



Role of central vagal 5-HT₃ receptors in gastrointestinal physiology and pathophysiology

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Vagal neurocircuits are vitally important in the co-ordination and modulation of GI reflexes and homeostatic functions. 5-hydroxytryptamine (5-HT; serotonin) is critically important in the regulation of several of these autonomic gastrointestinal (GI) functions including motility, secretion and visceral sensitivity. While several 5-HT receptors are involved in these physiological responses, the ligand-gated 5-HT₃ receptor appears intimately involved in gut-brain signaling, particularly via the afferent (sensory) vagus nerve. 5-HT is released from enterochromaffin cells in response to mechanical or chemical stimulation of the GI tract which leads to activation of 5-HT₃ receptors on the terminals of vagal afferents. 5-HT₃ receptors are also present on the soma of vagal afferent neurons, including GI vagal afferent neurons, where they can be activated by circulating 5-HT. The central terminals of vagal afferents also exhibit 5-HT₃ receptors that function to increase glutamatergic synaptic transmission to second order neurons of the nucleus tractus solitarius within the brainstem. While activation of central brainstem 5-HT₃ receptors modulates visceral functions, it is still unclear whether central vagal neurons, i.e., nucleus of the tractus solitarius (NTS) and dorsal motor nucleus of the vagus (DMV) neurons themselves also display functional 5-HT₃ receptors. Thus, activation of 5-HT₃ receptors may modulate the excitability and activity of gastrointestinal vagal afferents at multiple sites and may be involved in several physiological and pathophysiological conditions, including distention- and chemical-evoked vagal reflexes, nausea, and vomiting, as well as visceral hypersensitivity.

Keywords: vagus, vagal afferent, 5-HT, plasticity, gastrointestinal

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VAGO-VAGAL REFLEX CONTROL OF GI TRACT

Despite intrinsic (enteric) neural plexuses that allow a considerable degree of autonomy over digestive functions, the central nervous system (CNS) provides extrinsic neural inputs to the GI tract that govern, regulate and modulate these functions. The GI tract receives extrinsic neural inputs from both parasympathetic and sympathetic pathways derived (or controlled) from caudal brainstem nuclei (Browning and Travagli, 2014). While the sympathetic nervous system exerts a predominantly inhibitory effect upon GI muscle and mucosal secretion and regulates GI blood flow via neurally-dependent vasoconstriction, the parasympathetic nervous system exerts both excitatory and inhibitory control over gastric and intestinal motility and tone suggesting a more finely tuned regulation of GI functions (Travagli et al., 2006). The esophagus, stomach, and upper GI tract, in particular, receive a dense parasympathetic innervation, the intensity of which decreases as one progresses distally through the intestine (Berthoud et al., 1991).

The parasympathetic innervation to the stomach, small intestine and proximal colon is provided by the vagus nerve. A mixed nerve, containing both sensory and motor fibers, the vagus contains approximately 70–80% sensory fibers that transduce physiological events within the GI tract and relay this information to the CNS. Anatomical and physiological studies have characterized several different types of vagal afferent fibers that can be distinguished based upon their responses to muscle tension or pressure (mostly low-threshold mechanosensors although high-threshold nociceptors are also present), the location of the afferent fibers receptive field (muscle, mucosal, or serosal/mesenteric) and their principle stimulus modality (chemical, osmotic, mechanical) as well as the region of the GI tract they innervate (Powley and Phillips, 2002; Beyak and Grundy, 2005).

The cell bodies of vagal sensory afferents, which lie within the paired nodose ganglia or nodose-jugular complex, serve the classic afferent functions and relay the peripheral sensory information from the GI tract to the brainstem via a glutamatergic synapse at the level of the nucleus tractus solitarius (NTS). NTS neurons assimilate this enormous volume of sensory information and integrate it with inputs received from other brainstem and higher CNS centers involved in autonomic homeostatic functions. Indeed, the NTS has either reciprocal connections with, or receives inputs from, the hypothalamus, amygdala, nucleus accumbens, raphe, trigeminal, vestibular, and parabrachial nuclei as well as the area postrema, all of which help to sculpt and shape these vagal afferent visceral sensory inputs. The integrated signal is then relayed from the NTS to the adjacent dorsal motor nucleus of the vagus (DMV) which contains the preganglionic parasympathetic motoneurons which supply the parasympathetic output to the upper GI tract via the efferent vagus nerve (**Figure 1**; Travagli et al., 2006; Browning and Travagli, 2014).

