Published in final edited form as:

Auton Neurosci. 2006 April 30; 125(1-2): 42–52. doi:10.1016/j.autneu.2006.01.014.

Role of brainstem TRH/TRH-R1 receptors in the vagal gastric cholinergic response to various stimuli including sham-feeding

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Abstract

Pavlov's pioneering work established that sham-feeding induced by sight or smell of food or feeding in dogs with permanent esophagostomy stimulates gastric acid secretion through vagal pathways. Brain circuitries and transmitters involved in the central vagal regulation of gastric function have recently been unraveled. Neurons in the dorsal vagal complex including the dorsal motor nucleus of the vagus (DMN) express thyrotropin-releasing hormone (TRH) receptor and are innervated by TRH fibers originating from TRH synthesizing neurons in the raphe pallidus, raphe obscurus and the parapyramidal regions. TRH injected into the DMN or cisterna magna increases the firing of DMN neurons and gastric vagal efferent discharge, activates cholinergic neurons in gastric submucosal and myenteric plexuses and induces a vagal-dependent, atropine-sensitive stimulation of gastric secretory (acid, pepsin) and motor functions. TRH antibody or TRH-R1 receptor oligodeoxynucleotide antisense pretreatment in the cisterna magna or DMN abolished vagal-dependent gastric secretory and motor responses to sham-feeding, 2-deoxy-D-glucose, cold exposure and chemical activation of cell bodies in medullary raphe nuclei. TRH excitatory action in the DMN is potentiated by co-released prepro-TRH-(160–169) flanking peptide, Ps4 and 5-HT, and inhibited by a number of peptides involved in the stress/immune response and inhibition of food-intake. These neuroanatomical, electrophysiological and neuropharmacological data are consistent with a physiological role of brainstem TRH in the central vagal stimulation of gastric myenteric cholinergic neurons in response to several vagal dependent stimuli including sham-feeding.

Keywords

TRH; Vagus; pChAT; Myenteric neurons; Gastric acid secretion; Dorsal motor nucleus

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1. Introduction

At the beginning of last century, Ivan Pavlov's pioneer discovery of the "psychic phase" of gastric acid secretion provided one of the first experimental evidence of brain–gut axis. He established a model of sham-feeding in dogs with permanent esophagostomy, and demonstrated that the anticipation of eating and the sight and smell of food were powerful stimulants of both gastric acid and pepsin secretion, and the gastric response required the vagal innervation (Pavlov, 1910). In humans, Cushing reported in 1932 that patients with intracranial lesions had gastric hypersecretion and developed ulcers (Cushing, 1932). Thereafter, a number of experiments using electrical stimulations and lesions of various brain areas defined specific nuclei responsible for influencing gastric acid secretion through vagal pathways (reviewed in Taché, 1987). Despite this auspicious beginning establishing that gastric acid secretion is stimulated by central vagal pathways, it has only been in the past few decades that brain circuitries and chemical messengers involved in vagal regulation of gut function have been unraveled (Taché, 1987; Hornby et al., 1991).

The present review will focus on convergent sets of evidence illustrating that brain medullary thyrotropin-releasing hormone (TRH) is involved in the neuronal cascade mediating the vagal cholinergic-dependent stimulation of gastric function in response to various stimuli including sham-feeding.

2. Brain medullary TRH is a physiological vagal stimulant of gastric secretion: neuroanatomical and electrophysiological evidence

TRH was originally isolated from mammalian hypothalami and named after its property to stimulate the release of thyroid-stimulating hormone (TSH) from the pituitary (review in Guillemin, 2005). However, the widespread distribution of TRH in the brain (Hokfelt et al., 1975; Yarbrough, 1979; Jackson and Lechan, 1983; Horita et al., 1986; Lechan and Segerson, 1989) and its neuropharmacological effects (Taché et al., 1977;Yarbrough, 1979) suggested that TRH may exert biological functions that expand far beyond its pivotal hypophysiotrophic role (Metcalf and Dettmar, 1981). In particular, we initially showed that TRH injected intracisternally (i.c.) acts in the brain to induce a vagally mediated and atropine-sensitive stimulation of gastric acid secretion (Taché et al., 1980). This report provided the first evidence that a peptide increased gastric acid secretion through central vagal pathways (Taché et al., 1980). Further studies uncovered neuroanatomical, electrophysiological and neuropharmacological evidence implicating the brain medullary TRH pathway in the central vagal regulation of gastric secretory and motor function to various stimuli (Taché et al., 1993).

