

Thyrotropin releasing hormone (TRH) in the brainstem: Role of Pavlov's vagally mediated cephalic phase of gastric secretion

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Abstract. Pavlov's seminal observation that sham feeding in dogs stimulates gastric acid secretion through the vagus nerve pioneered the concept of the cephalic phase of digestion. This has been subsequently extended to a wide range of mammals including humans. In the last decades, experimental evidence in rats established that the three amino acid peptide thyrotropin-releasing hormone (TRH) expressed in the brainstem plays a key role in the vagal stimulation of digestive secretory-motor function. The dorsal motor nucleus of the vagus (DMN) neurons expresses TRH receptor subtype 1 (TRH-R1) and receives input of TRH containing fibers arising from TRH synthesizing neurons in medullary raphe nuclei. The activation of TRH-TRH-R1 signaling excites the firing of DMN neurons leading to the activation of vagal efferent discharges and gastric myenteric cholinergic neurons. This results in a vagally mediated and atropine-sensitive stimulation of gastric secretory and propulsive motor function, along with duodenal and pancreatic secretion. Importantly, the blockade of TRH or TRH-R1 in the brainstem inhibits the gastric acid response to sham feeding in rats. Collectively, these convergent data support the physiological relevance of medullary TRH-TRH-R1 signaling as the end effector of the vagally mediated stimulation of digestive process in the cephalic phase.

Keywords: dorsal vagal complex, cephalic phase, gastric secretion, thyrotropin releasing hormone (TRH), TRH receptor, sham feeding, vagus.

Introduction

At the beginning of the last century, Ivan Pavlov pioneered contributions to the field of integrative physiology by providing experimental evidence of the existence of a "psychic" stimulation of gastric acid secretion now known as the cephalic phase of digestion (Pavlov 1910). This was achieved by developing an experimental model in dogs equipped with an esophagus and gastric fistula whereby sham feeding consisting of swallowing food without reaching the stomach was shown to stimulate gastric acid secretion. Pavlov (1910) also found that in dogs with gastric intact and vagally denervated pouches (Heidenhain pouch) the gastric response to the vision and smell of food

along with gustative input in the oral cavity required the integrity of the vagus nerve.

Thereafter, the cephalic phase has been extended to a wide range of experimental mammals (Zafra et al. 2006). In humans, the gastric acid secretion initiated by meal expectations, visual, olfactory, and gustatory stimuli contributes up to 50% of the postprandial gastric secretory output and is mediated by vagal cholinergic pathways (Feldman, Richardson 1986). Subsequent investigations also showed that, in addition to acid, the cephalic phase encompasses the stimulation of a vast number of gastrointestinal (GI) digestive processes (Katschinski et al. 1992; Power, Schulkin 2008). Among those, the saliva is the first secretion to be increased by cephalic stimuli and the presence of food

in the mouth (Mattes 1997). Others relevant important secretory components are the enhanced GI hormone release, namely, gastrin (Goldschmiedt et al. 1990; Kovacs et al. 1997), ghrelin (Simonian et al. 2005), leptin (Sobhani et al. 2002) localized in the gastric mucosa within the gastric G, X/A, and mucosal cells respectively (Rindi et al. 2004), insulin (Guemes et al. 2019) and pancreatic polypeptide (Simonian et al. 2005) secreted from the pancreatic endocrine cells, as well as enzyme and bicarbonate from exocrine pancreatic secretion (Ohara et al. 1988). Concomitantly with the secretions, sham feeding increases GI motility (Rogers et al. 1993; Power, Schulkin 2008). The anticipatory GI secretory-motor responses induced by the cephalic phase are integrative and adaptive in nature to prime the gut to optimize the digestive, metabolic and absorptive processes under conditions of impending nutrient ingestion (Giduk et al. 1987; Katschinski 2000; Power, Schulkin 2008; Smeets et al. 2010).

Contrasting with the extended characterization of the peripheral GI changes evoked by the cephalic phase (Smeets et al. 2010), the underlying chemical coding in the brain mediating the vagally mediated response lagged behind. This was largely due to the lack of methodological approaches in dogs or humans to investigate the activation of these circuitries particularly in the brainstem (DelParigi et al. 2005). By contrast, a number of experimental studies in rodents have unraveled transmitters involved in vagal regulation of GI function in the brainstem (Hornby et al. 1991; Taché et al. 1995; Powley et al. 2000).

The present review will focus on convergent neuroanatomical and functional evidence accumulated during the past decades in rats supporting a role of thyrotropin releasing hormone (TRH)-TRH receptor 1 (TRH-R1) signaling in the brainstem in the vagal dependent stimulation of GI function and the possible physiological relevance as local medullary effector of the vagally mediated cephalic phase of digestion.

Hindbrain TRH-TRH receptor signaling and gastric vagal myenteric activation

We made the initial observation in rats that TRH injected the hindbrain cerebrospinal fluid at the level of the cisterna magna induces a rapid and potent increase of gastric acid secretion through vagal and atropine-sensitive pathways while peripherally administered, the peptide had no effect (Taché et al. 1980). This provided the first evidence of the central action of a peptide to induce a vagal stimulation of gastric secretion (Taché et al. 1981). However, to delineate the physiological relevance

of this observation in the vagal stimulation of gastric function several criteria had to be fulfilled. Namely, TRH should be present in fibers/terminals projecting on preganglionic vagal motor neurons of the dorsal motor nucleus of the vagus (DMN) innervating the gut. TRH receptors (TRH-R) should be expressed in DMN neurons and TRH-TRH-R activation should induce activation of vagal efferent fibers activity that innervate target cells involved in stimulating GI function. Importantly, blockade of TRH and/or TRH-R within the dorsal vagal complex (DVC) should inhibit the vagal dependent stimulation of gastric function evoked by stimuli acting through brain-vagal pathways as those recruited during the cephalic phase. So far, TRH-TRH-R signaling in the brainstem is the only ligand-receptor interaction for which these combined neuroanatomical, electrophysiological and functional criteria have been fulfilled (Taché et al. 1993; 2006; 2014).

