & Neuhuber, 2005). It has been demonstrated that neuronal nitric oxide synthase (nNOS) was highly colocalized with vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), galanin and Met-enkephalin in enteric nerve terminals on esophageal motor endplates (Kuramoto & Endo, 1995; Neuhuber et al., 2001; Neuhuber et al., 1994; Wörl et al., 1998; Wörl et al., 1994; Wörl et al., 1997; Wu et al., 2003). These markers are suggestive of inhibitory modulation of vagally-induced striated muscle contraction (Wörl & Neuhuber, 2005). Since morphological studies revealed further that spinal afferent nerve fibers closely innervate myenteric neurons in the esophagus (Holzer, 1988; Kuramoto et al., 2004; Mazzia & Clerc, 1997; Wörl & Neuhuber, 2005), the presence of 'a peripheral mechanism' regulating the motility of esophageal striated muscle including afferent and enteric neurons in the esophagus was suggested (Neuhuber et al., 2001; Wörl & Neuhuber, 2005).

### 2.2.2 Functional aproaches

Efforts have been made to demonstrate 'a peripheral mechanism' regulating the motility of esophageal striated muscle by functional experiments, but it had been difficult to prove the hypothesis. For example, in an approach using a vagus nerve–esophagus preparation from the rat, Storr et al. tested effects of exogenous application of VIP, galanin, a NOS inhibitor, and an NO-donor on vagally induced contraction of the striated esophageal muscle, but no significant effect could be ascertained (Storr et al., 2001). They also demonstrated inhibitory effects of exogenous application of endomorphin-1 and -2 on striated and smooth muscle contraction in the rat esophagus but did not provide evidences that endogenously released intrinsic neural components can affect the esophageal motility (Storr et al., 2000).

However, our research group demonstrated roles of intrinsic neuorns in the esophageal striated muscle by functional studies using stimulants of sensory neurons such as capsaicin and piperine, which are main pungents from red pepper and black pepper, respectively (Boudaka et al., 2007a; Boudaka et al., 2007b; Boudaka et al., 2009; Izumi et al., 2003; Shiina et al., 2006). 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 acetylcholine release from the vagus nerve. In addition, the inhibitory effects of capsaicin or piperine on the contractile responses were blocked by inhibitors to prevent funtions of several neurotransmitters in enteric or sensory neurons such as NO, tachykinins and galanin (Boudaka et al., 2007a; Boudaka et al., 2007b; Boudaka et al., 2009; Izumi et al., 2003; Shiina et al., 2006). The experiments demonstrated that capsaicin or piperine can induce release of endogenous neurotransmitters, which exert the inhibitiory effects on motility of the esophagus. These findings indicate that the mammalian esophagus has a putative local neural reflex that regulates the motility of striated muscle by inhibiting acetylcholine release from vagal motor neurons pre-synaptically (Figs. 4, 5 and 6), which solidify and extend the recently raised hypothesis on the basis of results of morphological studies (Wörl & Neuhuber, 2005). This reflex arc consists of capsaicin-sensitive, transient receptor potential vanilloid 1 (TRPV1)-positive, afferent neurons and inhbitory myenteric neurons. The local neural reflex might be involved in coordinating esophageal peristalsis in the striated muscle portion (Shiina et al., 2010).

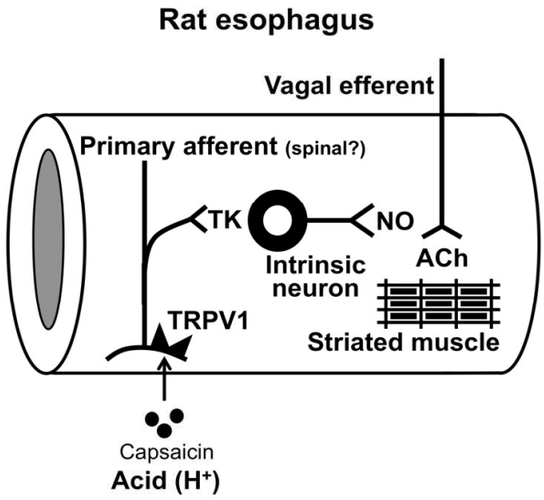



Fig. 4. Local neural reflex in the striated muscle portion of the rat esophagus. Acid as well as capsaicin can stimulate primary afferent neurons and then activate the local reflex arc. ACh; acetylcholine. TK; tachykinin. NO; nitric oxide. TRPV1; transient receptor potential vanilloid 1.