2.1. TRH and TRH receptor localization in the brainstem

The dorsal vagal complex (DVC) encompasses the dorsal motor nucleus of the vagus (DMN) and the nucleus tractus solitarius (NTS). Tracing studies by Powley et al. (1991) established that the DMN is the source of vagal efferent fibers innervating the gut, and more prominently, the stomach. In particular, the medial parts of the right and left DMN contain neurons that project ipsilaterally to form the anterior and posterior branches of the gastric

vagus, respectively (Fox and Powley, 1985). There is also evidence that dendrites of DMN neurons reached the overlying NTS more densely in the subnucleus gelatinosus of the dorsal medial NTS just rostral to the obex where gastric vagal afferent fibers project (Rinaman and Miselis, 1990). TRH-immunoreactive (IR) fibers are densely present in the DVC (Fig. 1A) and TRH-containing nerve terminals make synaptic contacts with dendrites of DMN neurons projecting to the stomach in rodents (Rinaman et al., 1989; Rinaman and Miselis, 1990). In humans, TRH-IR fibers innervating the DMN also constitute the most prominent network compared with that of twelve other neuropeptides (Fodor et al., 1994). TRH-IR fibers in the DVC do not originate from TRH-expressing neurons in the paraventricular nucleus of the hypothalamus but from direct projections from TRH synthetizing neurons located exclusively in brainstem nuclei, namely the raphe pallidus, raphe obscurus and parapyramidal regions, as delineated by knife cut and tracing methods (Palkovits et al., 1986; Segerson et al., 1987; Lynn et al., 1991; Bayliss et al., 1994) (Fig. 1B, C).

Consistent with a physiological role of TRH terminals in the DVC to regulate gastric function, the highest density of TRH binding sites detected by autoradiography is found in the medial column of the DMN (Manaker and Rizio, 1989) (Fig. 1D) where the majority of preganglionic motor neurons contribute to the vagal efferent innervation of the stomach (Powley et al., 1991). So far the two cloned TRH receptor subtypes, TRH-R1 and TRH-R2, are membrane proteins belonging to the family of G-protein coupled receptors (Gershengorn and Osman, 1996; Cao et al., 1998). Mapping of TRH-R1 and TRH-R2 gene expression in the rat brainstem revealed that TRH-R1 is the only subtype present in the DMN and NTS, while TRH-R2 is mainly located in the reticular formation, dorsal tegmental nucleus and spinal trigeminal nucleus which are areas processing sensory information (Heuer et al., 2000).

2.2. Activation of preganglionic vagal motor neurons and vagal efferent fibers

The expression of TRH receptors on preganglionic vagal motor neurons is indicative of a TRH modulatory action on parasympathetic outflow. Several reports showed that TRH induces an immediate and long acting excitation of individual DMN units identified electrophysiologically in urethane-anesthetized rats and in guinea pig or rat brainstem slice preparations (McCann et al., 1989; Raggenbass et al., 1990; Travagli et al., 1992; Livingston and Berger, 1993). The responsiveness to TRH observed in DMN neurons located rostral or caudal to the obex is no longer observed or decreased after repeated injections indicating that there is a sensitization or tachyphylaxis to TRH (Travagli et al., 1992; Livingston and Berger, 1993). TRH acts directly on DMN neurons since the excitatory response was still observed after synaptic blockade and was not affected by glutamate or muscarinic antagonists ruling out an action through presynaptic release of glutamate and acetylcholine (McCann et al., 1989; Raggenbass et al., 1990; Travagli et al., 1992; Livingston and Berger, 1993). The mechanisms underlying the excitatory effect involve an increase in excitatory postsynaptic currents and a reduction of fast transient A-type potassium current and calcium-dependent slow after-hyperpolarization (Travagli et al., 1992).

In line with the activation of preganglionic vagal motor neurons, i.c. or intracerebroventricular (i.c.v.) injection of TRH or the stable TRH analog, RX 77368 results

in a doserelated sustained stimulation of efferent discharges recorded in the cervical or ventral gastric branch of the vagus in anesthetized rats (Somiya and Tonoue, 1984; Taché et al., 1985; O-Lee et al., 1997) (Fig. 2).

2.3. Activation of gastric myenteric cholinergic neurons

Earlier electrophysiological studies by Schemann and Grundy (1992) revealed that a high percentage of myenteric neurons in guinea pig stomach receives direct fast excitatory postsynaptic potential input from vagal efferent fibers. Anatomical support for these observations came from elegant tracing studies depicting direct input of vagal efferent fibers on gastric myenteric neurons (Berthoud, 1995; Holst et al., 1997). In the stomach, vagal efferent terminals were found to encircle or make putative contacts with all gastric myenteric and submucosal neurons (Berthoud, 1995; Holst et al., 1997). The i.c. injection of TRH provided a relevant tool to assess the activation of gastric myenteric neurons by central vagal activation in conscious rats using double labeling with Fos as a nuclear marker of neuronal synaptic activation (Krukoff, 1993) and PGP 9.5 as a neuronal marker (Krammer et al., 1993). We showed that the TRH analog, RX 77368 injected i.c., at a dose that activates gastric vagal efferent discharge (O-Lee et al., 1997), induced Fos expression in the majority (90%) of neuronal cell bodies located in the corpus and antral submucosal and myenteric ganglia (Miampamba et al., 2001; Yuan et al., 2005) (Fig. 3). Fos expression was observed in neurons densely surrounded with cholinergic fibers identified by the vesicular acetylcholine transporter (Miampamba et al., 2001). The Fos response to i.c. RX 77368 was 90% abolished by hexamethonium, but not altered by atropine (Miampamba et al., 2001). Using selective vagal denervation in the rat stomach, Fos expression in response to electrical vagal stimulation occurs in gastric myenteric neurons except in the vagally denervated area, arguing against a role of interneuronal spreading of the activation, but rather a direct cholinergic input (Zheng and Berthoud, 2000). It is well established electrophysiologically that acetylcholine acting at nicotinic acetylcholine receptors mediates most of the fast excitatory postsynaptic potentials in the enteric nervous system (Galligan, 2002). Taken together these data support that central vagal cholinergic activation-induced widespread Fos expression in gastric myenteric neurons occurs through acetylcholine acting at nicotinic acetylcholine receptors located on myenteric neurons (Kirchgessner and Liu, 1998; Galligan, 2002) although their distribution in rats myenteric neurons is still to be established.