Brain distribution by immunostaining showed that dense TRH-immunoreactive (IR) fibers are present in the rat DVC composed of the nucleus tractus solitarius (NTS) and DMN (fig. 1A). Electron microscopic studies further provided neuroanatomical evidence that TRH-IR localized in the DVC nerve terminals create asymmetric synaptic (excitatory) contacts on dendrites of DMN neurons contributing vagal efferent innervation of the stomach in rodents (Rinaman et al. 1989; Rinaman, Mislis 1990). Of translational relevance, TRH-IR fibers innervating the DMN in humans constitute the most prominent network compared to twelve other peptides immunostained under the same conditions (Fodor et al. 1994). Additional brainstem mapping studies with the combined use of knife cut and tracing methods have identified that TRH-IR fibers localized in the DVC do not originate from the hypothalamus but from TRH expressing neurons located in medullary raphe nuclei. Namely, the raphe obscurus (Rob), raphe pallidus (Rpa), and parapyramidal region synthesizing TRH containing neurons send direct projections to the DVC in rats (Lynn et al. 1991) and rabbits (Iwase et al. 1988) (fig. 1B-C).

The abundance of TRH-IR fibers and terminals in the DVC is paired with the presence of TRH-R expression. The initial autoradiography studies showed that TRH binding sites have the highest density within the medial column of the DMN (Manaker, Rizio 1989; Bayliss et al. 1994) (fig. 1D) where neurons contributing to the vagal efferent innervation to the stomach are most prominently localized (Powley et al. 1991; Holst et al. 1997). The subsequent cloning of G-protein coupled membrane bound proteins TRH-R subtype 1

(TRH-R1) and TRH-R2 in rodents (Gershengorn, Osman 1996) showed that only the TRH-R1 mRNA subtype is expressed in the DMN and NTS (Barnes et al. 2010). The TRH-R2 is found mainly in cortical and thalamic areas implicated in the processing of somatosensory signals (Heuer et al. 2000; O'Dowd et al. 2000).

The activation of TRH-R1 by exogenously applied TRH on *in vitro* rat brainstem slice preparations or *in vivo* results in the excitation of gastric projecting DMN neurons in rats and guinea pigs (McCann et al. 1989; Raggenbass et al. 1990; Travagli et al. 1992; Livingston, Berger 1993). This represents a direct excitatory action by TRH on DMN neurons since synaptic blockade and glutamate or muscarinic antagonists did not alter the response (McCann et al. 1989; Raggenbass et al. 1990; Travagli et al. 1992; Livingston, Berger 1993). Along with the activation of preganglionic vagal motor neurons, there is a robust increase in efferent discharges in the cervical or ventral gastric branch of the vagus evoked by TRH or the stable TRH agonist — dimethyl proline TRH (RX-77368) — injected into the cerebrospinal fluid of anesthetized rats (Somiya, Tonoue 1984; O-Lee et al. 1997). Additionally, RX-77368 injected intracisternally, at a dose that stimulates efferent activity in the gastric branch of the vagus (fig. 2A), activates 90% of submucosal and myenteric cholinergic neurons located in the gastric corpus and antrum in rats (Miampamba et al. 2001; 2011; Yuan et al. 2005). This was demonstrated in conscious rats by double immunostaining of gastric enteric neurons with Fos, the nuclear marker of synaptic activation and PGP 9.5, a neuronal marker (Krammer et al. 1993), or peripheral acetyl cholinergic transferase (Yuan et al. 2005) (fig. 2B) that was blocked by hexamethonium (Miampamba et al. 2001). Collectively, these data indicate that TRH injection into the brainstem increases vagal efferent outflow to the stomach leading to a nicotinic-mediated activation of gastric enteric postganglionic cholinergic neurons in rats (fig. 2).

Brainstem TRH and the stimulation of gastrointestinal function

To assess whether the endogenous TRH circuitry in the medulla oblongata plays a physiological role in the vagal activation, we used low doses of kainic acid to activate TRH synthesizing neurons located in the medullary raphe nuclei or parapyramidal region and innervating the DVC (Taché et al. 1995). This resulted in a vagal-dependent, atropine-sensitive stimulation of gastric acid and pepsin secretion, mucosal blood flow and motility mimicking the gastric responses to microinjection of TRH

or a TRH stable agonist into the DMN in rats and cats (Taché et al. 1984; Yang et al. 1993; 2000; Kaneko et al. 1998; Kiraly et al, 1998; White et al. 1991; Garrick et al. 1994). It also resulted in stimulation of pancreatic secretion (Okumura et al. 1995; Yang et al. 2002; Yoneda et al. 2005). Moreover, polyclonal TRH antibody selectively microinjected bilaterally into the DVC to neutralize endogenous TRH or antisense oligodeoxynucleotides pretreatment given intracisternally to block TRH-R1 prevented the stimulation of gastric acid secretion, motility, and blood flow induced by the microinjection of kainic acid into the Rpa, Rob or parapyramidal region (Yang et al. 1993; 2000; Kaneko, Yang, Ohning, Taché 1995; Kaneko, Kaunitz, Taché 1998; Garrick et al. 1994; Sivarao et al. 1997).

Next, we assess in rats whether the TRH-TRH-R1 signaling pathway plays a role as part of hindbrain mechanisms stimulating the vagus under conditions of central-vagally mediated gastric secretion. Martínez et al. (Martínez et al. 2002) developed a new model of gastric acid secretion in response to sham feeding induced by exposing fasted rats to sensory, visual and olfactory stimuli of smell and vision of Purina Chow without accessing to it. This induced an elevation of basal acid secretion within 10 min after the onset of sham-feeding reaching a peak increase of 130% over baseline at 20 min followed by a decline to basal levels thereafter. Moreover, the intracisternal injection of TRH-R1 antisense oligodeoxynucleotides given at doses that suppress gastric acid output stimulated by intracisternal TRH, blocked the acid response to the sight and smell of food while a TRH-R1 mismatched oligodeoxynucleotide had no effect under similar experimental conditions (Martínez et al. 2002) (fig. 3).