For these experiments, hamsters, rats and mice have been used. Interestingly, neuronal pathways for the inhibitory effects of capsaicin or piperine are slightly different depending on the species. In the rat esophagus, the inhibitory effect of capsaicin on contractile responses was blocked by a NOS inhibitor or a tachykinin $NK_1$ receptor antagonist, suggesting that the local neural reflex invloves tachykininergic afferent neurons and intrinsic nitrergic neurons (Shiina et al., 2006) (Fig. 4). Hamsters and mice also have a similar neural pathway (Figs. 5 and 6). In addition to trials using capsacin as a stimulator for

afferents, piperine was used in experiments with mice and hamsters. In the hamster esophagus, the piperine-activated neural pathway seems to be similar to the capsaicin-activated one, which invloves caisain-sensitive afferent neurons and myenteric nitrergic neurons (Izumi et al., 2003) (Fig. 5).

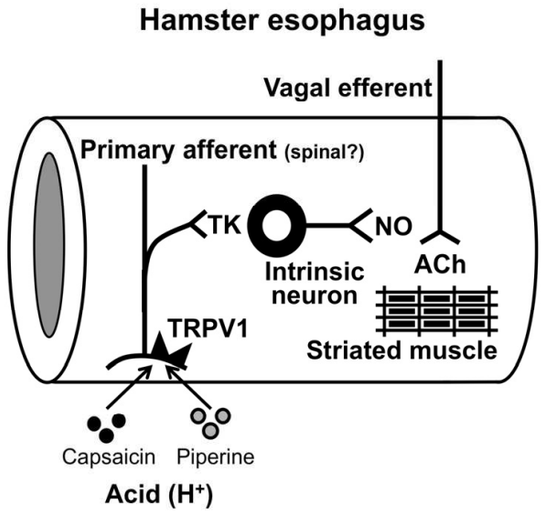



Fig. 5. Local neural reflex in the striated muscle portion of the hamster esophagus. Acid as well as capsaicin and piperine can stimulate primary afferent neurons and then activate the local reflex arc. ACh; acetylcholine. TK; tachykinin. NO; nitric oxide. TRPV1; transient receptor potential vanilloid 1.

However, in the mouse esophagus, these two pathways are independent because piperine can exert inhibitory action on esophageal contractions even after desentitization of capsaisin-sensitive neurons by pretreatment with capsaicin (Boudaka et al., 2007a) (Fig. 6). This is supported by evidence that the capsaicin-mediated inhibition was reversed by a NOS inhibitor or a tachykinin $NK_1$ receptor antagonist but that the piperine-sensitive pathway was not affected by the same treatments (Boudaka et al., 2007a). In addition, it has been demonstrated that mice have another neural reflex arc including myenteric galaninergic neurons in the esophagus (Boudaka et al., 2009) (Fig. 6).

Rodents including the rat, mouse, guinea pig and hamster have mainly been used as model animals for analysis of the intrinsic nervous system in the esophageal striated muscle because their esophagi are composed entirely of striated muscles (Wörl & Neuhuber, 2005). *Suncus murinus* (a house musk shrew; 'suncus' used as a laboratory name) is a small laboratory animal that belongs to a species of insectivore (Tsutsui et al., 2009; Ueno et al., 1987). Suncus has the ability to vomit in response to mild shaking or ingestion of chemicals (Andrews et al., 1996; Ueno et al., 1987). Since rodents including rats and mice do not show an emetic reflex, suncus has been extensively used to examine the mechanism of emetic responses and to develop antiemetic drugs (Andrews et al., 1996; Cheng et al., 2005; Sam et al., 2003; Uchino et al., 2002; Yamamoto et al., 2009). Hempfling et al. reported that the suncus esophagus has morphological features similar to those in rats and mice: intrinsic nitrergic nerves innervate motor endplates on striated muscle cells, which is called 'enteric co-innervation' (Hempfling et al., 2009). In addition, our examinations demonstrated

functionally that the striated muscle portion in the suncus esophagus has a peripheral neuronal mechanism by nitrergic neurons as in rodent esophagi (unpublished data). This fact indicates that the presence of intrinsic nervous regulation on esophageal striated muscle is across species, which might imply pathological and physiological significance of the intrinsic nervous system in the regulation of esophageal motility.

It should be noted that the majority of findings described is related to the striated muscle of the animal esophagus and cannot be simply transferred to the human esophagus. Thus, more progress in basic research on the human esophagus may be required to elucidate the pathogenesis of GERD.