The neurochemical phenotype of myenteric neurons activated by central vagal stimulation was identified to include over 90% of gastric intrinsic cholinergic neurons that represent two-thirds of total submucosal and myenteric immunoreactive neurons (Nakajima et al., 2000; Yuan et al., 2005) (Fig. 3). This was established using immunostaining with peripheral choline acetyltransferase (pChAT), a splice variant of ChAT that is expressed only in the peripheral nervous system (Tooyama and Kimura, 2000; Yuan et al., 2005). These observations provided anatomical and functional support to the vagal dependent and hexamethonium and atropine sensitive gastric acid response to i.c. injection of TRH or TRH analog in rats or medullary raphe activation in cats (Taché et al., 1980, 1984; Yanagisawa et al., 1990; White et al., 1991).

3. Involvement of medullary TRH signaling in the vagal stimulation of gastric function

The blockade of receptors by selective antagonists is a commonly used approach to assess the physiological role of endogenous transmitters and peptides. However, with regard to TRH, no specific receptor antagonists have yet been developed. Alternative strategies relied on the TRH-R1 antisense oligodeoxynucleotides to inhibit in vivo TRH-R1 expressed in the DVC (Suzuki et al., 1995; Sivarao et al., 1997) and polyclonal TRH antibody to immunoneutralize endogenous TRH localized and released in the DVC (Rinaman et al., 1989; Rinaman and Miselis, 1990).

3.1. Gastric stimulation induced by activation of TRH synthetizing neurons

Convergent reports showed that the chemical activation of TRH synthesizing cell bodies by microinjection of kainic acid into the Rpa, Rob and parapyramidal regions that project to the DVC (Lynn et al., 1991; Taché et al., 1995a) results in a vagal-dependent, atropine-sensitive stimulation of gastric acid and pepsin secretion, motility and mucosal blood flow and alterations of the resistance of the gastric mucosa to injury; these changes mimicked the gastric responses elicited by TRH or its stable analog microinjected directly into the DMN in rats and cats (Taché et al., 1984; White et al., 1991; Yang et al., 1993, 1999b, 2000a,b; Garrick et al., 1994; Kaneko et al., 1995, 1998; Kaneko and Taché, 1995). In addition, TRH antibody injected into the cisterna magna or selectively microinjected bilaterally into the DVC, or i.c. pretreatment with TRH-R1 oligodeoxynucleotide antisense prevented the stimulation of gastric acid secretion, motility and blood flow, and changes in the resistance of the gastric mucosa to injury induced by microinjection of kainic acid into the raphe obscurus or raphe pallidus (Yang et al., 1993, 2000b; Garrick et al., 1994; Kaneko et al., 1995, 1998; Kaneko and Taché, 1995; Sivarao et al., 1997). Collectively these results indicate that the excitation of TRH-synthesizing raphe medullary neurons activates endogenous TRH–TRH-R1 signaling cascade within the DMN and thereby elicits vagal cholinergic myenteric stimulation of gastric acid secretory and motor function and mucosal blood flow.

3.2. Gastric responses to acute cold exposure

Early reports established cold exposure as a model to induce vagal-dependent atropine sensitive development of gastric lesions in fasted rats (Senay and Levine, 1967). Since then, convincing data support the involvement of brain medullary TRH as part of the mechanisms underlying gastric alterations induced by cold exposure (Taché et al., 1995b). First, brain medullary proTRH mRNA expression is increased in a time-related manner by cold exposure for 1 to 3 h and in situ hybridization histochemistry revealed that this occurs exclusively in the raphe pallidus and raphe obscurus (Yang et al., 1994). Second, cold exposure activates TRH synthesizing neurons in the raphe pallidus, raphe obscurus and parapyramidal region as shown by Fos and prepro-TRH double staining (Bonaz and Taché, 1994; Wang et al., 1996; Yang et al., 2000b). Cold exposure also activates DMN neurons (Bonaz and Taché, 1994; Wang et al., 1996), vagal efferent discharge (Cho et al., 1996) and over 90% of antral and corpus submucosal and myenteric cholinergic neurons (Yuan et al.,

2001, 2005) (Fig. 3). Third, acute cold exposure mimics the functional gastric responses evoked by i.c. or DMN injection of TRH or TRH analogs and induces a vagally mediated atropine-sensitive stimulation of gastric acid and pepsin secretion, motility and hemorrhagic lesion formations (Goto and Taché, 1985; Taché et al., 1988; Hernandez and Emerick, 1988; Yang et al., 1994; Okumura et al., 1994). Lastly, TRH antibody microinjected into the DVC or cisterna magna or i.c. pretreatment with the TRH-R1 oligodeoxynucleotide antisense prevents acute cold exposure-induced stimulation of gastric acid secretion, emptying, motility and lesion formation (Basso et al., 1988; Hernandez et al., 1990; Niida et al., 1991; Martinez et al., 1998).