Of interest is also the demonstration that TRH in the brainstem-induce vagal stimulation of gastric secretory and motor function can be inhibited by several peptides innervating the DVC including those that play a role in the immune (interleukin-1, tumor necrosis factor- α) or stress (corticotrophin releasing factor, urocortin 1) responses, as well as other peptides innervating the DVC through their projections from the paraventricular nucleus of the hypothalamus (gastrin releasing peptide/bombesin) or central amygdala (calcitonin gene related peptide/adrenomedullin) (Morrow et al. 1995; Hughes et al. 1984; Martínez, Taché 2000; Hermann et al. 1999; Heymann et al. 1991; Chen et al. 2002; Taché, Bonaz 2007). It may be speculated that the centrally mediated inhibitory action of these peptides may have significance to curtail the cephalic phase of digestion under conditions of infections, stress, pain or fear, although it remains to be investigated.

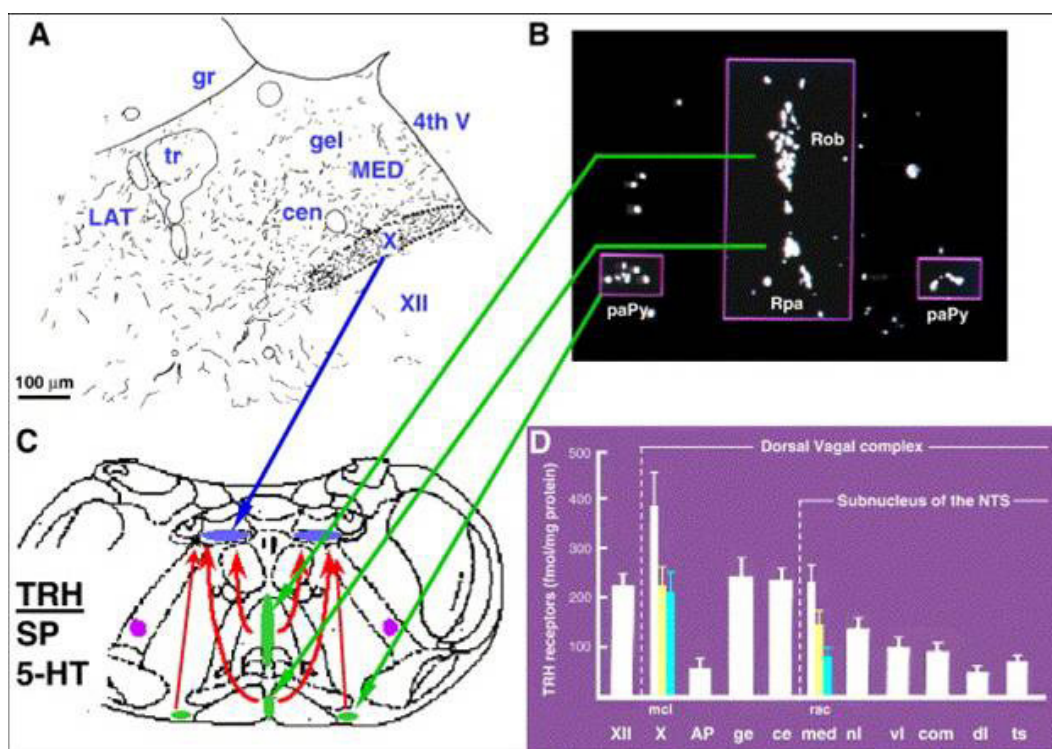
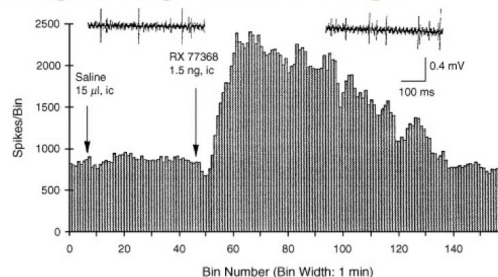


Fig. 1. TRH/TRH-R1 signaling pathways in the rat brain stem. Neuroanatomical evidence for a physiological role of brain medullary TRH. (A): Drawing of dense distribution of TRH-IR fibers in rats dorsal vagal complex (DVC) rostral to the obex. (B): TRH synthesizing neurons shown by *in situ* hybridization in the rat raphe obscurus (Rob), pallidus (Rpa) and bilateral parapyramidal nuclei (paPy). (C): Schematic representation of the rat medulla and projections of TRH synthesizing neurons to the dorsal motor nucleus. (D): High expression of TRH binding sites in the dorsal motor nucleus (X) including the medial portion projecting to the stomach

Intracisternal (ic) injection of RX 77368 (a stable TRH analog):

➤ A. Stimulates gastric vagal efferent discharges



O-Lee et al. *al. Peptides* 1997; 18:3-9

➤ B. induces a vagal dependent activation of gastric cholinergic myenteric neurons

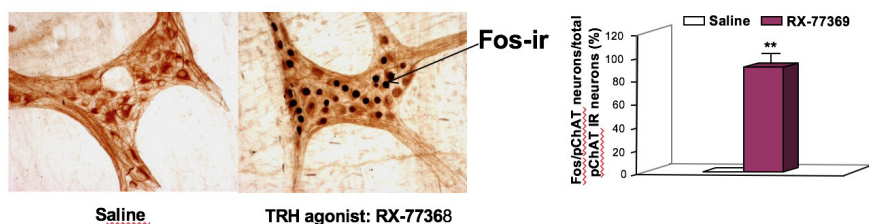


Fig. 2. Intracisternal injection of TRH analog activates efferent spike activity in the gastric branch of the vagus in urethane anesthetized rats (A) and gastric myenteric cholinergic neurons in conscious rats as showed by double labeling of Fos, a marker of neuronal activation, and peripheral acetyl cholinergic transferase as a marker of cholinergic neurons (B). (From O-Lee et al. 1997 and Yuan et al. 2005)

The cephalic phase of gastric acid secretion in rats: role of medullary TRH shown by blocking TRH-R1 synthesis