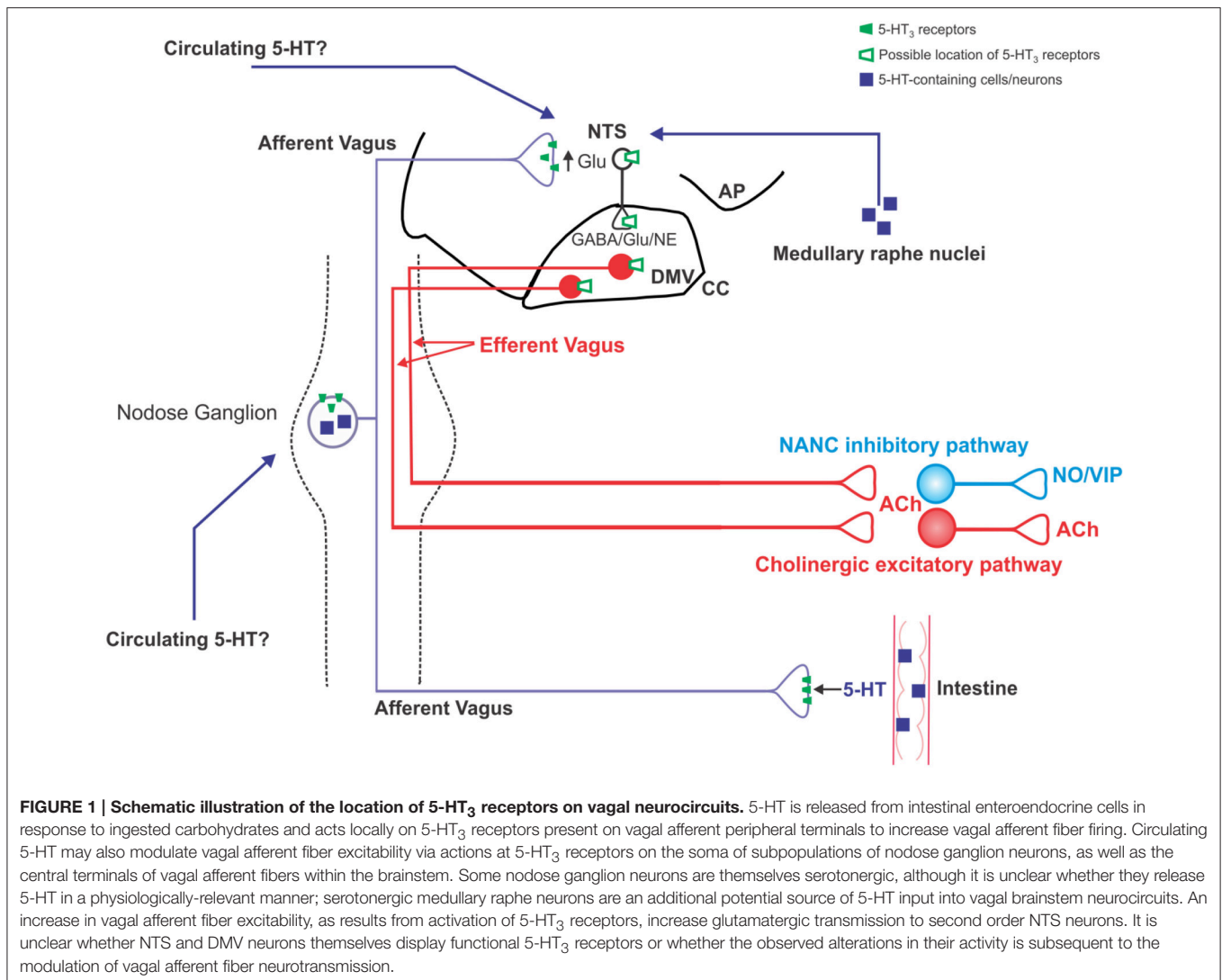
5-HT₃ RECEPTORS AND VAGAL SENSORY FUNCTIONS