3.3. Gastric responses to 2-deoxy-D-glucose

Glucodeprivation induced by 2-deoxy-D-glucose, which impairs glucose utilization, is a well-established pharmacological tool to induce food intake and central vagal-dependent stimulation of gastric acid secretion, emptying and experimental ulcers in rats and dogs (Hirschowitz and Sachs, 1965; Smith and Epstein, 1969; Maeda-Hagiwara and Watanabe, 1983; Okumura et al., 1995b). Brain nuclei influenced by peripheral administration of 2-deoxy-D-glucose include neurons in the DMN as shown by induction of Fos expression which is indicative of activation of preganglionic vagal motor neurons (Ritter and Dinh, 1994). It is likely that brain medullary TRH plays a role in these DMN and gastric responses since i.c. injection of TRH antibody prevents the acceleration of gastric emptying and erosion formation induced by intravenous injection of 2-deoxy-D-glucose in conscious rats (Okumura et al., 1995a,b).

3.4. Gastric acid responses to sham-feeding

The peripheral mechanisms of the cephalic phase of gastric acid secretion has been extensively studied in dogs and in humans, however, little is known on brain circuits and transmitters involved in this vagally mediated response (Richardson et al., 1977; Feldman and Richardson, 1986; Konturek et al., 1987). In an effort to gain understanding on central mechanisms, Martinez et al. (2002) developed a rat model to study the cephalic phase of acid secretion in rats. Olfactory and visual sensory inputs of food resulted in the stimulation of gastric acid secretion in fasted rats with chronic gastric cannula and constant perfusion and titration of acid (Fig. 4A). Under these conditions, the basal acid secretion averages 22.0 ±1.6 μmol/10 min and increased within 10 min after the onset of sham-feeding to reach a 3-fold increase at 20 min, and declined to basal levels thereafter (Martinez et al., 2002) (Fig. 4B). The acid response to sham-feeding in rats is mediated by the activation of TRH–TRH-R1 signaling pathways in the brain medulla. This was established by the blockade of the acid response to sham-feeding and i.c. TRH by i.c. pretreatment with TRH-R1 antisense oligodeoxynucleotides, while TRH-R1-mismatched oligodeoxynucleotide pretreatment under similar conditions had no effect (Martinez et al., 2002) (Fig. 4B, C). Lastly, both sham-feeding and central injection of TRH, in addition to stimulate acid secretion, induce a vagal stimulation of gastroduodenal blood flow and motor function and pancreatic exocrine and endocrine secretion in experimental animals (Giduck et al., 1987; Taché et al., 1989b; Okumura et al., 1995c; Kiraly et al., 1998; Katschinski, 2000; Yang et al., 2002). Although to be further established, these data would suggest that the activation of medullary TRH and TRH-R1 in the DMN may also contribute to other digestive components of the cephalic

phase of digestion that subserve optimizing the digestive (acid pepsin, propulsive motility) and metabolic processes under conditions of impending meal ingestion (Nicolaidis, 1969).

However, activation of medullary TRH–TRH-R1 signaling does not represent a common final pathway of vagally mediated gastric response since the i.c. injection of somatostatin analog, peptide YY (PYY) or pancreatic polypeptide that induces a vagal atropine-sensitive stimulation of gastric motor function and resistance of the mucosa to ethanol injury are not blocked by TRH-R1 antisense oligodeoxynucleotide pretreatment (Okumura et al., 1995b; Martinez et al., 1998; Yang et al., 1999a). In addition, this brain TRH pathway is not involved in the basal regulation of gastric function in the experimental models investigated since the i.c. pretreatment with the TRH antibody or TRH-R1 antisense oligodeoxynucleotides did not significantly influence basal gastric emptying or acid secretion (Okumura et al., 1995b; Martinez et al., 1998, 2002).

4. Modulation of medullary TRH action by other brain peptides

There is growing evidence that TRH excitatory action on DMN neurons does occur in concert with other potentiating influences. These modulatory effects are exerted by neuropeptides or neurotransmitters co-localized with TRH in raphe nuclei and co-released in the DVC, and through input from direct peptidergic projections to the DVC from other brain areas (Taché et al., 1995a).

4.1. Potentiation of TRH action in the dorsal vagal complex by Ps4 and 5-HT

The proteolytic cleavage of TRH prohormone generates five copies of TRH and the connecting peptides, including prepro-TRH-(160–169) (Ps4), which is co-released with TRH (Ladram et al., 1994). When Ps4 is co-injected into the DMN with TRH, the peptide potentiates the stimulation of gastric acid secretion in response to TRH, while having no effect by itself (Yang and Taché, 1994).

Serotonin (5-HT) is a neurotransmitter that is co-localized in neurons synthesizing TRH in medullary raphe nuclei and parapyramidal regions (Helke et al., 1989; Kachidian et al., 1991), and released in the DVC in response to excitation of medullary raphe neurons (Mohammed et al., 1995). Functional studies showed that 5-HT potentiates exogenous or endogenous TRH action in the DVC to stimulate gastric acid secretion and motility while 5-HT microinjected alone into the DMN did not alter basal gastric function (McCann et al., 1988; McTigue et al., 1992; Yoneda and Taché, 1995; Chi et al., 1996). Likewise, fluoxetine, a 5-HT reuptake inhibitor that enhanced extraneuronal 5-HT levels in the brain, injected i.c. potentiates i.c. RX 77368-induced increase in gastric acid secretion (Shockley et al., 1992). Pharmacologic studies using selective 5-HT receptor agonists and antagonists suggest that 5-HT action in the DVC involved interaction with 5-HT_2 receptors (Yoneda and Taché, 1995; Varanasi et al., 1997).