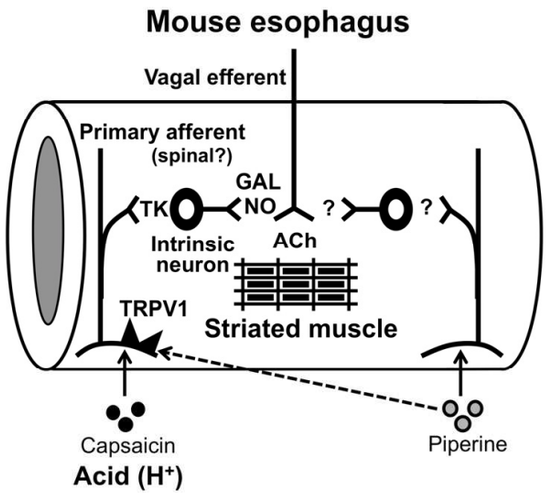



Fig. 6. Local neural reflex in the striated muscle portion of the mouse esophagus. Acid as well as capsaicin can stimulate primary afferent neurons and then activate the local reflex arc. ACh; acetylcholine. TK; tachykinin. NO; nitric oxide. GAL; galanin. TRPV1; transient receptor potential vanilloid 1.

### 2.3 LES

The LES is a specialized region of the esophageal circular smooth muscle that allows the passage of a swallowed bolus to the stomach and prevents reflux of gastric contents into the esophagus (Farre & Sifrim, 2008; Clouse & Diamant, 2006; Conklin & Christensen, 1994; Goyal & Chaudhury, 2008). Appropriate opening and closure of the LES is controlled by neuronal mechanisms that normally maintain tonic contration of the musculature to prevent reflux and cause relaxation during swallowing (Mittal et al., 1995; Yuan et al., 1998). The LES is innervated by both extatory and inhibitory motor neurons that are located in the myenteric plexus of the LES and the esophgeal body (Brookes et al., 1996). Acetylcholine and NO are the main excitatory and inhibitory neurotransmitters involved in LES contraction and relaxation, respectively (Farre & Sifrim, 2008). In addition, VIP, ATP, carbon monoxide (CO), and calcitonin gene-related peptide (CGRP) also have been proposed as putative neurotransmitters in the LES (Chang et al., 2003; Farre et al., 2006; Farre & Sifrim, 2008; Uc et al., 1999). A subclass of intrinsic neurons are innervated by vagal preganglionic fibers as postganglionic neurons (Diamant, 1989; Goyal & Chaudhury, 2008). Neural controls of motility in the LES are illustrated in Fig. 7.

## 3. Dysmotility of the esophagus and GERD

As described above, esophageal motility is regulated centrally by vagal motor neurons and peripherally by myenteric neurons, especially cholinergic and nitrergic neurons (Figs. 2 and 3). Here, we have discussed the hypothesis that dysmotility of the esophagus is involved in the pathogenic mechanisms of GERD.

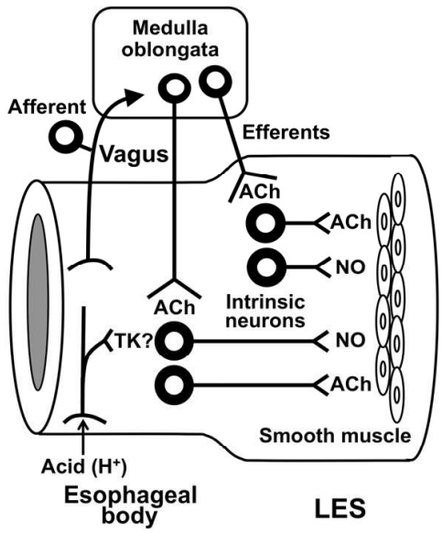



Fig. 7. Neural control of the the lower esophageal sphincter (LES). Acid can stimulate primary afferent neurons and then activate intrinsic motor neurons. ACh; acetylcholine. TK; tachykinin. NO; nitric oxide.

### 3.1 Gastroesophageal reflux and dysfunction of neural controls of esophageal motility

GERD is caused mainly by acid reflux due to abnormal relaxation of the LES and/or low activity of clearance in the esophageal body (DeMeester et al., 1979; Grossi et al., 2006; Grossi et al., 1998; Moayyedi & Talley, 2006; Nagahama *et al.*, 2003). Gastroesophageal reflux itself occurs in almost all individuals to some degree (Holloway, 2000; Vandenplas & Hassall, 2002). The esophageal body is a major component of the antireflux mechanism. Once reflux has occured, the reflux contents can be cleared by peristaltic sequences (Holloway, 2000). An intact peristaltic mechanism is essential for effective acid clearance. Thus, disruption of esophageal persistalsis affects clearance of the refluxate, resulting in exceccive acid reflux and then onset of GERD (Kahrilas et al., 1988; Moayyedi & Talley, 2006).

