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Vagal neurocircuitry and its influence on gastric motility

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Abstract

A large body of research has been dedicated to the effects of gastrointestinal peptides on vagal afferent fibres, yet multiple lines of evidence indicate that gastrointestinal peptides also modulate brainstem vagal neurocircuitry, and that this modulation has a fundamental role in the physiology and pathophysiology of the upper gastrointestinal tract. In fact, brainstem vagovagal neurocircuits comprise highly plastic neurons and synapses connecting afferent vagal fibres, second order neurons of the nucleus tractus solitarius (NTS), and efferent fibres originating in the dorsal motor nucleus of the vagus (DMV). Neuronal communication between the NTS and DMV is regulated by the presence of a variety of inputs, both from within the brainstem itself as well as from higher centres, which utilize an array of neurotransmitters and neuromodulators. Because of the circumventricular nature of these brainstem areas, circulating hormones can also modulate the vagal output to the upper gastrointestinal tract. This Review summarizes the organization and function of vagovagal reflex control of the upper gastrointestinal tract, presents data on the plasticity within these neurocircuits after stress, and discusses the gastrointestinal dysfunctions observed in Parkinson disease as examples of physiological adjustment and maladaptation of these reflexes.

A rich body of literature spanning the past few decades describes the intrinsic neural circuits of the myenteric and submucosal plexuses as well as the interstitial cells of Cajal (ICCs), and the role these structures have in confer ring the gastrointestinal tract with substantial autonomy over physiological functions including motility, secretion and absorption^{1–3}. Extrinsic neural inputs originating in the central nervous system (CNS) provide fine modulation of these functions, especially in the upper gastrointestinal tract. In particular, brainstem vagovagal parasympathetic neurocircuits have the most prominent role in the CNS-mediated control of upper gastrointestinal tract motility; the lower third of the

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Author contributions

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Competing interests statement

The authors declare no competing interests.

Review criteria

For this Review we conducted PubMed database searches involving combinations of terms that included “vagus, brainstem, gastric motility, stress, Parkinson’s disease, Huntington, ALS, fibromyalgia”. Together, the authors have a combined ~30 years of experience in the field of vagal pathophysiology with much of their work associated with electrophysiology, pharmacology, immunohistochemistry and *in vivo* animal models of gastrointestinal motility. This combined experience formed the basis of this Review.

oesophagus and stomach are heavily dependent on extrinsic neural pathways originating in the CNS³⁻⁵.

Historically, vagovagal neurocircuits and reflexes were believed to be 'static' in their contribution to the control of gastrointestinal functions, whereby sensory signals conveyed from the gut to the brainstem generate a motor response that is relayed back to the gut in a reflexive manner (that is, the synaptic signal is not modulated by input from other neurocircuits). However, this viewpoint has changed in the past few years and the plasticity and integrative capacities of these neurocircuits are now recognized in both physiological and pathological states⁵⁻⁸. The importance of vagal reflexes is also highlighted by observations that increased vagal tone is linked with higher resilience and adaptation to stress, whereas low vagal tone reflects vulnerability to pathological states⁹⁻¹¹.

Vagovagal neurocircuits

Vagovagal neurocircuits comprise specific nuclei, all of which are located within the caudal brainstem: the nucleus tractus solitarius (NTS), the dorsal motor nucleus of the vagus (DMV) and the nucleus ambiguus (FIG. 1). NTS neurons receive visceral sensory information, whereas the DMV and the nucleus ambiguus are the nuclei of origin of vagal motor fibres. The efferent fibres from the nucleus ambiguus and the DMV form synaptic contacts with postganglionic neurons located in the target organ and, ultimately, modulate gastric motility as well as other visceral functions.

NTS

Second-order neurons of the NTS comprise neurochemically and biophysically distinct neurons that receive sensory information conveyed by vagal, aortic depressor and glossopharyngeal nerves from the subdiaphragmatic gastrointestinal viscera, as well as from gustatory, oesophageal and cardiorespiratory areas^{4,12-14}. Several types of vagal afferent fibres carry a large volume of mechanical, chemical or osmotic information from the viscera to the NTS, where it undergoes integration with brainstem, limbic and hypothalamic signals and, ultimately, provides appropriate coordination of gastric reflexes, motility and emptying^{15,16}. Independently of the type of sensory information relayed to the CNS, afferent vagal fibres use glutamate as their main neurotransmitter, which activates ionotropic and metabotropic receptors^{5,12,13}. However, the NTS subnucleus receiving the afferent input varies according to the visceral source. For example, the NTS centralis subnucleus receives information exclusively related to the oesophagus, whereas subsets of neurons of the NTS medialis receive information from the stomach as well as from the aortic depressor nerve. The NTS intermedialis and interstitialis sub nuclei receive sensory information from both the larynx and pharynx, and neurons of the rostral NTS integrate taste-related signals. The separate sub nuclei within the NTS are therefore more easily identified by the origin of the visceral inputs than the morphological, neurochemical or biophysical characteristics of the NTS neuron itself^{12,14,17-21}. Although subgroups of neurons have defined neurochemical phenotypes, these neurons are not located in defined NTS subnuclei nor are they linked to specific visceral organs^{18,22-25}.

NTS neurons are of medium size (10–15 μm diameter) and contain a large array of receptors and neurotransmitters, including fast neurotransmitters such as γ -aminobutyric acid (GABA), glutamate, catecholamines and glycine, as well as a vast range of neuropeptides such as somatostatin, glucagon-like peptide 1 (GLP-1) and enkephalins, which have fundamental roles in the modulation of neuronal activity^{5,23,26–28}. The majority of NTS neurons do not fire action potentials spontaneously, and are instead activated by synaptic activity originating from vagal afferent inputs and circulating hormones that reach the circumventricular areas of the NTS^{12,29,30} or by inputs from other brainstem areas or higher nuclei, such as the paraventricular nucleus (PVN) of the hypothalamus or the medullary raphe nuclei⁵. NTS neurons integrate this information and send axonal projections to adjacent motor nuclei, such as the DMV (involved in the fine modulation of gastric motility) or the caudal ventrolateral medulla (involved in baroreceptor neurocircuits), as well as more distant higher CNS centres, such as the hypothalamus (involved in homeostasis)^{5,31–33}.

Nucleus ambiguus

Neurons of the nucleus ambiguus provide the parasympathetic innervation of the pharynx and larynx—and the lower third of the oesophagus in species in which this organ is composed of striated muscle, such as the rat^{13,34}. As in the NTS, nucleus ambiguus neurons are organized in a viscerotopic manner, whereby neurons innervating the oesophagus are located in the rostral compact formation, whereas neurons innervating the pharynx and the larynx are located in the intermediate and caudal semi-compact portions of the nucleus, respectively¹³. In rodents, nucleus ambiguus neurons have no direct projections to the stomach and do not seem to play a prominent part in the control of upper gastrointestinal and gastric motility; we refer the reader to more specialized reviews on motor control of the oesophagus^{13,35}.