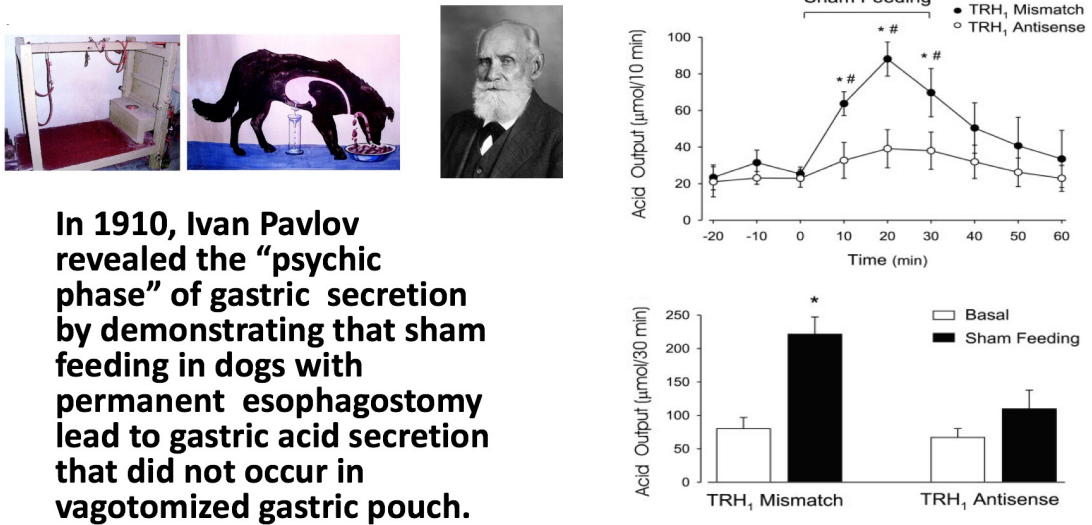


Fig. 3. The psychic phase of gastric secretion demonstrated in dogs by Pavlov and reproduced in rats by a sham feeding-induced increase in gastric acid output: suppression by selective blockade of TRH receptor 1 in the brainstem supporting a role of TRH signaling in the cephalic phase. (From Martínez et al. 2002)

Perspectives

Convergent experimental evidence supports that TRH synthesizing neurons in medullary raphe nuclei projecting to the DVC and TRH-R1 recep-

tors in the DVC have a physiological relevance in the vagal cholinergic dependent regulation of GI and pancreatic secretion and other vagally mediated gut response during the cephalic phase (fig. 4).

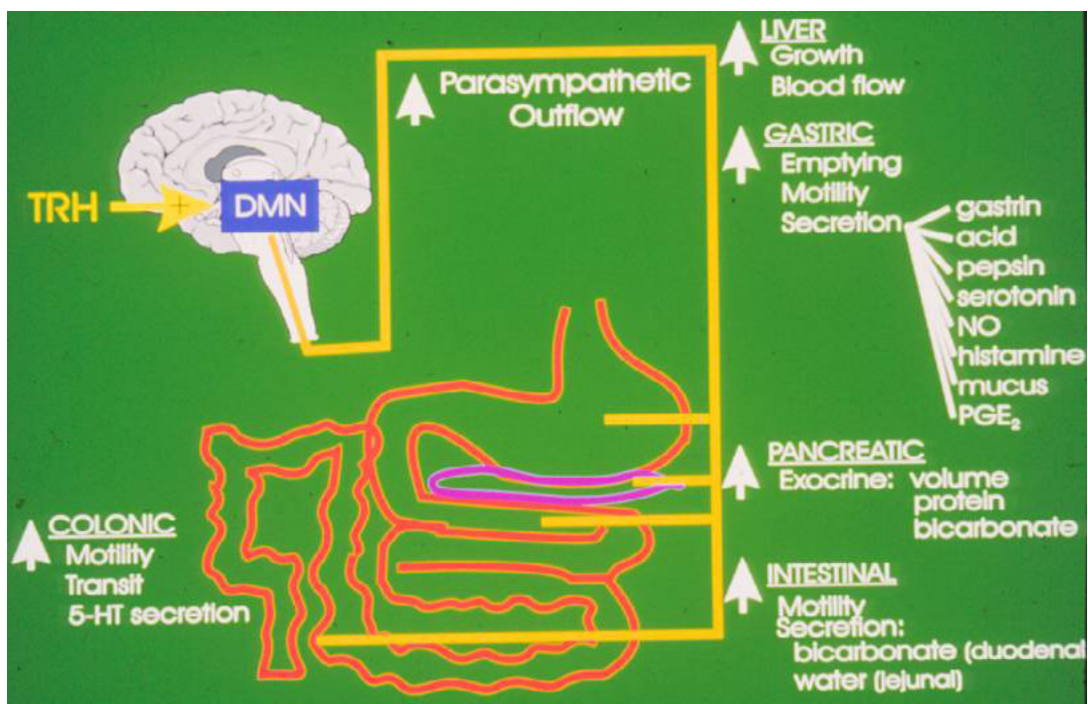


Fig. 4. Schematic representation of TRH interacting with TRH 1 receptor expressed on dorsal motor nucleus neurons as well as stimulation of gastric, pancreatic and intestinal function through the activation of vagal pathways

The DVC receives direct projections from forebrain sites including the parabrachial nucleus, mesencephalic periaqueductal gray, paraventricular and dorsomedial nucleus of the hypothalamus, lateral hypothalamus, central nucleus of amygdala, bed nucleus of stria terminalis, insular cortex, anterior cingulate cortex, and orbitofrontal cortex (Van der Kooy et al. 1984). It also gets input from gustatory afferents in the oral cavity (Van der Kooy et al. 1984). These circuits offer potential pathways by which sensory information of gustatory, olfactory, or visual nature

involved in the cephalic phase can influence neurons of the DVC. Whether the activation of TRH-TRH-R1 signaling in the brainstem represents a common final effector mechanism activated by forebrain and hindbrain neuronal circuit recruited during the cephalic phase warrant further investigations.