In fact, it has been suggested that the pathogenesis of some esophageal disorders icluding GERD is involved in dysfunction of neural regulation such as imbalance of excitatory and inhibitory components of neurons and disruption of neural components (Banerjee et al., 2007; Kim et al., 2008; Mittal & Bhalla, 2004; Shiina et al., 2010). In GERD patients, ineffective esophageal motility (IEM), a typical hypocontractile disorder, is the most common motor abnormality (Lemme et al., 2005). IEM patients have more than the normal number of nNOS-positive neurons in circular muscle in the esophagus, which might result in enhancement of inhibitory neural components (Leite et al., 1997; Lemme et al., 2005). On the

other hand, esophageal dysfunctions and then GERD occur frequently in patients with diabetes mellitus (Phillips et al., 2006; Sellin & Chang, 2008). This is a typical symptom of diabetic neuropathy in which enteric neurons decrease (Chandrasekharan & Srinivasan, 2007). These facts indicate that imbalance of excitatory and inhibitory innervations, resulting in disfunction of esophageal persistalsis in the esophageal body, can be associated with onset of GERD possibly via attenuation of clearance activity and then excessive acid reflux.

### 3.2 Involvement of excessive activation of the local inhibitory neural reflex in onset of GERD

We have reported that application of capsaicin remarkably can attenuate the mechanical activity of the esophageal striated muscle via activation of the local neural reflex including primary afferents and intrinsic neuorns in our experimental conditions *in vitro* (Boudaka et al., 2007a; Boudaka et al., 2007b; Izumi et al., 2003; Shiina et al., 2006). Thus, the local neural reflex might be involved in not only coordinating esophageal peristalsis but also dysmotility of the esophagus and then the pathogenesis of GERD. Acid exposure not only induces inflammation in the esophageal mucosa (Rieder et al., 2010) but also might influence afferent neurons expressing TRPV1, which can be stimulated by protons (Tominaga & Tominaga, 2005). If acid excessively activates local neural reflex in the esophageal body, esophageal motility might be attenuated, resulting in decrease of clearance activity (Figs. 4, 5, 6). In accordance with this, low pH can attenuate contractile activity in isolated esophageal segments from rats and mice like as capsaicin and piperine (unpublished data). In addition, functional changes of TRPV1 by proinflammatory mediators such as prostaglandin E2 (Adcock, 2009; Lopshire & Nicol, 1998) might facilitate activation of the inhibitory local neural reflex, resulting in low clearance activity. Decrease of clearance activity might permit further acid reflux, which would cause severe symptoms of GERD. Therefore, it is presumed that excessive activation of the local inhibitory neural reflex might be involved in the pathophysiology of GERD.

Challenge of acid exposure enhances TRPV1 and substance P expression in TRPV1-positive neurons accompanying esophageal mucosa inflammation (Banerjee et al., 2007). In accordance with this, acid-induced esophagitis is not so severe in TRPV1-deficient mice (Fujino et al., 2006). Interestingly, it has been reported that TRPV1-positive neurons are local effectors of mucosal protection (Bass et al., 1991) and are associated with a protective effect of an $H_2$-receptor antagonist on reflux esophagitis (Nagahama et al., 2003). Enhancement of TRPV1 and tachykinins expression also might result in intensification of local neural regulation, which is an exacerbating factor of GERD.

Of course, dysmotility of the striated muscle portion of the esophagus described here might not directly be involved in gastroesophageal reflux in human because the external muscle layer in the distal portion of human esophagus is composed with smooth muscle fibers (Wörl & Neuhuber, 2005). The inhibitory neural pathway activated by acid reflex has not been demonstrated in smooth muscle of the human esophagus. In fact, spastic contractions are induced by acid reflux in the distal esophagus (diffuse esophageal spasm), which frequently are responsible of chest pain in GERD (Richter, 2007; Tutuian & Castell, 2006). This excessive contraction of smooth muscle is in contrast to the inhibition of striated muscle contraction via the local neural reflex activated by acid reflex.