DMV

In humans, cats, rabbits and ferrets, in which the lower oesophagus is composed of smooth muscle, the DMV encompasses the preganglionic parasympathetic neurons that provide the vagal motor output to the gastro intestinal tract, from the lower oesophagus to the transverse colon³⁶ (FIG. 1). DMV neurons are organized in rostrocaudal spanning columns, which represent the five subdiaphragmatic branches of the vagus nerve: the anterior gastric, hepatic and accessory coeliac branches originate from neurons of the left DMV, whereas the posterior gastric and the coeliac branches originate from neurons of the right DMV^{37,38}. In humans, the DMV comprises nine subnuclei with six different neuronal groups that can be distinguished based on their cytoarchitectural and chemoarchitectural features³⁹. In rats and mice, DMV neurons do not seem to be segregated into distinguishable subnuclei, although in rats DMV neurons can be differentiated based on a combination of their morphological and biophysical features^{40–42}, which seem to be related to the organs they project to rather than the function they control^{40,43}.

A distinguishing feature of DMV neurons is their slow, spontaneous intrinsic pacemaking activity⁴⁴, a corollary of which is that major changes in vagal motor output to the stomach can be obtained by synaptically driven changes in the membrane potential of DMV neurons of only a few millivolts⁴⁵. The synaptic inputs to DMV neurons that are most relevant to the

modulation of vagovagal reflexes originate in the NTS⁴⁴. Of these synapses, GABAergic projections seem to have the most important role in the control of DMV neuronal action potential firing rate and hence regulation of vagal efferent output that controls gastric tone and motility^{45,46}. Indeed, blockade of GABAergic transmission between the NTS and DMV by the GABA_A antagonist bicuculline increases the firing rate of most DMV neurons⁴⁵ and increases gastric motility and tone⁴⁶.

The size of DMV neurons seems similar across species (~20–25 µm in diameter)^{39–41,43} and their membranes contain a vast assortment of receptors that are activated by diverse ligands. These ligands include circulating hormones such as cholecystokinin (CCK) or GLP-1 (discussed later) and neurotransmitters released by synaptic projections arising from adjacent structures, such as the NTS^{17,44}, the area postrema⁴⁷ and the medullary raphe nuclei⁴⁸, as well as by projections from higher centres such as the PVN of the hypothalamus⁵.

The vast majority of DMV neurons are cholinergic^{18,49} and release acetylcholine onto nicotinic receptors located on the postganglionic neurons within the organ of interest⁵⁰. Other neurotransmitter-synthesizing enzymes are also found within the DMV, including nitric oxide synthase and tyrosine 3-monooxygenase (also known as tyrosine 3-hydroxylase). Both of these enzymes are found in the medial–caudal or the rostralateral areas of the DMV, areas that purportedly send inhibitory projections to the stomach; the role of brainstem nitergic or catecholaminergic DMV neurons in the control of gastric motility, however, is still unclear^{18,49,51,52}.

Gastric vagal efferent fibres contact nearly all postganglionic neurons within the ganglionated myenteric plexus of the rat stomach and proximal duodenum³⁶. The number of neuronal contacts and thereby the influence of the efferent vagus on gastrointestinal motor and secretory functions declines dramatically in the aboral direction, such that a direct vagal influence seems absent in structures distal to the splenic flexure^{4,36}. Postganglionic neurons of the myenteric plexus are embedded between the longitudinal and circular smooth muscle of the gastrointestinal tract, and form two distinct effector pathways that influence gastrointestinal motility: a tonic excitatory pathway that uses acetylcholine to induce muscarinicreceptor-mediated contraction of the smooth muscle; and a nonadrenergic noncholinergic (NANC) inhibitory pathway that, upon stimulation, induces smooth muscle relaxation via release of vasoactive intestinal poly peptide (VIP) or nitric oxide^{4,53}. Notably, the postganglionic cholinergic pathway seems to have a major role in setting the level of basal gastric tone and motility. Systemic administration of the muscarinic receptor antagonist atropine markedly reduces both gastric tone and motility⁴. Conversely, systemic administration of nitric oxide synthase or VIP inhibitors has minimal effect on gastric tone and motility⁴, suggesting the NANC inhibitory pathway is not active tonically.

Neuroanatomy of vagovagal reflexes

The proper pattern of gastric contractile activity is determined by the complex interplay between the enteric nervous system (ENS), ICCs, smooth muscle cells and their vagal inputs. Although there are many types of vagovagal reflexes, including oesophagogastric

(receptive relaxation), gastrogastic (accommodation) and duodenogastric (duodenal brake) reflexes, they share common features, notably the activation of mechanoreceptors and/or chemoreceptors within the walls of the gastrointestinal tract, followed by feedback regulation of gastric compliance, motility and emptying. Although the fine details of the neurocircuitry underlying these reflexes remains elusive, it probably involves a sensory–motor loop that comprises the NTS and the DMV, which together with the area postrema make up the brainstem vagal structures of the dorsal vagal complex (DVC) (FIG. 2).

The receptive relaxation reflex

One of the brainstem vagovagal neurocircuits that has provided a wealth of neurophysiological information in the past few years is the oesophagogastric or receptive relaxation reflex (RRR), first described by Walter Cannon in seminal manuscripts at the beginning of the 20th century^{54,55}. The RRR is triggered by distention of the distal oesophagus and induces an increase in gastric compliance (that is, a reduction of gastric tone), thereby allowing the bolus of ingested material to enter the gastric fundus with, under physiological conditions, a minimal increase in intragastric pressure. The RRR has been modelled experimentally; for example, inflation of a latex balloon inserted into the lower oesophagus decreases fundic motility and tone⁵⁶. Neurophysiological and anatomical studies have shown that the initial stimulation of low threshold mechanoreceptive vagal sensory oesophageal afferents activates catecholaminergic neurons of the NTS centralis which, in turn, excite preganglionic neurons of the DMV, resulting in the activation of inhibitory NANC vagal efferent projections and gastric relaxation via release of nitric oxide. At the same time, a distinct and separate subgroup of DMV neurons is inhibited by oesophageal inflation; inhibition of these preganglionic vagal neurons of the DMV probably induces reduced activity in the tonically active excitatory cholinergic, muscarinic efferent motor pathways. The result obtained upon oesophageal distention is the vagally mediated gastric relaxation characteristic of the RRR^{4,56–58}.

The RRR is probably altered in pathological conditions; for example, alterations of vagal sensory–motor functions are found in many patients with functional dyspepsia and underlie the presence of symptoms such as early satiety, impaired gastric emptying and reduced gastric compliance^{59–62}. However, the mechanism(s) responsible for these pathophysiological alterations in vagal neurocircuitry are unclear and in dire need of further investigation in animal models. One such investigation using an animal model was described a few years ago in a study by Liu *et al.*⁶³. Neonatal rat pups were gavaged for 6 days with a mild irritant (0.1% iodoacetamide); 8–10 weeks later, gastric motor function and behavioural, visceromotor and nerve fibre responses following gastric balloon distention were investigated. This model demonstrated that early gastric irritation induced delayed hypersensitivity and gastric motor dysfunction similar to observations in patients with functional dyspepsia. Surprisingly, given the paucity of alternative models, this animal model has not been investigated further and experimental progress on the mechanistic understanding of functional dyspepsia in rodents has not continued as expected.