Conflict of interest

The author confirms that this article content has no conflict of interest.

References

- Barnes, M. J., Rogers, R. C., Van Meter, M. J., Hermann, G. E. (2010) Co-localization of TRHR1 and LepRb receptors on neurons in the hindbrain of the rat. *Brain Research*, vol. 1355, pp. 70–85. PMID: 20691166. DOI: 10.1016/j.brainres.2010.07.094 (In English)
- Bayliss, D. A., Viana, F., Kanter, R. K. et al. (1994) Early postnatal development of thyrotropin-releasing hormone (TRH) expression, TRH receptor binding, and TRH responses in neurons of rat brainstem. *Journal of Neurosciences*, vol. 14, no 2, pp. 821–833. PMID: 8301363. DOI: 10.1523/JNEUROSCI.14-02-00821.1994 (In English)
- Chen, C.-Y., Million, M., Adelson, D. W. et al. (2002) Intracisternal urocortin inhibits vagally stimulated gastric motility in rats: Role of CRF(2). *British Journal of Pharmacology*, vol. 136, no. 2, pp. 237–247. PMID: 12010772. DOI: 10.1038/sj.bjp.0704713 (In English)
- DelParigi, A., Chen, K., Salbe, A. D. et al. (2005) Sensory experience of food and obesity: A positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. *Neuroimage*, vol. 24, no. 2, pp. 436–443. PMID: 15627585. DOI: 10.1016/j.neuroimage.2004.08.035 (In English)
- Feldman, M., Richardson, C. T. (1986) Role of thought, sight, smell and taste of food in the cephalic phase of gastric acid secretion in humans. *Gastroenterology*, vol. 90, no. 2, pp. 426–433. PMID: 3940915. DOI: 10.1016/0016-5085(86)90943-1 (In English)
- Fodor, M., Pammer, C., Görcs, T., Palkovits, M. (1994) Neuropeptides in the human dorsal vagal complex: An immunohistochemical study. *Journal of Chemical Neuroanatomy*, vol. 7, no. 3, pp. 141–157. PMID: 7848571. DOI: 10.1016/0891-0618(94)90025-6 (In English)
- Garrick, T., Prince, M., Yang, H. et al. (1994) Raphe pallidus stimulation increases gastric contractility via TRH projections to the dorsal vagal complex in rats. *Brain Research*, vol. 636, no. 2, pp. 343–347. PMID: 7912160. DOI: 10.1016/0006-8993(94)91035-9 (In English)
- Gershengorn, M. C., Osman, R. (1996) Molecular and cellular biology of thyrotropin-releasing hormone receptors. *Physiological Reviews*, vol. 76, no. 1, pp. 175–191. PMID: 8592728. DOI: 10.1152/physrev.1996.76.1.175 (In English)
- Giduck, S. A., Threatte, R. M., Kare, M. R. (1987) Cephalic reflexes: Their role in digestion and possible roles in absorption and metabolism. *The Journal of Nutrition*, vol. 117, no. 7, pp. 1191–1196. PMID: 3302135. DOI: 10.1093/jn/117.7.1191 (In English)
- Goldschmiedt, M., Redfern, J. S., Feldman, M. (1990) Food coloring and monosodium glutamate: Effects on the cephalic phase of gastric acid secretion and gastrin release in humans. *American Journal of Clinical Nutrition*, vol. 51, no. 5, pp. 794–797. PMID: 2333838. DOI: 10.1093/ajcn/51.5.794 (In English)
- Güemes, A., Herrero, P., Bondia, J., Georgiou, P. (2019) Modeling the effect of the cephalic phase of insulin secretion on glucose metabolism. *Medical & Biological Engineering & Computing*, vol. 57, no. 6, pp. 1173–1186. PMID: 30685858. DOI: 10.1007/s11517-019-01950-x (In English)
- Hermann, G. E., Tovar, C. A., Rogers, R. C. (1999) Induction of endogenous tumor necrosis factor- α : Suppression of centrally stimulated gastric motility. *The American Journal of Physiology*, vol. 276, no. 1, pp. R59–R68. PMID: 9887178. DOI: 10.1152/ajpregu.1999.276.1.R59 (In English)
- Heuer, H., Schäfer, M. K., O'Donnell, D. et al. (2000) Expression of thyrotropin-releasing hormone receptor 2 (TRH-R2) in the central nervous system of rats. *The Journal of Comparative Neurology*, vol. 428, no. 2, pp. 319–336. PMID: 11064370 (In English)
- Heymann-Mönnikes, I., Taché, Y., Trauner, M. et al. (1991) CRF microinjected into the dorsal vagal complex inhibits TRH analog- and kainic acid-stimulated gastric contractility in rats. *Brain Research*, vol. 554, no. 1–2, pp. 139–144. PMID: 1933296. DOI: 10.1016/0006-8993(91)90181-t (In English)