5-HT is an important neurotransmitter in several GI functions, and >90% of the total body 5-HT is contained within the GI tract, either within specialized enteroendocrine cells, termed enterochromaffin (EC) cells or within neurons. Excellent recent reviews have provided in depth coverage of the role of 5-HT within the GI tract (Gershon and Tack, 2007; Mawe and Hoffman, 2013); this review, therefore, will concentrate on the role of 5-HT₃ receptors in gut-brain and brain-gut signaling outside the GI tract itself. Electrophysiological studies have demonstrated functionally active 5-HT₃ receptors on vagal afferent neurons and fibers (Leal-Cardoso et al., 1993; Hillsley et al., 1998; Kreis et al., 2002; Moore et al., 2002; Lacolley et al., 2006a; Babic et al., 2012) and activation of 5-HT₃ receptors induces a short latency, transient increase in firing rate of vagal afferents (Hillsley and Grundy, 1998; Hillsley et al., 1998) or a brief, rapid inward current (or membrane depolarization), in isolated neurons (Leal-Cardoso et al., 1993; Peters et al., 1993; Babic et al., 2012) consistent with its function as a ligand-gated cation channel (Derkach et al., 1989).

When released from EC cells, 5-HT triggers smooth muscle activity via activation of 5-HT₃ receptors on intrinsic primary afferent neurons (IPANs; Tuladhar et al., 1997; Zhou and Galligan, 1999; Bertrand et al., 2000; Gwynne and Bornstein, 2007). Such motor responses can, and do, activate extrinsic vagal and spinal afferent fibers, possibly via 5-HT₂ receptors secondary to smooth muscle activity (Blackshaw and Grundy, 1993; Hillsley and Grundy, 1998; Hillsley et al., 1998). The released 5-HT also activates extrinsic primary afferent terminals directly, however, via activation of 5-HT₃ receptors (Paintal, 1951; Hillsley et al., 1998). EC cells release 5-HT in response to mechanical (Bulbring and Lin, 1958; Blackshaw and Grundy, 1993; Mazda et al., 2004) as well as chemical stimulation. Luminal micronutrient content, in particular carbohydrates and hyperosmotic stimuli, induce strongly the release of 5-HT (Raybould and Zittel, 1995; Zhu et al., 2001; Raybould et al., 2003; Wu et al., 2005). Vagal afferent nerve terminals innervate the apical tips of mucosal villi as well as intestinal crypts and are likely, therefore, to be in close apposition to GI neurohormones, including 5-HT, released from mucosal enteroendocrine cells (Powley et al., 2011). While a large proportion of the 5-HT from EC cells may be released in close proximity to 5-HT₃-containing primary afferent terminals, a significant amount is still absorbed into the bloodstream, and circulating platelet-free 5-HT levels rise almost three-fold following a meal (Houghton et al., 2003). In this regard, it is important to note that (1) 5-HT₃ receptors are also present on nodose neuronal membranes (Leal-Cardoso et al., 1993; Moore et al., 1999, 2002; Lacolley et al., 2006a), including those innervating the GI tract (Daly et al., 2011; Babic et al., 2012), (2) 5-HT₃ receptors are also present on the central terminals of vagal afferents within the brainstem (Glaum et al., 1992; Ramage and Miufflin, 1998; Wan and Browning, 2008b; Takenaka et al., 2011; Cui et al., 2012; Hosford et al., 2014), and (3) circulating mediators have far freer access to vagal soma and the brainstem than perhaps thought previously (**Figure 1**; Lacolley et al., 2006b; Baptista et al., 2007). This suggests that EC-derived circulating 5-HT has the potential to modulate vagal afferent neuronal activity at sites distinct from the GI tract and may, therefore, prolong or amplify local GI signaling.