One immediate implication that can be derived from the neurophysiological organization of vagovagal reflexes is that the stomach, even at rest, is the recipient of a vagal motor outflow

that is continuously sculpted by either sensory vagal, descending CNS or humoral afferent inputs. This postulate infers that a large degree of adaptive plasticity is required to ensure that vagally mediated gastrointestinal reflexive functions respond appropriately to both intrinsic and external factors.

Modulation of neurotransmitter release

As mentioned previously, vagal afferent fibres use fast synaptic transmission by ionotropic glutamate receptors to relay sensory signals to NTS neurons. In addition, these vagal afferent fibres probably also project onto the dendrites of DMV neurons that extend into the NTS gelatinosus⁶⁴, although the neurotransmitter used has not yet been identified. Concomitant to the activation of ionotropic receptors, glutamate released from vagal afferent fibres also activates metabotropic glutamate receptors (mGluRs), which produce long-lasting effects on the excitability of vagal afferent fibres and synaptic transmission to NTS and DMV neurons^{7,65–70}. Of particular importance for the vagally mediated modulation of gastric motility is the ongoing activation of group II and III mGluRs, which inhibit adenylyl cyclase and consequently inhibit GABAergic synaptic transmission selectively^{71,72}.

Levels of cAMP in the brainstem neurocircuits comprising GABA synapses between the NTS and DMV are also important modulators of neurotransmitter release within brainstem vagal nerve terminals, and under certain circumstances such as stress or following food ingestion (discussed later), cAMP can control the release of neurotransmitters or the insertion of receptors into the neuronal membrane⁵. Several studies have shown that the interplay between vagal afferent fibres, mGluRs and cAMP levels within the DVC has the ability to modulate GABAergic synaptic transmission between the NTS and the DMV. *In vitro* experiments have shown that vagal afferent fibres provide tonic activation of group II mGluRs^{68,73}; overcoming the effects of group II mGluR activation and increasing levels of cAMP within the DVC can be achieved by surgical removal of vagal afferent fibres, pharmacological blockade of group II mGluRs or by direct activation of adenylyl cyclase^{68,73–76}. Interestingly, levels of cAMP within the DVC are modulated not only by vagal afferent fibre activity or mGluR activation but also by neurohormones released from adjacent CNS structures, such as thyrotropin releasing hormone (TRH) or the stress-related hormone corticotropin-releasing factor (CRF, BOX 1)⁵, and/or by circulating gastrointestinal peptides, such as CCK or GLP-1, that reach DVC neurons either through the surrounding leaky blood–brain barrier or via specialized transporters and ultimately activate adenylyl cyclase^{77–81}.

Box 1

Corticotropin-releasing factor as a mediator of stress

The effect of stress on the function of visceral organs is well recognized, as is the pivotal role that corticotropin-releasing factor (CRF) plays in a large number of stress-related disorders^{155,219,220}. CRF and urocortins (urocortin 1 and 3) are members of the CRF family that activate two distinct receptors: corticotropin-releasing factor receptor (CRFR)1 and CRFR2. These receptors are part of the seven-transmembrane domain G protein receptor family, share a high level of homology with each other, undergo a high

level of alternative splicing and stimulate adenylyl cyclase activity. CRF and urocortin 1 have a high affinity for CRFR1, whereas CRFR2 has a high affinity for urocortin 1, 2 and 3 but a lower affinity for CRF itself.

In experimental conditions, injections of CRF in the lateral ventricles, cisterna magna, the paraventricular nucleus of the hypothalamus (PVN) or the dorsal vagal complex (DVC) mimic stereotypical stressor behaviour, including slowed gastric and small intestinal motility but accelerated colonic motility^{155,179}. These responses are consistent with the localization of CRF-immunoreactive neurons in the PVN and Barrington nuclei projecting to the DVC and spinal cord^{221,222}. The importance of CRF signalling is further emphasized by the observations that CRF levels are upregulated in acute and repetitive heterotypic (variable) stress^{165,166}, and both CRF-induced and stress-related gastric effects are blocked by pretreatment with selective CRFR2 receptor antagonists^{156,179}. Interestingly, CRF does not seem to have a role in controlling basal gastrointestinal tone and motility as CRFR antagonists do not modulate gastrointestinal functions in non-stressed animals, suggesting that the effects of CRF are restricted to central modulation of gastrointestinal functions in time of stress only^{223,224}.

The functional consequence of increased cAMP levels in the NTS–DMV synapse is the trafficking of G protein-coupled receptors and exposure of the modulation of GABAergic currents by neurotransmitters, such as serotonin⁸², opioids⁸³ or neuropeptide Y⁸⁴, which otherwise do not modulate GABAergic synaptic transmission^{82,85,86}. As a result, vagal afferent fibres, via activation of mGluRs, modulate the levels of cAMP within the GABAergic NTS–DMV synapse, thereby providing a metabolically inexpensive means by which brainstem neurocircuits can adapt and provide appropriate responses to nutritional, environmental and/or pathophysiological conditions originating in the gastrointestinal tract. For example, the interdigestive period (phase III of the migrating motor complex) necessitates dampening the influence of the vagus nerve and a potential, albeit speculative, means by which this goal could be achieved is via the tonic release of low levels of glutamate in the NTS. By activating group II mGluRs, this process would reduce cAMP levels and maintain the vagovagal neurocircuitry in a resting state, preventing the modulation of GABAergic currents by circulating neuroactive substances. Conversely, following the release of neurohormones after food ingestion, the resulting increase in cAMP levels within the DVC would enable activation and modulation of vagal neurocircuits and prime the upper gastrointestinal tract for proper digestive processes. However, in pathophysiological conditions such as functional dyspepsia, inappropriate activation of vagal inputs could result in elevated cAMP levels that might enable an increased state of activation of GABAergic synaptic transmission, which could consequently affect vagal efferent outflow and hence gastric motility and tone. The experimental testing of this possible arrangement could be conducted using the Liu *et al.*⁶³ model of functional dyspepsia described previously.

Gastrointestinal peptides

A large number of neuroactive peptides are released from specialized intestinal cells following ingestion of nutrients; several of these gastrointestinal peptides induce

physiological, vagally mediated alterations in gastric motility, promote pancreatic secretions, and/or modulate satiety^{87–90}. Overall, the role of gastro intestinal peptides is to modulate the gastrointestinal reaction, whether motility or secretion, to produce an appropriate response to ingested substances.