- Holst, M. C., Kelly, J. B., Powley, T. L. (1997) Vagal preganglionic projections to the enteric nervous system characterized with Phaseolus vulgaris-leucoagglutinin. *The Journal of Comparative Neurology*, vol. 381, no. 1, pp. 81–100. PMID: 9087421. DOI: 10.1002/(sici)1096-9861(19970428)381:1<81::aid-cne7>3.0.co;2-g (In English)
- Hornby, P. J., Rossiter, C. D., Kuhn, D. H. Jr. et al. Neuroactive substances in medullary nuclei that control parasympathetic outflow to the stomach. In: Y. Taché, D. L. Wingate (eds.). *Brain-gut interactions*. Boca Raton: CRC Press, pp. 23–43. (In English)
- Hughes, J. J., Levin, A. S., Morley, J. E. et al. (1984) Intraventricular calcitonin gene-related peptide inhibits gastric acid secretion. *Peptides*, vol. 5, no. 4, pp. 665–667. PMID: 6436796. DOI: 10.1016/0196-9781(84)90003-2 (In English)
- Iwase, M., Homma, I., Shioda, S., Nakai, Y. (1988) Thyrotropin-releasing hormone-like immunoreactive neurons in rabbit medulla oblongata. *Neuroscience Letters*, vol. 92, no. 1, pp. 30–33. PMID: 3141847. DOI: 10.1016/0304-3940(88)90737-9 (In English)
- Kaneko, H., Kaunitz, J., Taché, Y. (1998) Vagal mechanisms underlying gastric protection induced by chemical activation of the raphe pallidus in rats. *The American Journal of Physiology*, vol. 275, no. 5, pp. G1056–G1062. PMID: 9815036. DOI: 10.1152/ajpgi.1998.275.5.G1056 (In English)
- Kaneko, H., Yang, H., Ohning, G., Taché, Y. (1995) Medullary TRH is involved in gastric protection induced by low dose of kainic acid into the raphe pallidus. *The American Journal of Physiology*, vol. 268, no. 4, pp. G548–G552. PMID: 7733282. DOI: 10.1152/ajpgi.1995.268.4.G548 (In English)
- Katschinski, M. (2000) Nutritional implications of cephalic phase gastrointestinal responses. *Appetite*, vol. 34, no. 2, pp. 189–196. PMID: 10744909. DOI: 10.1006/appe.1999.0280 (In English)
- Katschinski, M., Dahmen, G., Reinshagen, M. et al. (1992) Cephalic stimulation of gastrointestinal secretory and motor responses in humans. *Gastroenterology*, vol. 103, no. 2, pp. 383–391. PMID: 1634057. DOI: 10.1016/0016-5085(92)90825-j (In English)
- Király, A., Sütö, G., Guth, P. H., Taché, Y. (1998) Peripheral mediators involved in gastric hyperemia to vagal activation by central TRH analog in rats. *The American Journal of Physiology*, vol. 274, no. 1, pp. G170–G177. PMID: 9458786. DOI: 10.1152/ajpgi.1998.274.1.G170 (In English)
- Kovacs, T. O., Lloyd, K. C., Lawson, D. C. et al. (1997) Inhibition of sham feeding-stimulated acid secretion in dogs by immunoneutralization of gastrin. *The American Journal of Physiology*, vol. 273, no. 2, pp. G399–G403. PMID: 9277419. DOI: 10.1152/ajpgi.1997.273.2.G399 (In English)
- Krammer, H. J., Karahan, S. T., Rumpel, E. et al. (1993) Immunohistochemical visualization of the enteric nervous system using antibodies against protein gene product (PGP) 9.5. *Anatomischer Anzeiger*, vol. 175, no. 4, pp. 321–325. PMID: 8363037. DOI: 10.1016/s0940-9602(11)80029-4 (In English)
- Livingston, C. A., Berger, A. J. (1993) Response of neurons in the dorsal motor nucleus of the vagus to thyrotropin-releasing hormone. *Brain Research*, vol. 621, no. 1, pp. 97–105. PMID: 8221078. DOI: 10.1016/0006-8993(93)90302-4 (In English)
- Lynn, R. B., Kreider, M. S., Miselis, R. R. (1991) Thyrotropin-releasing hormone-immunoreactive projections to the dorsal motor nucleus and the nucleus of the solitary tract of the rat. *The Journal of Comparative Neurology*, vol. 311, no. 2, pp. 271–288. PMID: 1753019. DOI: 10.1002/cne.903110208 (In English)
- Manaker, S., Rizio, G. (1989) Autoradiographic localization of thyrotropin-releasing hormone and substance P receptors in the rat dorsal vagal complex. *The Journal of Comparative Neurology*, vol. 290, no. 4, pp. 516–526. PMID: 2559109. DOI: 10.1002/cne.902900406 (In English)
- Martínez, V., Barrachina, M. D., Ohning, G., Taché, Y. (2002) Cephalic phase of acid secretion involves activation of medullary TRH receptor subtype 1 in rats. *American Journal of Physiology*, vol. 283, no. 6, pp. G1310–G1319. PMID: 12388176. DOI: 10.1152/ajpgi.00222.2002 (In English)
- Martínez, V., Taché, Y. (2000) Bombesin and the brain-gut axis. *Peptides*, vol. 21, no. 11, pp. 1617–1625. PMID: 11090915. DOI: 10.1016/s0196-9781(00)00293-x (In English)
- Mattes, R. D. (1997) Physiologic responses to sensory stimulation by food: Nutritional implications. *Journal of American Dietetic Association*, vol. 97, no. 4, pp. 406–413. DOI: 10.1016/S0002-8223(97)00101-6 (In English)
- McCann, M. J., Hermann, G. E., Rogers, R. C. (1989) Thyrotropin-releasing hormone: Effects on identified neurons of the dorsal vagal complex. *Journal of Autonomic Nervous System*, vol. 26, no. 2, pp. 107–112. PMID: 2498419. DOI: 10.1016/0165-1838(89)90158-6 (In English)
- Miampamba, M., Million, M., Taché, Y. (2011) Brain-gut interactions between central vagal activation and abdominal surgery to influence gastric myenteric ganglia Fos expression in rats. *Peptides*, vol. 32, no. 5, pp. 1078–1082. PMID: 21376096. DOI: 10.1016/j.peptides.2011.02.018 (In English)
- Miampamba, M., Yang, H., Sharkey, K. A., Taché, Y. (2001) Intracisternal TRH analog induces Fos expression in gastric myenteric neurons and glia in conscious rats. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, vol. 280, no. 5, pp. G979–G991. PMID: 11292608. DOI: 10.1152/ajpgi.2001.280.5.G979 (In English)
- Morrow, N. S., Quinonez, G., Weiner, H. et al. (1995) Interleukin-1 beta in the dorsal vagal complex inhibits TRH analogue-induced stimulation of gastric contractility. *The American Journal of Physiology*, vol. 269, no. 2, pp. G196–G202. PMID: 7653558. DOI: 10.1152/ajpgi.1995.269.2.G196 (In English)