### 3.3 Abnormal relaxation of the LES and GERD

Abnormal relaxation of the LES is one of causes for GERD. LES hypotension may be due to a number of potential disturbances, including abnormality of the muscle function itself, lack of normal cholinergic activation, decreased reflex excitation, decreased responsiveness to circulating substances such as gastrin, and activation of inhibitory system (Clouse & Diamant, 2006). The LES is innervated by inhbitory and excitatory intrinsic neurons that are located in the myenteric plexus not only of the LES but also of the esophgeal body (Fig. 7) (Brookes et al., 1996). Abnormal activation of vagal afferents and/or efferents might activate inhibitory intrinsic neurons and cause LES relaxation and then excessive acid reflux from the stomach to the esophagus (Mittal et al., 1995). Kuramto et al. reported that a subpopulation of myenteric nitrergic neurons is immunoreactive for a tachykinin receptor in the rat esophageal body (Kuramoto et al., 2004). Considering that myenteric neurons are closely innervated by spinal afferents in which TRPV1 and tachykinins might be expressed in the esophagus (Holzer, 1988; Kuramoto & Endo, 1995; Mazzia & Clerc, 1997; Wörl & Neuhuber, 2005) as well as vagal afferent neurons, it is possible that acid can induce release of tachykinins from afferent neurons and subsequently tachykinins would act on intrinsic nitrergic neurons innervated to the LES (Fig. 7). This suggests that excessive acid reflux to the esophageal body might evoke abnormal relaxation of the LES by NO, resulting in severe GERD.

### 3.4 A putative vicious circle in onset and exacerbation of GERD

Chronic esophagitis, a symptom of GERD, may damage not only the mucosa but also intrinsic neurons (Rieder et al., 2010). In fact, it has been reported that proinflammatory cytokines contribute to reducing esophageal contraction by inhibiting release of acetylcholine from myenteric neurons (Cao et al., 2004). Esophageal dysmotility might subject the mucosa to further acid exposure, which would cause more severe inflammation by directly influencing the mucosa or neurogenic mechanism via TRPV1-positive neurons and peptidergic neurotransmitters (Bozic et al., 1996; Richardson & Vasko, 2002). Considering that the severity of myenteric plexus damage is positively correlated with the duration of history of esophageal diseases (Gockel et al., 2008), there might be a vicious circle in GERD (Fig. 8).

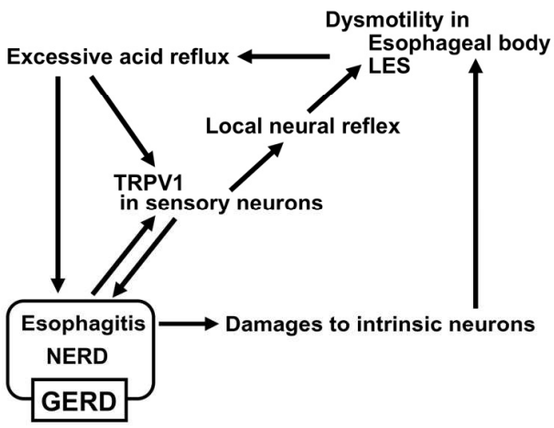



Fig. 8. A predicted vicious circle model of GERD. The circle might exacerbate GERD. GERD; gastroesophageal reflux disease. NERD; nonerosive reflux disease. LES; lower esophageal sphincter. TRPV1; transient receptor potential vanilloid 1.

## 4. Conclusion

Motor functions of the esophagus are controlled by both vagal neurons arising in the brainstem and locally intrinsic neurons in the striated and smooth muscles. The pathogenesis of GERD might be involved in dysfunction of neural networks in the esophagus. We propose new aspects of the involvement of pathophysiology of GERD in excessive activation of the local neural reflex by intrinsic neurons on the basis of results of our morphological and functional studies on esophageal motility.

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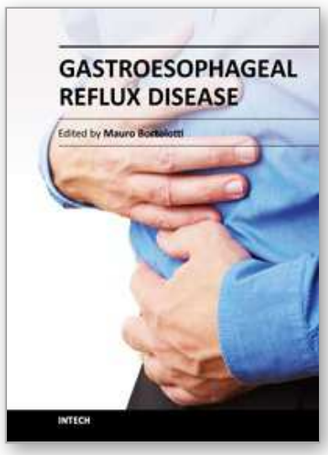
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Gastroesophageal reflux disease affects many patients. This disease not only lowers their quality of life, but it also threatens some of them with an underhand risk of cancer. Additionally, it becomes an economic burden for the patients and society. The aim of this book on gastroesophageal reflux disease is to provide advice and guidance to gastroenterologists to help them understand and manage some aspects of this proteiform disease.

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