For some of these gastrointestinal peptides, the site and mechanism of action is controversial. In fact, on the basis of data from capsaicin administration experiments, many studies have proposed that the vagally mediated effects of peptides such as CCK (which is used as the main example of a neuroactive gastrointestinal peptide from here onwards), GLP-1 or ghrelin occur almost exclusively via a paracrine action on the peripheral endings of capsaicin-sensitive vagal C-type afferent fibres^{87,88,91–95}. The postulate for this almost exclusively paracrine effect of CCK on C-type vagal afferent fibres stems from the belief that administration of capsaicin, either systemically (15–50 mg/kg bodyweight) or directly onto the vagus nerve (1% perivagal capsaicin, 33 mmol/l^{88,96–99}), induces selective ablation of only C-type fibres. With this presumption in mind, abolition of the effects of CCK on gastric or pancreatic functions by capsaicin pretreatment was assumed as proof of a paracrine site of action^{88,96–104}.

A large body of evidence (summarized later) indicates that capsaicin is not selective for vagal afferent fibres at the concentration or doses used in these studies, suggesting that caution should be used in the interpretation of the resulting data. Despite this evidence, the use of systemic or perivagal capsaicin for the assessment of a vagal afferent fibre-mediated mechanism of action has been *de facto* accepted, while toxicological, anatomical, functional and electrophysiological evidence of capsaicin and CCK-mediated alterations of visceral function via action at sites other than vagal afferent fibres has been downplayed or dismissed. The off-target effects of perivagal capsaicin application might be even more troubling than its systemic administration; the efferent (motor) vagus nerve comprises less than 15–20% of the total vagal fibres, hence even minor capsaicin-induced damage has a major effect on the vagal motor output¹⁰⁵.

Anatomical and toxicological experiments have shown that systemic capsaicin administration induces mitochondrial and perikarya degeneration, thereby suggesting nonspecific actions of capsaicin in many areas: nonsensory regions, such as mesencephalic dopaminergic neurons; brainstem and pontine nuclei; hypothalamic areas including the anterior preoptic area; as well as nuclei that do not contain vanilloid receptors^{106–112}. Functional experiments have shown that systemic or perivagal capsaicin administration reduces the vagally mediated gastric secretion response induced by 2-deoxy-d-glucose treatment¹¹³ or by intracisternal administration of TRH analogues¹¹⁴. Likewise, selective vagal deafferentation or perivagal capsaicin treatment does not prevent the DVC-mediated effects of CCK or its secretagogue, casein, on either c-Fos activation or pancreatic secretion^{115–118}. A physiological study published in 2013 also demonstrated that perivagal capsaicin administration induces degeneration of DMV neurons, reduces their membrane response and diminishes the increase in gastric tone and motility induced in response to central activation of vagal efferent motor neurons by TRH¹⁰⁵. Finally, electrophysiological studies have shown excitatory effects of CCK on nodose or brainstem vagal neurons^{119–126};

similar excitatory actions are also reported as a consequence of capsaicin administration^{127–129}.

Although the presence of CCK receptors on vagal afferent fibres and the contribution of paracrine actions of CCK on peripheral vagal terminals of C-fibres is not disputed, it should be borne in mind that, as discussed previously, there are major drawbacks with capsaicin as a tool to determine the mechanism of action of vagally dependent gastrointestinal neurohormones such as CCK. Other sites of CCK action, including vagal neurons of the nodose ganglia, NTS and DMV, should be considered.

In this regard, it is important to remember that large areas of the DVC, as well as the whole adjacent area postrema, are located outside the blood–brain barrier, have a large network of fenestrated capillaries and contact specialized neurons lining the ependymal layer of the central canal and fourth ventricle^{29,78,79,130}. This anatomical arrangement, combined with the non-selective toxicity of capsaicin, suggests strongly that the mechanism(s) of action of CCK, as well as that of many other gastrointestinal peptides, is not exclusively paracrine and involves other areas, including neurons of the DVC, where CCK receptors and CCK-containing neurons are also located^{22,131,132}.

The data provide strong support for circulating CCK exerting effects through both paracrine and non-paracrine mechanisms of action (FIG. 3). A hormonal effect of CCK on DVC neurons is probable; in rats, brainstem microinjections of CCK8s decrease gastric tone and motility, reduce the gastric response to oesophageal distention (the RRR)¹³³ and increase pancreatic exocrine secretion¹¹⁸. Underestimating the potentially adverse effects of capsaicin on vagal efferent function would, therefore, lead to overestimation of the vagal afferent contribution to the actions of CCK and other gastrointestinal neuropeptides.

Indeed, other peptides such as GLP-1 and ghrelin are also released from specialized enteroendocrine cells in the gastrointestinal tract and supposedly influence gastrointestinal functions via a paracrine action on capsaicin-sensitive vagal afferent fibres^{91,92,134,135} (FIG. 3). However, as described previously for CCK, a large body of evidence demonstrates that these peptides also affect neurons in the nodose ganglia, NTS, DMV or area postrema to regulate neural excitability, exocrine pancreatic secretion or gastric motility^{136–142}.

Peptide YY (PYY) is released from enteroendocrine L-cells in the distal small intestine and proximal colon^{143,144}. These cells colocalize with GLP-1 and α -gustducin¹⁴⁵ and are probably chemosensors. PYY is released in response to lipid ingestion as part of the ileal brake reflex mechanism; because PYY release occurs before the arrival of dietary lipids to the distal small intestine¹⁴⁶, its actions to induce gastric relaxation and delayed emptying probably include neural mechanisms, possibly via vagally mediated pathways. Upon release from L-cells, PYY is cleaved to PYY3–36 by the enzyme dipeptidyl peptidase 4. Of the neuropeptide-Y-selective receptors, circulating PYY3–36 interacts with neuropeptide Y receptor type 2 (NPY2R) preferentially, rather than with type 1, type 3, type 4 or type 5 receptors¹⁴³, to inhibit gastrointestinal motility and transit. As PYY3–36 readily crosses the blood–brain barrier¹⁴⁶, an effect on neurons of the DMV is probable; in fact, brainstem microinjections of PYY induce either excitation or inhibition of gastric motility, depending

on the basal activity of the stomach^{147–151}. Electrophysiological recordings confirm a Y2 receptor-mediated response of PYY on identified vagal motor neurons^{84,86} as well as on enteric neurocircuits¹⁵². The mechanism of action of PYY on vagal motor neurons varied in concert with brainstem levels of cAMP⁸⁴, suggesting a means to explain the puzzling opposing responses (either excitation or inhibition of gastric motility) observed in the *in vivo* experiments on gastric motility^{147,148}. For a more detailed analysis of the aforementioned and other gastrointestinal peptides, we refer the reader to more comprehensive and specialized reviews elsewhere^{153,154}.