- O'Dowd, B. F., Lee, D. K., Huang, W. et al. (2000) TRH-R2 exhibits similar binding and acute signaling but distinct regulation and anatomic distribution compared with TRH-R1. *Molecular Endocrinology*, vol. 14, no. 1, pp. 183–193. PMID: 10628757. DOI: 10.1210/mend.14.1.0407 (In English)
- Ohara, I., Otsuka, S., Yugari, Y. (1988) Cephalic phase response of pancreatic exocrine secretion in conscious dogs. *The American Journal of Physiology*, vol. 254, no. 3, pp. G424–G428. PMID: 3348407. DOI: 10.1152/ajpgi.1988.254.3.G424 (In English)
- Okumura, T., Taylor, I. L., Pappas, T. N. (1995) Microinjection of TRH analogue into the dorsal vagal complex stimulates pancreatic secretion in rats. *American Journal of Physiology*, vol. 269, no. 3, pp. G328–G334. DOI: 10.1152/ajpgi.1995.269.3.G328 (In English)
- O-Lee, T. J., Wei, J. Y., Taché, Y. (1997) Intracisternal TRH and RX 77368 potently activate vagal efferent discharge in rats. *Peptides*, vol. 18, no. 2, pp. 213–219. PMID: 9149293. DOI: 10.1016/s0196-9781(96)00281-1 (In English)
- Pavlov, I. P. (1910) *The work of the digestive glands*. 2nd ed. London: C. Griffin & Company limited, 266 p. (In English)
- Power, M. L., Schulkin, J. (2008) Anticipatory physiological regulation in feeding biology: Cephalic phase responses. *Appetite*, vol. 50, no. 2–3, pp. 194–206. PMID: 18045735. DOI: 10.1016/j.appet.2007.10.006 (In English)
- Powley, T. L. (2000) Vagal circuitry mediating cephalic-phase responses to food. *Appetite*, vol. 34, no. 2, pp. 184–188. PMID: 10744908. DOI: 10.1006/appe.1999.0279 (In English)
- Powley, T. L., Berthou, H.-R., Precht, J. C., Fox, A. E. (1991) Fibers of the vagus regulating gastrointestinal function. In: Y. Taché, D. Wingate (eds.). *Brain-gut interactions*. Boca Raton: CRC Press, pp. 73–82. (In English)
- Raggenbass, M., Vozzi, C., Tribollet, E. et al. (1990) Thyrotropin-releasing hormone causes direct excitation of dorsal vagal and solitary tract neurones in rat brainstem slices. *Brain Research*, vol. 530, no. 1, pp. 85–90. PMID: 2125519. DOI: 10.1016/0006-8993(90)90659-y (In English)
- Rinaman, L., Miselis, R. R. (1990) Thyrotropin-releasing hormone-immunoreactive nerve terminals synapse on the dendrites of gastric vagal motoneurons in the rat. *The Journal of Comparative Neurology*, vol. 294, no. 2, pp. 235–251. PMID: 2110196. DOI: 10.1002/cne.902940208 (In English)
- Rinaman, L., Miselis, R. R., Kreider, M. S. (1989) Ultrastructural localization of thyrotropin-releasing hormone immunoreactivity in the dorsal vagal complex in rat. *Neuroscience Letters*, vol. 104, no. 1–2, pp. 7–12. PMID: 2510095. DOI: 10.1016/0304-3940(89)90320-0 (In English)
- Rindi, G., Leiter, A. B., Kopin, A. S. et al. (2004) The “normal” endocrine cell of the gut: Changing concepts and new evidences. *Annals of the New York Academy of Sciences*, vol. 1014, pp. 1–12. PMID: 15153415. DOI: 10.1196/annals.1294.001 (In English)
- Rogers, J., Raimundo, A. H., Misiewicz, J. J. (1993) Cephalic phase of colonic pressure response to food. *Gut*, vol. 34, no. 4, pp. 537–543. PMID: 8491403. DOI: 10.1136/gut.34.4.537 (In English)
- Simonian, H. P., Kresge, K. M., Boden, G. H., Parkman, H. P. (2005) Differential effects of sham feeding and meal ingestion on ghrelin and pancreatic polypeptide levels: Evidence for vagal efferent stimulation mediating ghrelin release. *Neurogastroenterology and Motility*, vol. 17, no. 3, pp. 348–354. PMID: 15916622. DOI: 10.1111/j.1365-2982.2004.00634.x (In English)
- Sivarao, D. V., Krowicki, Z. K., Abrahams, T. P., Hornby, P. J. (1997) Intracisternal antisense oligonucleotides to TRH receptor abolish TRH-evoked gastric motor excitation. *The American Journal of Physiology*, vol. 272, no. 6, pp. G1372–G1381. PMID: 9227472. DOI: 10.1152/ajpgi.1997.272.6.G1372 (In English)
- Smeets, P. A. M., Erkner, A., de Graaf, C. (2010) Cephalic phase responses and appetite. *Nutrition Reviews*, vol. 68, no. 11, pp. 643–655. PMID: 20961295. DOI: 10.1111/j.1753-4887.2010.00334.x (In English)
- Sobhani, I., Buyse, M., Goïot, H. et al. (2002) Vagal stimulation rapidly increases leptin secretion in human stomach. *Gastroenterology*, vol. 122, no. 2, pp. 259–263. PMID: 11832440. DOI: 10.1053/gast.2002.31385 (In English)
- Somiya, H., Tonoue, T. (1984) Neuropeptides as central integrators of autonomic nerve activity: Effects of TRH, SRIF, VIP and bombesin on gastric and adrenal nerves. *Regulatory Peptides*, vol. 9, no. 1–2, pp. 47–52. PMID: 6150518. DOI: 10.1016/0167-0115(84)90006-5 (In English)
- Taché, Y., Adelson, D., Yang, H. (2014) TRH/TRH-R1 receptor signaling in the brain medulla as a pathway of vagally mediated gut responses during the cephalic phase. *Current Pharmaceutical Design*, vol. 20, no. 16, pp. 2725–2730. PMID: 23886382. DOI: 10.2174/13816128113199990578 (In English)
- Taché, Y., Bonaz, B. (2007) Corticotropin-releasing factor receptors and stress-related alterations of gut motor function. *The Journal of Clinical Investigation*, vol. 117, no. 1, pp. 33–40. PMID: 17200704. DOI: 10.1172/JCI30085 (In English)
- Taché, Y., Goto, Y., Hamel, D. et al. (1985) Mechanisms underlying intracisternal TRH-induced stimulation of gastric acid secretion in rats. *Regulatory Peptides*, vol. 13, no. 1, pp. 21–30. PMID: 3937184. DOI: 10.1016/0167-0115(85)90083-7 (In English)
- Taché, Y., Goto, Y., Lauffenburger, M., Lesiege, D. (1984) Potent central nervous system action of p-Glu-His-(3,3'-dimethyl)-Pro NH₂, a stabilized analog of TRH, to stimulate gastric secretion in rats. *Regulatory Peptides*, vol. 8, no. 1, pp. 71–78. DOI: 10.1016/0167-0115(84)90030-2 (In English)
- Taché, Y., Stephens, R. L., Ishikawa, T. (1989) Central nervous system action of TRH to influence gastrointestinal function and ulceration. *Annals of the New York Academy of Sciences*, vol. 553, pp. 269–285. PMID: 2497674. DOI: 10.1111/j.1749-6632.1989.tb46649.x (In English)