4.2. Inhibition of TRH action in the dorsal vagal complex by peptides

Several peptides innervating the DVC exert an inhibitory influence on TRH-induced stimulation of gastric function. Substance P (SP) is expressed in TRH-containing neurons in the raphe pallidus, raphe obscurus and parapyramidal regions projecting to the DVC

(Kachidian et al., 1991; Taché et al., 1995a). Retrograde labeling studies showed that DMN neurons projecting to the stomach are in contact with SP terminals and express neurokinin-1 receptors (NK_1) (Ladic and Buchan, 1996). The activation of NK_1 receptors in the DMN reduces the gastric secretory and motor stimulatory responses to exogenous TRH microinjected into the DVC or endogenously released by stimulation of Rpa or Rob (Yang and Taché, 1997; Krowicki and Hornby, 2000). Therefore, SP co-released with TRH in the DVC dampens the excitatory action of TRH.

A number of other brain peptides co-injected with TRH into the DMN or cerebrospinal fluid inhibit the vagal-dependent stimulation of gastric secretory and motor function induced by TRH. Among them are those that are involved in the stress/immune response, including corticotrophin-releasing factor (CRF), urocortin 1, opioid peptides, interleukin-1 and tumor necrosis factor-α (Morley et al., 1981; Taché et al., 1983; Garrick et al., 1988; Saperas et al., 1990; Heymann-Mönnikes et al., 1991; Taché and Saperas, 1992; Hermann and Rogers, 1995; Hermann et al., 1999; Yang et al., 2000a; Chen et al., 2002), as well as peptides or conditions inhibiting food intake such as gastrin-releasing peptide/bombesin, PYY, Y_2 agonist, calcitonin gene-related peptide, adrenomedullin and i.v. glucose (Hughes et al., 1984; Chen et al., 1997; Martinez and Taché, 2000; Yuan and Yang, 2002; Doong and Yang, 2003).

These pharmacological observations may have relevance in the context of known inhibition of vagally mediated digestive function including acid, pepsin or upper gastrointestinal motility under stress conditions (Taché et al., 1989a). However, additional studies are still needed to establish the physiological relevance and mechanisms of actions that modulate TRH–TRH-R1-induced activation of DMN preganglionic neurons.

Acknowledgements

The authors' work was supported by the NIHDDK grant R01 30110 (YT) and DK 33061 (YT), the Center grant DK 41301 (Animal Core, YT), VA Senior Scientist Award (YT), DK 50255 (HY) and VA Merit Award (HY). The authors thank Miss Teresa Olivas for her help in the preparation of the manuscript.

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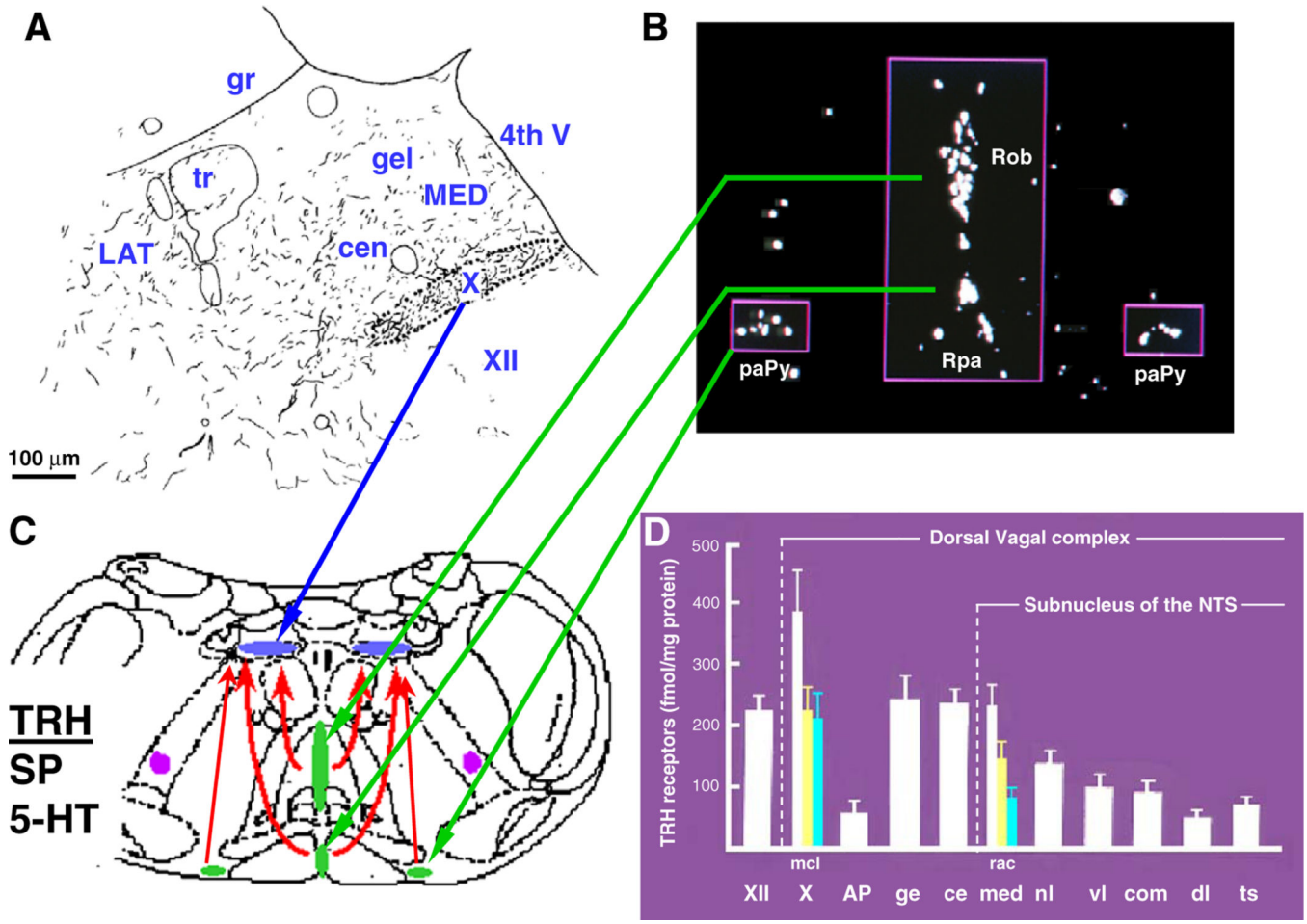