Vagal neuroplasticity in stress

An extensive network of interconnected neurocircuits regulate visceral, emotional and feeding vagal pathways, and include projections originating from cortical, subcortical and midbrain areas that impinge on brainstem vagal neurons⁵. These neurocircuits theoretically offer a high degree of integrative capacity to facilitate adaptive processes. Furthermore, bidirectional communication between the brain and the gut influences homeostasis through alterations in gastrointestinal, immune, central and autonomic nervous systems. These brainstem vagal neurocircuits, however, have long been thought of as static and only in the past decade has it been recognized that they are neuroplastic.

A rapid response to either acute internal or external stressors is a reflexive protective mechanism that necessitates adaptive modifications of relatively brief duration. As described previously, the DVC undergoes rapid (activated within ~5 min) and short-lasting (inactivated within ~60 min) cAMP-mediated neuroplastic changes of the availability to modulation of receptors that control the GABAergic synapse between the NTS and DMV^{82–84}. A situation of acute stress can therefore be mimicked by a temporally restricted exposure to CRF, which results in decreased gastric motility¹⁵⁵. Conversely, prolonged stress represents a more serious challenge and requires the ability to adapt to ongoing insults. However, the lack of resilience or adaptability to adverse events results frequently in dysfunction of gastric (delayed emptying) and colonic (accelerated) motility¹⁵⁶. Such a dichotomy in the adaptive response to stress whereby some individuals demonstrate a high degree of resistance whereas others show vulnerability presents a unique opportunity to investigate the neurocircuits underlying stress and address the question of why some people are more prone to gastrointestinal-related dysfunctions than others.

Functional gastrointestinal disorders, including functional dyspepsia and IBS, are correlated highly with stress^{157,158}, and stressful situations exacerbate gastrointestinal symptoms in susceptible individuals¹⁵⁶. At times of stressful life events, positive social interactions help to reduce stress, and empathic responses as well as physical contact between human partners is positively correlated with increased circulating oxytocin levels^{159,160}. Thus, many studies have suggested that central oxytocin represents a potent anxiolytic, ameliorating both cortisol (corticosterone in non-human animals) release and anxiety-like states and, by consequence, might have an important role in buffering physiological responses to stressful life experiences^{161,162}. A series of studies have demonstrated a prominent role for oxytocin in modulating human and non-human social behaviour^{163,164} with relevant anxiolytic-like effects in rodents, including recovery of gastrointestinal motility to pre-stress levels^{165,166}.

In a series of elegant manuscripts, Takahashi's group has shown the central role of oxytocinergic neurons of the PVN in the gastrointestinal-related anxiolytic effects of oxytocin and their role in favouring stress resilience^{165–168}. Although some of the restoration of gastric motility mediated by oxytocin is related to its effects on the hypothalamus–pituitary–adrenal axis and/or decreased release of CRF from PVN neurons^{163,169,170}, one also has to consider the direct influence of hypothalamic oxytocin on vagal brainstem neurocircuits. Preautonomic PVN neurons are the sole source of oxytocinergic innervation to the DVC¹⁷¹ and are excited by stressful stimuli, social attachment and food intake¹⁷². Targeting these neurons could therefore represent a valuable pharmacological approach for alleviating stress-induced gastrointestinal dysmotility.

Upon its release onto brainstem vagal neurons, oxytocin interacts with its own Gq-coupled receptor (the oxytocin receptor) to depolarize DMV neurons via a cAMP-dependent mechanism^{173,174}, resulting, ultimately, in gastric relaxation and reduced motility^{171,175–177} (FIG. 4) mediated by the NANC pathway¹⁷⁷. Interestingly, central administration of oxytocin antagonists increases gastric motility, suggesting that the PVN–DMV pathway is active tonically^{175,176}.

As hypothalamic oxytocin has a major role in the recovery of gastric and colonic motility after stress adaptation^{165,166,178}, the question arises as to the vagally mediated mechanism of this anti-stress action. Either stress per se or central administration of CRF decreases gastric tone and motility^{156,179}, an outcome similar to the gastric inhibitory effects on gastric tone and motility following central administration of oxytocin. This apparent conundrum has been partially resolved with a series of manuscripts published in the past few years that have demonstrated a differential engagement of postganglionic vagal neurocircuits by oxytocin^{177,180} (FIG. 4). In control, non-stressed rats, microinjection of oxytocin into the DVC decreases gastric tone and motility via activation of a nitric-oxide-mediated pathway; however, following surgical or pharmacological reduction of vagal afferent fibre input, or pretreatment with CRF, this effect of oxytocin on gastric motility and tone is attenuated, abolished or even reversed, such that an increase in gastric tone is observed^{177,180}. The mechanism of action of this inverted effect includes activation of peripheral VIP–vagal and cholinergic–vagal pathways^{177,180}, which become engaged via a cAMP-dependent translocation of oxytocin receptors on brainstem vagal synapses¹⁸⁰. This translocation of receptors seems to be a mechanism common to other neurotransmitters, both in the DVC^{82–84,181} and in other CNS areas¹⁸².

Thus, it seems that the adaptive plasticity that promotes the anti-stress effects of oxytocin might do so by restoring coordinated, vagally determined gastric motility. This functional restoration of gastric motility is achieved via translocation of oxytocin receptors to the terminals of subsets of GABAergic NTS–DMV synapses, which leads to oxytocin-dependent inhibition of GABAergic transmission. Inhibition of GABAergic transmission results in disinhibition of vagal outputs and promotes a counter-regulatory effect that dampens and self-limits the actions of CRF under conditions of acute stress.

Although it is clear that an individual's ability to cope with stress is determined by neuroendocrine, neuroimmunological and psychological responses that combine to

determine the degree of stress resilience or susceptibility, the biological basis, the cellular mechanisms of adaptation and the factors that determine a pathophysiological outcome after stress have not yet been defined in detail. Certainly, a great deal of adaptive plasticity occurs in vagal brainstem neurocircuits, although several unresolved issues still linger. For example, in an acute stressful situation, what determines the engagement by oxytocin of one vagal neurocircuit rather than another? What are the effects on vagal neurocircuits of long-term exposure to high CRF levels or to repetitive chronic stress? How are these vagal neurocircuits rearranged in chronic pathologies such as functional dyspepsia? More generally, what determines the relative balance of strength between the inhibitory NANC and the excitatory cholinergic neurocircuits? How are these functionally segregated NANC and cholinergic neurocircuits primed to convey the appropriate gastric motility response as a consequence of environmental stimuli? A closer investigation of the interface between basic and clinical science is needed to elucidate which factors determine the pathophysiological response of vagal neurocircuits controlling gastric motility, and even closer collaborations should be encouraged between bench and clinical researchers.

Parkinson disease

Over the past decade a growing interest has been placed on degenerative disorders of the CNS that affect the gastrointestinal tract, possibly related to pathologies that affect the vagus nerve^{183–187}. Of particular interest is the observation that altered swallowing, constipation, dysphagia, early satiety and nausea, delayed gastric emptying and reduced gastric motility are core components of the parkinsonian clinical picture and can affect patients up to 10–15 years before the clinical diagnosis. Indeed, the occurrence of these disturbances in otherwise healthy people has been associated with an increased Parkinson disease risk^{187–189}.