- Taché, Y., Vale, W., Brown, M. (1980) Thyrotropin-releasing hormone-CNS action to stimulate gastric acid secretion. *Nature*, vol. 287, no. 5778, pp. 149–151. PMID: 6776408. DOI: 10.1038/287149a0 (In English)
- Taché, Y., Vale, W., Rivier J., Brown, M. (1981) Brain regulation of gastric acid secretion in rats by neurogastrointestinal peptides. *Peptides*, vol. 2, suppl. 2, pp. 51–55. PMID: 6123991. DOI: 10.1016/0196-9781(81)90010-3 (In English)
- Taché, Y., Yang, H., Kaneko, H. (1995) Caudal raphe-dorsal vagal complex peptidergic projections: Role in gastric vagal control. *Peptides*, vol. 16, no. 3, pp. 431–435. PMID: 7544464. DOI: 10.1016/0196-9781(94)00212-o (In English)
- Taché, Y., Yang, H., Miampamba, M. et al. (2006) Role of brainstem TRH/TRH-R1 receptors in the vagal gastric cholinergic response to various stimuli including sham-feeding. *Autonomic Neurosciences: Basic and Clinical*, vol. 125, no. 1–2, pp. 42–52. PMID: 16520096. DOI: 10.1016/j.autneu.2006.01.014 (In English)
- Taché, Y., Yang, H., Yoneda, M. (1993) Vagal regulation of gastric function involves thyrotropin-releasing hormone in the medullary raphe nuclei and dorsal vagal complex. *Digestion*, vol. 54, no. 2, pp. 65–72. PMID: 8319841. DOI: 10.1159/000201015 (In English)
- Travagli, R. A., Gillis, R. A., Vicini, S. (1992) Effects of thyrotropin-releasing hormone on neurons in the rat dorsal motor nucleus of the vagus, in vitro. *The American Journal of Physiology*, vol. 263, no. 4, pp. G508–G517. PMID: 1329553. DOI: 10.1152/ajpgi.1992.263.4.G508 (In English)
- Van der Kooy, D., Koda, L. Y., McGinty, J. F. et al. (1984) The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. *The Journal of Comparative Neurology*, vol. 224, no. 1, pp. 1–24. PMID: 6715573. DOI: 10.1002/cne.902240102 (In English)
- White, R. L. Jr., Rossiter, C. D., Hornby, P. J. et al. (1991) Excitation of neurons in the medullary raphe increases gastric acid and pepsin production in cats. *The American Journal of Physiology*, vol. 260, no. 1, pp. G91–G96. PMID: 1899009. DOI: 10.1152/ajpgi.1991.260.1.G91 (In English)
- Yang, H., Ohning, G., Taché, Y. (1993) TRH in dorsal vagal complex mediates acid response to excitation of raphe pallidus neurons in rats. *The American Journal of Physiology*, vol. 265, no. 5, pp. G880–G886. PMID: 8238517. DOI: 10.1152/ajpgi.1993.265.5.G880 (In English)
- Yang, H., Taché, Y., Ohning, G., Go, V. L. W. (2002) Activation of raphe pallidus neurons increases insulin through medullary thyrotropin-releasing hormone (TRH)-vagal pathways. *Pancreas*, vol. 25, no. 3, pp. 301–307. PMID: 12370543. DOI: 10.1097/00006676-200210000-00014 (In English)
- Yang, H., Yuan, P.-Q., Wang, L., Taché, Y. (2000) Activation of the parapyramidal region in the ventral medulla stimulates gastric acid secretion through vagal pathways in rats. *Neuroscience*, vol. 95, no. 3, pp. 773–779. PMID: 10670444. DOI: 10.1016/s0306-4522(99)00490-x (In English)
- Yoneda, M., Goto, M., Nakamura, K. et al. (2005) Thyrotropin-releasing hormone in the dorsal vagal complex stimulates pancreatic blood flow in rat. *Regulatory Peptides*, vol. 131, no. 1–3, pp. 74–81. PMID: 16040141. DOI: 10.1016/j.regpep.2005.06.010 (In English)
- Yuan, P.-Q., Kimura, H., Million, M. et al. (2005) Central vagal stimulation activates enteric cholinergic neurons in the stomach and VIP neurons in the duodenum in conscious rats. *Peptides*, vol. 26, no. 4, pp. 653–664. PMID: 15752581. DOI: 10.1016/j.peptides.2004.11.015 (In English)
- Zafra, M. A., Molina, F., Puerto, A. (2006) The neural/cephalic phase reflexes in the physiology of nutrition. *Neuroscience & Biobehavioral Reviews*, vol. 30, no. 7, pp. 1032–1044. PMID: 16678262. DOI: 10.1016/j.neubiorev.2006.03.005 (In English)