Within the brainstem, activation of 5-HT₃ receptors on vagal afferent terminals increases glutamatergic transmission to second order NTS neurons causing their activation (Glaum et al., 1992; Jeggo et al., 2005; Wan and Browning, 2008b; Takenaka et al., 2011; Cui et al., 2012; Hosford et al., 2014). NTS neurons are critically important in the regulation and modulation of a wide variety of autonomic homeostatic functions including cardiovascular as well as gastrointestinal processes (Andresen and Kunze, 1994; Travagli et al., 2006). Activation of vagal 5-HT₃ receptors has been shown to be important in baroreceptor and chemoreceptor reflex control of the cardiovascular system (Sévoz et al., 1996, 1997; Callera et al., 1997; Jeggo et al., 2005; Jordan, 2005; Ramage and Villalon, 2008) as well as pancreatic secretion (Mussa et al., 2008, 2010), meal termination, early satiety, and appetite regulation (Hayes and Covasa, 2006a; Wu et al., 2012).

The source of 5-HT activating 5-HT₃ receptors on the central terminals of vagal afferents is the subject of some debate. 5-HT₃ receptor selective antagonists decrease glutamatergic synaptic transmission from central vagal afferent terminals (Wan and



Browning, 2008b; Cui et al., 2012; Hosford et al., 2014) suggesting the receptors are active tonically, although other studies have not observed this ongoing receptor activation (Cui et al., 2012). Such disparities may be explained by either experimental differences, since tonic 5-HT₃ receptor activation was noted in studies employing coronal rather than horizontal brainstem slices, or species differences, being noted in studies involving rats, rather than mice. Immunohistochemical studies have demonstrated a dense serotonergic input into the dorsal vagal complex (i.e., NTS, DMV, and area postrema from the raphe nuclei (Steinbusch, 1981; Thor and Helke, 1987, 1989) the projections of which are more likely to remain intact in the coronal plane. It should also be noted, however, that the dorsal vagal complex is essentially a circumventricular organ with fenestrated capillaries and a leaky blood brain barrier (Cottrell and Ferguson, 2004; Fry and Ferguson, 2007) and circulating neurohormones or neuromodulators may have freer access to neurons within these areas (Baptista et al., 2007). It remains to be determined, however, whether elevations in circulating platelet-free 5-HT

levels that occur in response to meal ingestion or mechanical stimulation exert any modulatory role on central vagal afferent neurotransmission. It should also be noted, however, that a subpopulation of nodose ganglion neurons have been shown to synthesize 5-HT (Gaudin-Chazal et al., 1982; Thor et al., 1988; Nosjean et al., 1990), although it is unclear whether vagal afferents are able to release 5-HT centrally under physiological conditions.

5-HT₃ RECEPTORS AND VAGAL MOTOR FUNCTIONS

Surprisingly, it is not clear whether NTS and DMV neurons themselves display functional 5-HT₃ receptors. Extracellular brainstem recordings have certainly demonstrated an alteration in NTS and DMV neuronal activity in response to both peripheral and central administration of 5-HT₃ receptor agonists (Wang et al., 1996; Pires et al., 1998; Jeggo et al., 2005; Ramage

and Villalon, 2008) while nerve recordings have demonstrated that vagal efferent activity is modulated following activation of 5-HT₃ receptors (Mussa et al., 2010). The location of these 5-HT₃ receptors has not been elucidated precisely; electron microscopy has shown that 5-HT₃ receptors are present on neurons and glial cells within the brainstem suggesting an involvement in modulating postsynaptic neuronal responses as well presynaptic neurotransmitter release (Huang et al., 2004). Indeed, one relatively early study (Glaum et al., 1992) demonstrated that NTS neurons were depolarized by exogenous application of a 5-HT₃ receptor agonist in a manner resistant to synaptic blockade, suggesting a postsynaptic receptor location. The alteration in neuronal activity in the majority of the remaining studies, however, could conceivably be the downstream response following increased glutamate release subsequent to activation of vagal afferent terminal 5-HT₃ receptors.