Most experimental effort in the context of parkinsonian signs has been devoted to the study of abnormalities of the lower gastrointestinal tract^{190–192}, with less attention placed upon gastric dysfunctions. However, delayed gastric emptying occurs at all stages of Parkinson disease, affecting up to 90% of patients^{193,194}, and contributes to the problematic fluctuations in absorption rate, and therefore response to pharmaceutical treatments. Levodopa, for example, is absorbed in the proximal small intestine and its effective dosage is determined by the rate of gastric emptying, which can be further slowed by dopaminergic medications such as levodopa itself. Thus, it is necessary to conduct tightly regulated studies in the search for effective prokinetic agents to use in patients with parkinsonian signs, and/or resume studies on proven, effective prokinetics, such as domperidone, whose mechanisms of action are yet to be determined in full.

Although several mouse and rat models can be utilized for Parkinson disease research¹⁹⁵, gastrointestinal research in the context of Parkinson disease, in particular gastric research, has been focused on immunohistochemical studies of the ENS, with less attention being paid to functional studies or investigations at the level of the DVC^{196–204}. One of the most common rat models of non-motor Parkinsonian defects involves the unilateral degeneration of dopaminergic neurons by micro-injection of the toxin 6-hydroxydopamine (6-OHDA) into either the substantia nigra pars compacta or the medial forebrain bundle. In this model, gastrointestinal-related dysfunctions can be observed after ~4 weeks and consist primarily of

neurochemical alterations in the colon^{197,198} — consistent with the reported constipation observed in patients with parkinsonian syndromes — and delayed gastric emptying, possibly due to changes in the neurochemical phenotype of gastric myenteric and DVC neurons^{202,204}.

However, the prodromic involvement of the gastrointestinal tract suggests that the aetiology of Parkinson disease also involves a ‘bottom-up’ pathogenesis. The morphological hallmark of Parkinson disease is the presence of Lewy bodies and Lewy neurites in dopaminergic neurons of the basal ganglia²⁰⁵. Lewy bodies and Lewy neurites are characteristic intracellular proteinaceous inclusions composed primarily of misfolded α -synuclein protein²⁰⁶. When present in dopaminergic neurons of the basal ganglia, these inclusions are linked directly to the typical neuronal degeneration of Parkinson disease. Interestingly, several studies show a broad presence of Lewy bodies and Lewy neurites in the soma and processes of both enteric neurons and vagal motor neurons, as well as tissues from the submandibular gland and colon^{207,208}.

On the basis of this distinct distribution pattern of Lewy bodies within the ENS and DMV, and the early onset of gastrointestinal symptoms, Braak and colleagues have suggested that idiopathic Parkinson disease begins with absorption of an ingested environmental ‘unknown pathogen’ into the ENS, which is then transported to the CNS via the vagus nerve and, starting from the DMV, spreads to higher CNS areas^{209–211} (BOX 2). In this model, the DMV would represent the main intersection point in the CNS network affected by Parkinson disease. Indeed, although the Lewy body pathology in the DMV has been shown in Parkinson disease experimental models and in patients with the condition, and the involvement of the DMV in the disease is accepted^{200,204,212–214}, the direct involvement of the vagus nerve is highly possible (although the evidence is as yet circumstantial). Braak’s hypothesis is still controversial; some authors and experimental evidence are supportive, whereas others are more sceptical^{215–218}.

Box 2

The spread of α -synuclein

In both the enteric nervous system (ENS) and central nervous systems (CNS), the neurons that develop α -synuclein inclusions are projection neurons with long, poorly myelinated axons²¹¹. Together with the presence of Lewy bodies, this set of observations led Braak’s group to formulate the hypothesis that ENS neurons (as well as neurons in the olfactory bulb) might provide the first pathogenic link in Lewy body pathology, which would then spread to the dorsal motor nucleus of the vagus (DMV) at the earliest stages of Parkinson disease²¹¹.

According to this hypothesis, the involvement of other CNS areas rostral to the DMV occurs progressively in six pathological stages, which include three premotor stages when α -synuclein is present in the ENS and lower brainstem (including the DMV and A6 area, among others), and the final stages of Parkinson disease, when Lewy body pathology affects both motor and cognitive areas, such as the substantia nigra pars compacta, the mesocortex and neocortex, and the functions of these regions²¹³.

The spread of Lewy body pathology between CNS areas occurs in a retrograde, prion-like manner^{210,225–227}, jumping synapses between adjacent neurons and ultimately causing their degeneration^{227,228}. Indeed, Olanow and Brundin have hypothesized that some types of Parkinson disease are due to a prion-like disorder, suggesting that native α -synuclein undergoes a conformational change that promotes its misfolding²²⁹.

The spread of α -synuclein from grafted to resident neurons, or from neurons to astroglia, in both humans and in animals^{217,225,230,231} makes the progression of Parkinson disease via neural connections a possibility that needs to be explored and exploited in the quest for novel therapeutic targets to treat patients with gastrointestinal-related parkinsonian symptoms.

Despite exerting a prominent burden on patient quality of life, parkinsonian-related gastrointestinal dysfunctions represent an underserved and understudied area of research, and progress in understanding both the aetiology and treatment of these gastrointestinal disorders has been hampered by a lack of rigorous, focused effort to understand the disease pathophysiology as well as the testing of therapeutic interventions. For example, what is the unknown pathogen(s) hypothesized by Braak's group to be responsible for the retrograde transport of α -synuclein inclusions? Environmental toxins, such as herbicides or pesticides, or exposure to high levels of manganese are known to induce Parkinson-disease-like motor symptoms¹⁹⁵. However, investigations into the Parkinson-disease-like gastric effects of these substances are still in their infancy. Similarly, the mechanisms responsible for the gastric neuronal degeneration observed following administration of 6-OHDA in the basal ganglia are still unresolved. What is the role of central dopaminergic neurotransmission in the development of parkinsonian gastrointestinal dysfunctions? Despite the common use of dopaminergic antagonists as prokinetic agents, few, if any, dopaminergic neurons are found within the ENS, suggesting that either these drugs target central dopaminergic neuro-circuits that are involved in the control of gastrointestinal motility or that the prokinetic actions of these drugs are not due to actions at dopamine receptors. Both of these cases represent an opportunity to focus research effort on characterizing the role of central dopaminergic transmission in the pathophysiology of the gastrointestinal tract and the preservation of dopaminergic neurons in Parkinson disease. In fact, the role of central dopaminergic neurotransmission in the control of gastrointestinal functions has not been investigated in either healthy or Parkinson disease experimental models. Which prokinetic agents can be used to tackle the gastrointestinal-related disturbances of patients with Parkinson disease effectively? Are there differences in the gastrointestinal-related disturbances between genetic and environmental origins of Parkinson disease? Providing answers to these, as well as other questions related to Parkinson disease aetiology, should be a prime target of interest not only for understanding the neural mechanisms of Parkinson-disease-related gastrointestinal dysfunctions but also for elucidating other neurodegenerative pathologies that result in an alteration of gastrointestinal functionality.