Fig. 1.

Neuroanatomical evidence for a physiological role of brain medullary TRH. (A) Drawing of TRH-IR fibers in rats dorsal vagal complex (DVC) rostrocaudal to the obex. Dense distribution in the dorsal motor nucleus of the vagus (DMN or X); cen: subnucleus centralis of the medial (MED) nucleus tractus solitarius (NTS); gel: subnucleus gelatinosus; adapted from Rinaman et al. (1989). (B) Dark field microscopy of cells in the raphe obscurus (Rob), raphe pallidus (Rpa) and parapyramidal area (PaPy) hydrized with the labeled antisense pro-TRH probe; adapted from Segerson et al. (1987). (C) Schematic representation of Rob, Rpa and PaPy direct projections to DMN (X) that provide TRH-IR, substance P (SP) and 5-HT innervation in the DVC. (D) Concentration of TRH receptors in the DVC; the DMN (X) is subdivided in medial (m), central (c) and lateral (l) and NTS in ge: gelatinosus, ce: central; med (medial: r, rostra; a, adjacent; and c, caudal to the area postrema); adapted from Manaker and Rizio (1989).

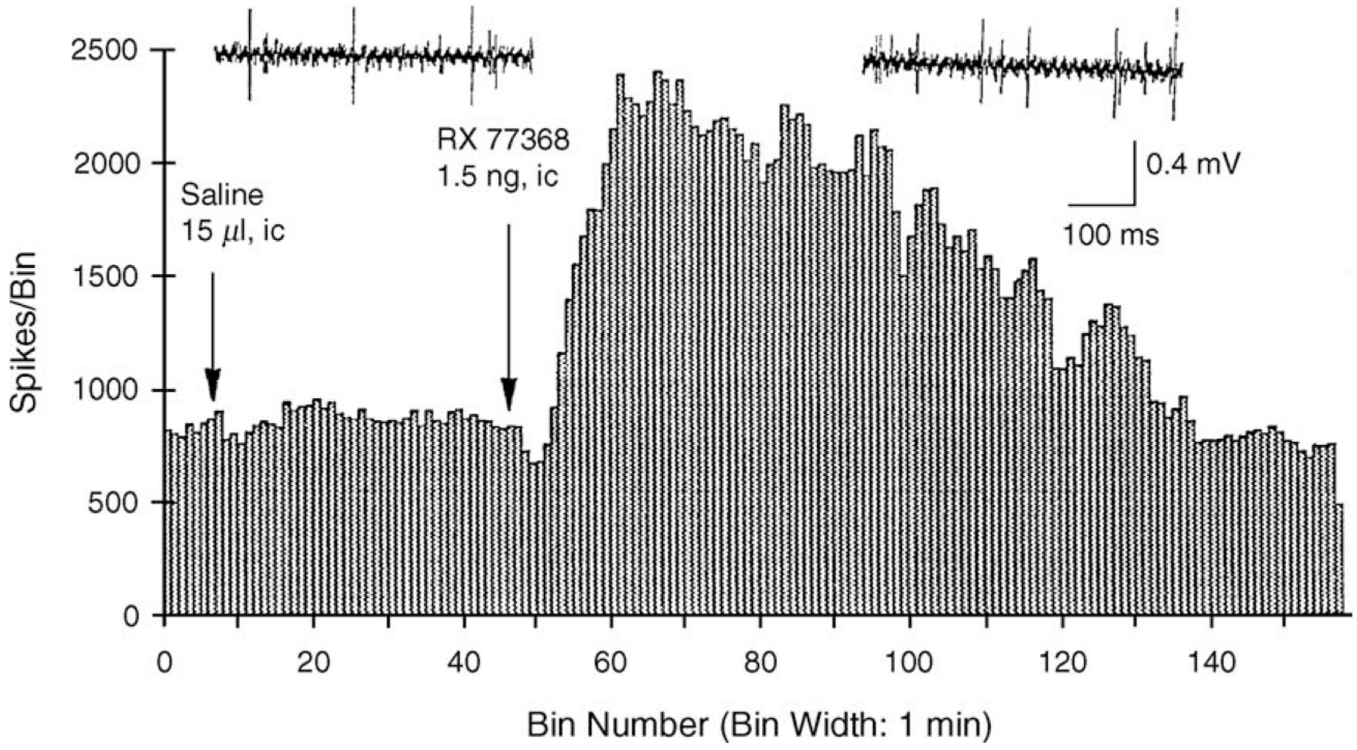

Fig. 2.

TRH analog, RX 77368 injected intracisternally (i.c.) stimulates gastric vagal efferent discharges (multi-unit activity) while i.c. saline had no effect in urethane anesthetized rats. Adapted from O-Lee et al. (1997).

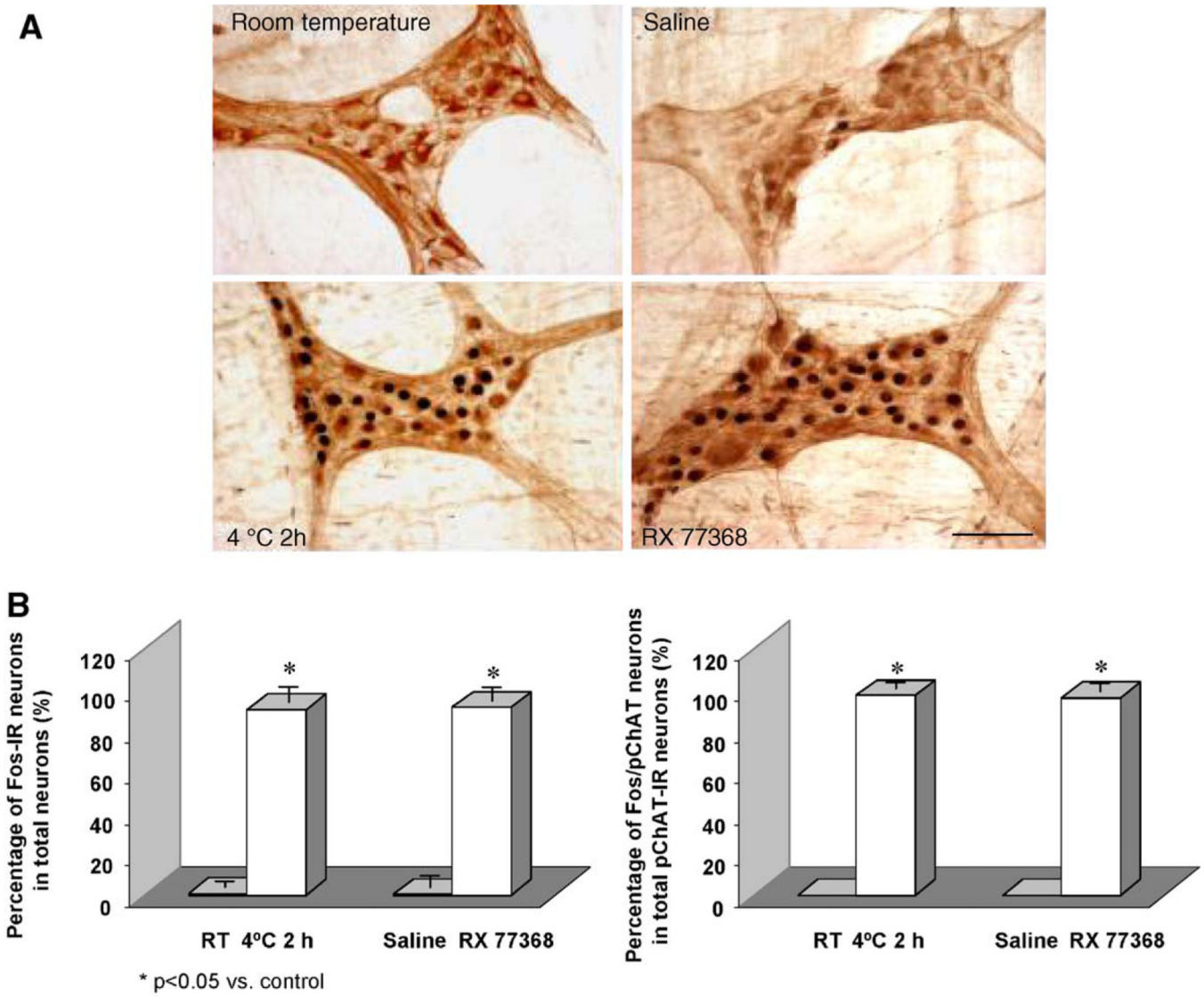

Fig. 3.