PHYSIOLOGICAL ROLES OF VAGAL 5-HT₃ RECEPTOR SIGNALING

The physiological, rather than pathophysiological, role of vagal afferent 5-HT₃ receptors following GI-mechanical or distention-related 5-HT release appears to still be open to debate. Several studies have demonstrated that mechanical stimulation of the GI tract activates vagal afferents; some studies describe this as direct activation of peripheral primary afferent 5-HT₃ receptors (Mazda et al., 2004; Hayes and Covasa, 2006b), while others show this clearly to be an indirect effect, secondary to stimulation of local motor activity in response to the released 5-HT (Blackshaw and Grundy, 1993; Hillsley and Grundy, 1998; Hillsley et al., 1998). Indeed, recent work has suggested that while release of 5-HT from intestinal EC cells may not be a requirement for either the initiation or propagation of colonic motor complexes, 5-HT certainly modulates these peristaltic reflexes in a manner that appears to involve 5-HT₃ receptors (Keating and Spencer, 2010; Spencer et al., 2011).

In contrast, chemically-stimulated 5-HT release has well-defined actions to activate vagal afferent 5-HT₃ receptors directly. Ingestion of carbohydrates such as glucose, for example, induces a vagally-dependent gastric relaxation and delay in gastric emptying that is dependent upon peripheral vagal afferent 5-HT₃ receptor activation; furthermore, peripheral application of 5-HT₃ receptor selective agonists decrease gastric motility and delay gastric emptying (MacGregor et al., 1976; Rayner et al., 2001; Zhu et al., 2001; Raybould et al., 2003). Indeed, peripheral vagal afferent 5-HT₃ receptor activation appears to play an ongoing modulatory role in the regulation of gastric motility and emptying since administration of 5-HT₃ receptor selective antagonists accelerates gastric transit, suggesting the receptors may be under some degree of tonic activation (Coleman et al., 2003; Raybould et al., 2003; Gentilcore et al., 2007). The physiological role that 5-HT₃ receptors on the central terminals of vagal afferents plays in the glucose-induced, vagally-dependent decrease in gastric motility and tone has still to be elucidated. Studies have demonstrated, however, that the response of vagal afferents to ingested glucose can be modulated

by intravenous glucose (Mei, 1978) implying that glucose is capable of modulating vagal activity at sites other than afferent terminals within the GI tract. Indeed, studies have shown that a some GI-vagal afferent neurons are glucose-sensitive, that is, glucose can modulate the excitability of a subpopulation of GI nodose ganglion neurons via actions at ATP-sensitive potassium channels, in a manner similar to the canonical model of pancreatic β -cells (Grabauskas et al., 2010). This implies that, in addition to increasing vagal afferent activity via 5-HT release and subsequent 5-HT₃ receptor activation, once absorbed from the GI tract, circulating glucose may also regulate nodose neuron excitability to modify the increase in vagal activity induced by luminal glucose. In addition to these actions of glucose, however, we have demonstrated that extracellular glucose levels are also able to modulate the density and function of 5-HT₃ receptors on GI nodose neurons. In particular, increasing extracellular glucose levels induces the trafficking of existing 5-HT₃ receptors to the membrane of GI-projecting vagal afferent neurons and increases the magnitude of the 5-HT-induced inward current, whereas decreasing glucose levels induce 5-HT₃ receptor internalization and decrease the 5-HT-dependent inward current (Babic et al., 2012). Thus, ingested glucose may be able to amplify and prolong its afferent signaling by first releasing 5-HT from intestinal EC cells, and then by increasing the number of 5-HT₃ receptors on vagal afferents available for activation.

The glucose-dependent modulation of 5-HT₃ receptor trafficking and function also appears to occur centrally. We, and others, have demonstrated that extracellular glucose regulates the density of 5-HT₃ receptors on vagal afferent central terminals; elevating extracellular glucose increases spontaneous and evoked glutamate release from vagal afferent terminals via actions in a 5-HT₃ receptor-dependent manner (Wan and Browning, 2008a; Hosford et al., 2014) although the role of vagal afferent 5-HT₃ receptors in the glucose-dependent modulation of gastric functions remains to be defined. Similarly, the concentration of glucose within the NTS parenchyma, and fluctuations in response to alterations in circulating glycemic levels, remain to be determined but concentrations within the cerebrospinal fluid are typically two-thirds those of circulating levels. As discussed previously, the dorsal vagal complex is a circumventricular organ and NTS neurons and fiber terminals may well be exposed to higher glucose levels than those measured elsewhere within the CNS (Dunn-Meynell et al., 2009). While the majority of electrophysiological studies in brainstem slice preparations certainly use non-physiological levels of glucose, we have demonstrated previously that glucose modulates glutamate release from vagal afferent terminals at much lower levels of extracellular glucose (0.5–5 mM; Browning, 2013) implying this is a physiological, rather than pathophysiological, phenomenon.