Conclusions

Although vagovagal reflex control of the gut is understood at a basic mechanistic level, there are many factors (for example, place in the environment, time of day, taste and absorption of

food, stress, pain, hormonal background and pathophysiological status, including presence of neurological degenerative diseases) that can radically alter gastrointestinal function. However, the neural mechanisms responsible for remodelling of gastrointestinal function as a result of these factors are poorly understood.

Functional gastrointestinal motility disorders are common conditions, often chronic and disabling, and they account for a large proportion of consultations with primary care and specialist physicians. The pathophysiology of these disorders remains incompletely understood, but several lines of evidence point toward impairment of the vagal sensory–motor loop connecting the gut to the CNS and vice versa. Nonetheless, big gaps in our knowledge still prevent an approach that goes beyond treating the symptoms of functional gastrointestinal motility disorders.

In summary, we are only just beginning to understand the mechanisms involved in the response of gastrointestinal vagovagal circuits to intrinsic and extrinsic factors. At first glance, the permutations for modification in these systems seem almost limitless. Although adaptive responses are essential to adjust to ever-changing physiological conditions, derangements or untimely deviations can have pathophysiological consequences, such as exacerbation of stress-induced functional dyspepsia. Similarly, neurodegenerative alterations of the vagal neurocircuitry induce dramatic impairments of gastrointestinal functions that, given the lack of insight into the underlying physiological mechanisms, are difficult to manage in clinical practice.

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Key points

- Brainstem vagovagal neurocircuits modulate the functions of the upper gastrointestinal tract
- Neuronal communications between vagal sensory (nucleus tractus solitarius, NTS) and motor (dorsal motor nucleus of the vagus, DMV) nuclei are highly specialized and probably specific for function and target organ
- NTS–DMV synaptic contacts are not static but undergo plastic changes to ensure that vagally regulated gastrointestinal functions respond appropriately to ever-changing physiological conditions or derangements
- Gastrointestinal peptides influence vagovagal circuits via actions on both vagal afferent fibres and brainstem nuclei
- Neurodegenerative alterations of the vagal neurocircuitry induce marked impairments of gastrointestinal functions

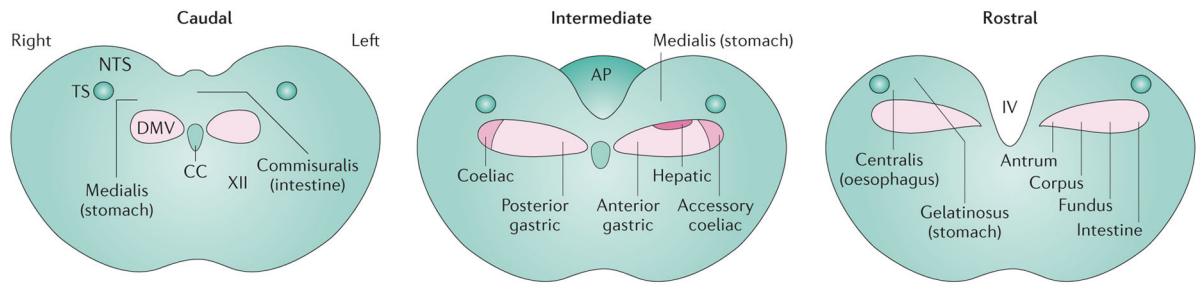


Figure 1. Anatomical organization of the nucleus tractus solitarius and the dorsal motor nucleus of the vagus

Coronal sections of the brainstem at caudal (caudal to area postrema), intermediate (at the level of the area postrema) and rostral (rostral to area postrema) levels. Brainstem areas lateral and ventral to the dorsal vagal complex (DVC) have not been represented. The location of the rostrocaudal columns representing areas of origin of the vagal branches within the dorsal motor nucleus of the vagus (DMV, pink areas) are shown in the intermediate coronal section, and the projections of rostrocaudal groups of motor neurons are shown in the rostral coronal section. The nucleus tractus solitarius (NTS) subnuclei and their main gastrointestinal-related inputs are shown in their approximate rostrocaudal locations. AP, area postrema; cc, central canal; IV, fourth ventricle; TS, tractus solitarius; XII, nucleus of the hypoglossus.

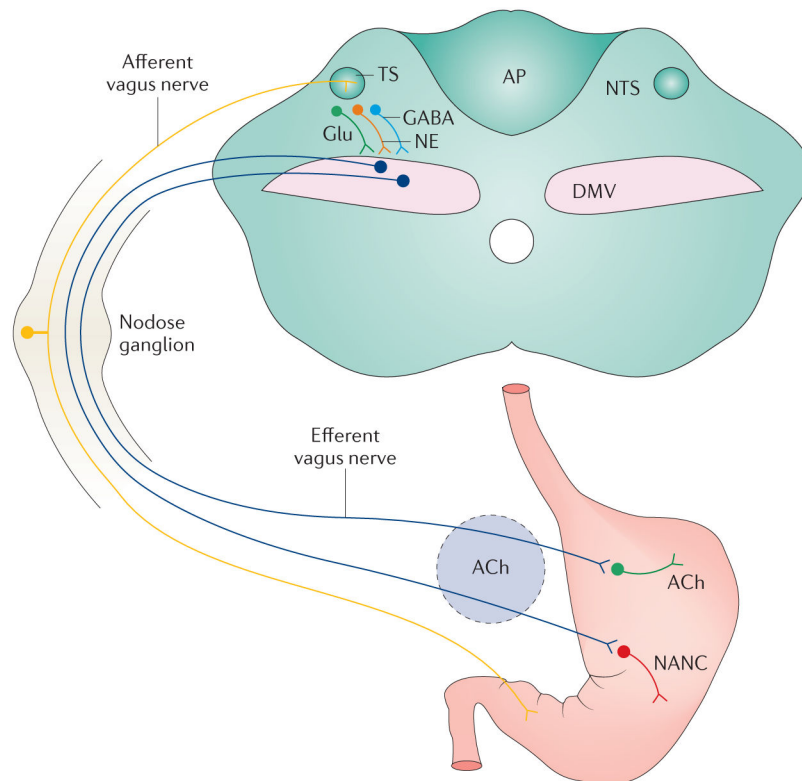


Figure 2. The brainstem neurocircuit comprising vagovagal reflexes

Vagal afferent fibres relay sensory information from the upper gastrointestinal tract, entering the CNS via the TS and transmitting sensory information to neurons of the NTS using glutamate as their main neurotransmitter^{5,13}. The NTS neurons integrate this visceral sensory information, which is then conveyed to higher centres, such as the PVN, as well as to the adjacent neurons of the DMV. Although a large array of neurotransmitters are used by NTS neurons, the main neurotransmitters are GABA, Glu and NE. Of these neurotransmitters, GABA seems to play a major part in controlling DMV neuronal firing rate and, by consequence, regulates vagal efferent outflow and modulation of gastric tone and motility^{45,46}. Preganglionic parasympathetic neurons of the DMV use ACh, which interacts with nicotinic receptors, to excite postganglionic myenteric neurons and/or interstitial cells of Cajal. Vagal motor activation can induce both excitatory and inhibitory effects via stimulation of postganglionic neurons, which either release ACh onto excitatory muscarinic receptors or release inhibitory NANC neurotransmitters such as nitric oxide or vasoactive intestinal polypeptide onto gastric smooth muscles. Notably, NANC neurotransmission has an effect on gastric tone and motility, but not secretion. Ach, acetylcholine; AP, area postrema; DMV, dorsal motor nucleus of the vagus; GABA, γ -aminobutyric acid; Glu, glutamate; NANC, non-adrenergic non-cholinergic; NE, noradrenaline; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus of the hypothalamus; TS, tractus solitarius.