Cold exposure or intracisternal (i.c.) injection of TRH analog activates gastric myenteric cholinergic neurons in conscious rats. (A) Photomicrographs of whole mount preparations of myenteric plexus showing double staining of Fos and pChAT in the gastric corpus of conscious rats semi-restrained either at room temperature or at 4 °C for 2 h or injected i.c. with saline or RX 77368 (50 ng/rat) and euthanized 60 min later. Fos immunoreactivity was revealed as the dark blue staining in the cell nuclei and pChAT immunoreactivity appeared as brown staining in the cytoplasm. Scale bar, 100 μm. (B) Cell counts of Fos-positive and double-labeled Fos/pChAT neurons expressed in percentage of total Fos positive neurons and total pChAT neurons induced by cold exposure for 2 h or i.c. injection of RX 77368. Each column represents the mean±S.E.M. of 3 rats. *P <0.05 compared with the values of rats at room temperature or injected i.c. with saline. Adapted from Yuan et al. (2005).

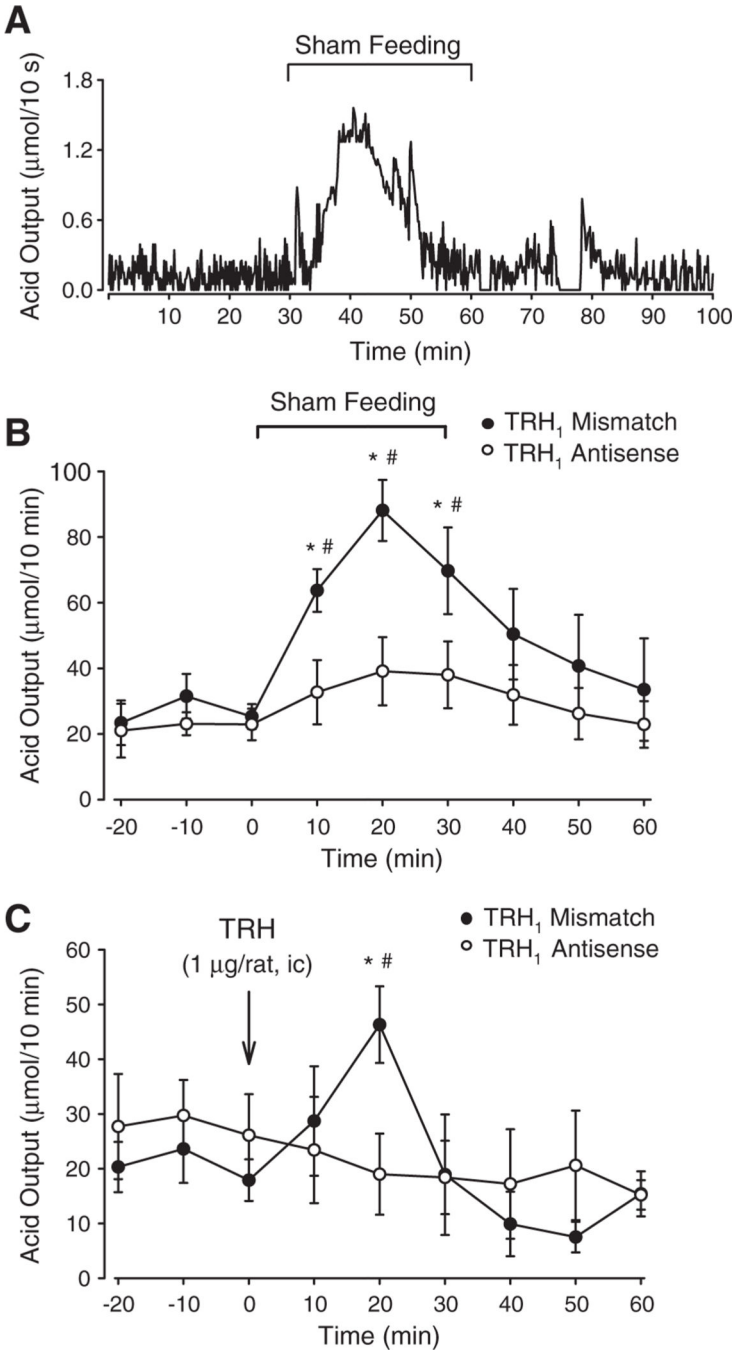

Fig. 4.

Activation of TRH–TRH-R1 signaling pathways mediates sham-feeding-induced gastric acid secretion in conscious rats. (A) Representative trace of increased gastric acid secretion induced by sham-feeding in conscious rats with chronic gastric fistula and constant perfusion with warm saline and constant recording of acid secretion while rats were maintained in a Bollman cage. Sham-feeding was induced by exposing fasted rats to the smell and sight of standard Purina chow for 30 min. (B) TRH-R1 antisense oligodeoxynucleotide pretreatment (100 µg twice, −48 and −24 h) prevents sham-feeding-

stimulated gastric aid secretion, while similar pretreatment with TRH-R1 mismatch oligodeoxynucleotides did not; time course study of gastric acid output/10 min with each point representing the mean±S.E.M. of 4 rats. (C) TRH-R1 antisense oligodeoxynucleotide pretreatment (100 μg twice, −48 and −24 h) prevents i.c. TRH-induced stimulation of gastric acid secretion, while similar pretreatment with TRH-R1 mismatch oligodeoxynucleotides did not; time course study of gastric acid output/10 min with each point representing the mean±S.E.M. of 4 rats. Adapted from Martinez et al. (2002).