PATHOPHYSIOLOGICAL ROLES OF VAGAL 5-HT₃ RECEPTOR SIGNALING

The sensory vagus nerve is generally considered to relay predominately non-noxious, interoceptive information from the

GI tract to the brainstem although growing evidence suggests the involvement of the vagus nerve in pain processing (see Randich and Gebhart, 1992). Certainly, some vagal afferent fibers appear responsive to nociceptive stimulation although the primary response to noxious vagal afferent stimulation may be nausea, rather than pain (Chen et al., 2008).

Vagal neurocircuits have a well-described role in nausea and vomiting (see Babic and Browning, 2014) and the role of vagal afferent fibers in emesis have been most extensively studied in the context of chemotherapy-induced nausea and vomiting (CINV) or postoperative nausea and vomiting (PONV). Several chemotherapy agents induce the release of 5-HT from EC cells which activates 5-HT₃ receptors on vagal afferent terminals (Endo et al., 1990, 2000; Horn et al., 2004); vagotomy decreases emesis induced by cytotoxic drugs while 5-HT₃ receptor selective antagonists are particularly efficacious clinically in preventing CINV and PONV (Hawthorn et al., 1988; Andrews et al., 1990; Endo et al., 2000; Darmani and Johnson, 2004; Andrews and Horn, 2006). The presumed site of action of these 5-HT₃ receptor selective antagonists is at peripheral vagal afferent terminals (Endo et al., 2000) although it should be noted that centrally applied 5-HT₃ receptor antagonists also attenuate CINV, suggesting actions at brainstem 5-HT₃ receptors (Leslie et al., 1990; Reynolds et al., 1991; Liu et al., 2003; Darmani and Ray, 2009) while 5-HT-induced disruptions in normal GI motility patterns may also contribute to CINV and PONV (Endo et al., 2000; Glatzle et al., 2002; Tonini, 2005). Similarly, the nausea and vomiting associated with several infectious agents, including rotavirus (Hagbom et al., 2011), *Salmonella typhimurium* (Jensen et al., 1997), and campylobacter (Blakelock and Beasley, 2003) has also been associated with the activation of vagal afferent 5-HT₃ receptors subsequent to intestinal 5-HT release.

The role of vagal afferent 5-HT₃ receptors in various forms of visceral hypersensitivity and nociceptive processing has been the focus of considerable attention from several groups although there are conflicting reports as to the extent of the involvement of vagal, rather than spinal, pathways. Several studies have suggested that vagal afferent fibers, and vagal afferent 5-HT₃ receptors in particular, are important in the inhibitory modulation of spinal nociceptive transmission. Briefly, when administered intravenously, 5-HT induces a dose-dependent inhibition of the tail flick reflex, and this anti-nociceptive effect is dependent upon intact vagal pathways since it is abolished by either cervical vagotomy, nodose ganglionectomy, or neonatal capsaicin pretreatment (Meller et al., 1992). In a similar manner, vagotomized rats display an enhanced visceromotor response to colorectal distention (allodynia), effects that are lost following application of the local anesthetic lidocaine to the abdominal vagus (Chen et al., 2008). The specific involvement of 5-HT₃ receptors in these responses was confirmed by studies investigating stress-induced visceral hyperalgesia, which demonstrated that subcutaneous administration of 5-HT₃ receptor selective antagonists increased the visceromotor response to colorectal distension, actions that were prevented by perivagal capsaicin (Bradesi et al., 2007, NB—it should be noted that perivagal capsaicin does not produce

a selective vagal deafferentation but also causes a significant degree of damage to vagal efferent motoneurons, Browning et al., 2013a). Thus, it appears that 5-HT₃ receptor-dependent activation of vagal afferents inhibits the noxious stimulation of spinal afferents although the central nuclei responsible for this descending modulation have not been defined fully (Ren et al., 1990; Randich and Gebhart, 1992).