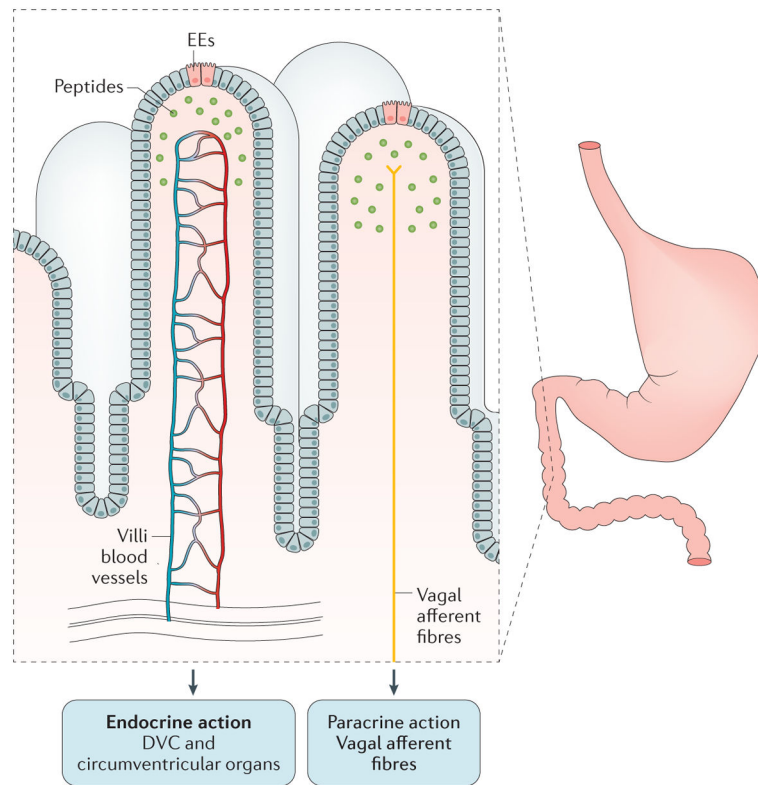


Figure 3. Neurocircuits activated by gastrointestinal peptides

The vagus nerve has a major role in the feedback control of gastric motility. After ingestion of nutrients, specialized enteroendocrine cells within the small intestine release gastrointestinal peptides, which, in most cases, induce a robust gastroinhibition (that is, feedback control). In the past few years, studies have shown that the mechanism of action of many of these peptides involves hormonal as well as paracrine effects. The hormonal activity of these peptides is facilitated by the close proximity of these specialized cells to the villi vasculature. Gastrointestinal hormones can therefore act at sites other than vagal afferent fibres, including the portions of the dorsal vagal complex (DVC) and the hypothalamus that lie outside the blood–brain barrier. DVC, dorsal vagal complex; EEs, enteroendocrine cells.

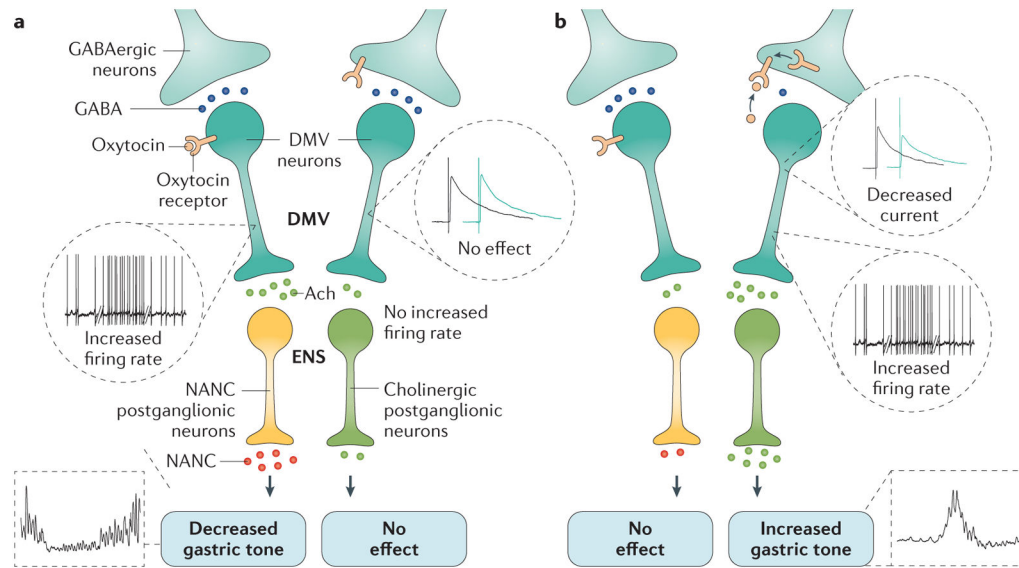


Figure 4. Oxytocin receptor trafficking in the dorsal vagal complex and changes in gastric motility

a | In control animals, oxytocin activates the oxytocin receptor on the surface of the subset of DMV neurons that control the NANC nitric oxide pathway. This interaction increases their firing rate and activates NANC postganglionic neurons, which ultimately decrease gastric tone and motility. The GABAergic terminals impinging on the subset of DMV neurons controlling pathways other than the NANC nitric oxide pathway are unaffected by oxytocin.

b | Following the increase in cAMP levels, the oxytocin receptors present in the subset of GABAergic terminals impinging onto the previously unresponsive DMV neurons that control pathways other than the NANC nitric oxide pathway are translocated to the terminal surface. Oxytocin binding to these translocated receptors reduces the amplitude of the GABA current and increases the firing rate of the DMV neurons, leading to increased release of acetylcholine in enteric neurons and increased gastric tone and motility. The relative influence of the NANC nitric oxide pathway is probably diminished by the increased activation of the cholinergic pathway, thereby resulting in the overall increase in tone and motility observed upon oxytocin perfusion. Ach, acetylcholine; DMV, dorsal motor nucleus of the vagus; ENS, enteric nervous system; GABA, γ -aminobutyric acid; NANC, nonadrenergic noncholinergic