Such an anti-nociceptive role of vagal afferent 5-HT₃ receptors appears consistent across several visceral hypersensitivity models suggesting common mechanistic pathophysiologies. In experimental models of duodenal acidification-induced gastric hypersensitivity, for example, intestinal acidification enhances the pressor response observed in response to gastric distention; this pressor response is enhanced by 5-HT₃ receptor selective agonists (Nakata-Fukuda et al., 2014) while administration of 5-HT₃ receptor selective antagonists inhibits the sensitization to distention that occurs in humans (Vanuytsel et al., 2011).

Activation of vagal afferent 5-HT₃ receptors also have well described roles in the immune responses elicited by antigen challenge in sensitized animal models, where 5-HT released following mast cell degranulation activates vagal afferents to modulate the visceral hypersensitivity and motor response to the immune challenge (Castex et al., 1995; Jiang et al., 2000; Chen et al., 2009). It should be noted, however, that other studies have suggested that the principle action of the sensory vagus in these antigen challenged models may be to monitor GI activity during the anaphylactic response, rather than playing a critical role in symptom generation (Scott et al., 1998). In this regard, studies have noted that the role of vagal afferents to inhibit nociceptive signaling may have temporally restricted actions, triggering endogenous antinociception at the early stages of allergen challenge and thereafter declining over time (Chen et al., 2009).

In part, this time-dependent decline in response may be related to the functional presence and activity of 5-HT₃ receptors on vagal afferents; prolonged activation of 5-HT₃ receptors leads to receptor desensitization and internalization (Freeman et al., 2006) and a decrease in receptor mRNA levels has been observed following chronic immune challenge (Chen et al., 2009). Also of relevance in this regard are the altered expression levels of serotonin transporters, particularly the serotonin-selective reuptake transporter (SERT) in several visceral hypersensitivity disorders. 5-HT signaling is terminated by reuptake into intestinal epithelium or nerve terminals via specialized transporter systems; alterations in SERT levels, therefore, are critical in regulating the availability, activity and duration of 5-HT signaling. SERT expression is downregulated in several hypersensitivity disorders including intestinal inflammatory conditions such as IBD as well as some, but not all, patients with diarrhea-predominant IBS (Coates et al., 2004; Camilleri et al., 2007; Foley et al., 2011). It is unclear whether such alterations in SERT contribute to dysregulated vagal afferent signaling in these groups, however. It is also unclear whether SERT expression levels are altered centrally in response to visceral hypersensitivity disorders; blocking SERT activity in the brainstem decreases glutamatergic synaptic transmission from the central terminals of vagal afferents due to the activation of

presynaptic 5-HT_{1A} receptors, the activity of which are more tightly regulated by physical proximity to uptake transporters (Hosford et al., 2014). An increase in brainstem 5-HT levels in response to altered SERT activity may, therefore, have the potential to dramatically alter the gain of GI vagal afferent information transfer.

Many chronic pain syndromes, including IBS, are significantly more prevalent in women suggesting a role for gonadal hormones in the modulation of visceral sensitivity (Mulak et al., 2014). Estradiol has been shown to increase the secretion of 5-HT from intestinal mucosal mast cells in rats (Yan et al., 2014) causing the activation vagal afferent 5-HT₃ receptors and an inhibition of the visceromotor response to colorectal distention in rats. It should also be noted, however, that estradiol has pronociceptive actions via spinal mechanisms; an imbalance between vagal antinociceptive and spinal pronociceptive pathways as estrogen levels fluctuate during the menstrual cycle may potentially exacerbate visceral sensitivity in susceptible IBS females (Yan et al., 2014).

Although, the regulation of food intake and energy homeostasis is generally considered to involve the integration of “higher” CNS centers with autonomic nuclei, the role of vago-vagal neurocircuits in the regulation of early satiety signaling has been the subject of renewed attention by several laboratory groups (Page et al., 2012; Dockray, 2013; de Lartigue, 2014; Kentish and Page, 2014). Diet-induced obesity is known to compromise the excitability and responsiveness of GI vagal afferent fibers (Covasa et al., 2000a,b; Swartz et al., 2010; Kentish et al., 2012) and neurons (Donovan et al., 2007; Paulino et al., 2009; Daly et al., 2011; de Lartigue et al., 2011). The mechanism responsible for this attenuated excitability has not been elucidated fully although studies in both obese mice and rats demonstrating a decreased membrane input resistance and increased membrane capacitance are suggestive of an increase in resting background potassium conductance(s) (Daly et al., 2011; Browning et al., 2013b). Studies have suggested that 5-HT₃ receptor expression is downregulated following short term exposure to a high fat diet (Nefti et al., 2009) and 5-HT₃-dependent activation of vagal afferent neurons is attenuated in diet-induced obese mice (Daly et al., 2011) but it is unclear whether this reflects the obesity-induced generalized decrease in vagal afferent excitability or a more specific decline in 5-HT₃ function. In our recent studies in pre-obese rats fed a high fat diet, however, we have not observed an attenuated or compromised response of gastric vagal afferent fibers to 5-HT₃ receptor activation (Troy et al., 2015), suggesting that obesity itself, rather than exposure to a high fat diet, may be responsible for the compromised 5-HT₃ receptor signaling.

Evidence from several fields have suggested that vagal neurocircuits are not static relay networks where afferent activation triggers formulaic and unmodulated output responses. Rather, vagal neurocircuits display a remarkable degree of plasticity with their excitability and responsiveness being modulated readily by diet, insult or injury (Browning and Travagli, 2001, 2011; Bielefeldt et al., 2002a,b; Kollarik and Udem, 2002; Dang et al., 2004; Kang et al., 2004, 2005; Tolstykh et al., 2004; Hermes et al., 2008; Kentish et al., 2012,

2014; Browning et al., 2013b). In this regard, it is interesting to note that allergic challenge in sensitized animals induces a 5-HT₃-dependent exposure of tachykinin receptor responses in respiratory vagal afferents and neurons (Weinreich et al., 1997; Moore et al., 1999, 2000, 2002); similar changes in GI afferents and neurons may also play a role in visceral hypersensitivity. Also of relevance is the finding that, despite being asynaptic, cross-talk exists between nodose ganglion neurons, where excitation of one neuron may influence that of a neighboring neuron by neurotransmitter-dependent and -independent means (Oh and Weinreich, 2002). The nodose ganglion (or nodose-jugular complex) houses the cell bodies of all vagal afferent neurons; although a generalized viscerotopic organization of soma has been proposed with neurons innervating the esophagus and aortic depressor nerve being located more rostrally with neurons innervating the stomach and pancreas being located more caudally (Zhuo et al., 1997), clearly cross-talk between neurons, may provide a means by which neurons innervating different visceral organs, or different GI areas, may influence or modulate activity of unrelated neurons.

CONCLUSIONS

5-HT and 5-HT₃ receptors in particular, are clearly important in gut-brain signaling and in the regulation and modulation of several vagally-mediated GI physiological reflexes and may play additional roles in several pathophysiological conditions. 5-HT₃ receptors also appear open to modulation; extracellular glucose levels, for example, traffic 5-HT₃ receptors to and from the neuronal membrane of GI nodose neurons amplifying or attenuating the 5-HT-induced response, while some, but not all, reports suggest alterations in receptor function by diet induced obesity. It would be surprising, however, if dietary micronutrients were the only mediators 5-HT₃ receptor plasticity. Antigen challenge, for example, has been shown to induce 5-HT₃ receptor dependent unmasking of tachykinin functions in respiratory nodose neurons; future studies investigating whether similar changes occur in GI nodose neurons may provide novel treatment strategies for allergen induced visceral hypersensitivity. Also intriguing is the apparent dichotomy between vagal afferent 5-HT₃ responses; excessive activation of vagal afferent 5-HT₃ receptors induces nausea and vomiting whereas several reports suggest an initial, temporally discrete anti-nociceptive response in stress-induced hypersensitivity. These (and other) diverse 5-HT₃ receptor-dependent responses present obvious problems to the therapeutic use of receptor selective agonists or antagonists yet their more readily accessible nature means that vagal afferent 5-HT₃ receptors still present an attract target for translational research.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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