AMERICAN JOURNAL OF PHYSIOLOGY

GASTROINTESTINAL AND LIVER PHYSIOLOGY

MINI-REVIEW

Neurogastroenterology and Motility

Glutamatergic plasticity within neurocircuits of the dorsal vagal complex and the regulation of gastric functions

 Courtney Clyburn and Kirsteen N. Browning
Department of Neural and Behavioral Sciences, Penn State University College of Medicine, Hershey, Pennsylvania

Abstract

The meticulous regulation of the gastrointestinal (GI) tract is required for the coordination of gastric motility and emptying, intestinal secretion, absorption, and transit as well as for the overarching management of food intake and energy homeostasis. Disruption of GI functions is associated with the development of severe GI disorders and the alteration of food intake and caloric balance. Functional GI disorders as well as the dysregulation of energy balance and food intake are frequently associated with, or result from, alterations in the central regulation of GI control. The faithful and rapid transmission of information from the stomach and upper GI tract to second-order neurons of the nucleus of the tractus solitarius (NTS) relies on the delicate modulation of excitatory glutamatergic transmission, as does the relay of integrated signals from the NTS to parasympathetic efferent neurons of the dorsal motor nucleus of the vagus (DMV). Many studies have focused on understanding the physiological and pathophysiological modulation of these glutamatergic synapses, although their role in the control and regulation of GI functions has lagged behind that of cardiovascular and respiratory functions. The purpose of this review is to examine the current literature exploring the role of glutamatergic transmission in the DVC in the regulation of GI functions.

brainstem; gastrointestinal; glutamate

INTRODUCTION

Precise control of the stomach and gastrointestinal (GI) system is critical for the maintenance of feeding patterns and energy homeostasis [reviewed in Refs. (1, 2)]. Dysregulation of GI functions affects not only food intake and caloric balance but is also associated with several GI disorders, including gastro-esophageal reflux disease (GERD), gastroparesis, functional dyspepsia, irritable bowel syndrome (IBS), and cyclical vomiting syndrome (CVS) [reviewed in Ref. (3)]. While the GI tract has a significant degree of autonomy over motor functions through the intrinsic enteric nervous system (reviewed in Ref. (4), the stomach, esophagus, and upper GI tract are under tonic extrinsic control from the central nervous system (CNS). The brainstem dorsal vagal complex (DVC), which comprises the dorsal motor nucleus of the vagus (DMV), the nucleus of the tractus solitarius (NTS), and the area postrema (AP), acts as a critical intersection between ascending sensory signals from the viscera and descending visceromotor signals [see Refs. (5, 6), for reviews].

Sensory vagal afferent neurons, the cell bodies of which lie in the nodose ganglion, relay ascending signals from the thoracic and subdiaphragmatic viscera via the tractus solitarius (TS) to the nucleus of the tractus solitarius (NTS). As a major integrating relay system, the NTS assimilates these visceral sensory inputs with signals from other brainstem nuclei and higher order nuclei involved in autonomic regulation (7). With respect to GI-related vago-vagal reflexes, the NTS integrates these ascending and descending inputs and relays the resulting output signal via glutamatergic, GABAergic, or catecholaminergic synapses to the neurons of the DMV (8–10). The DMV contains the preganglionic parasympathetic motor neurons that relay the integrated signal to peripheral targets via the efferent vagus nerve to regulate a variety of visceral autonomic functions including the GI tract (8, 11, 12), the pancreas (13, 14), and the liver (15, 16).

While DMV neurons are spontaneously active pacemaker neurons whose intrinsic biophysical properties allow action potential firing at a frequency of ~1 Hz (10), several studies from this and other laboratories have demonstrated that DMV neuronal excitability is modulated by both excitatory and inhibitory synaptic inputs, particularly from the adjacent NTS (8–10). Inhibitory GABAergic neurons appear to be the predominant regulator of vagal efferent neuron excitability, at least with regard to GI-projecting neurons, whereas, somewhat surprisingly, glutamatergic inputs do not appear to play as important a role in regulating vagal output under physiological conditions (10, 12). Indeed, DVC microinjection of glutamatergic antagonists has no effect on gastric

http://www.ajpgi.org

functions, unless GABAergic signaling has already been blocked (11). The evolutionary persistence of glutamatergic signaling within vagal neurocircuits suggests, however, this is still an important means of physiological signaling despite less attention being paid to its role in the physiological regulation of gastrointestinal vagal efferent output. Several recent studies have suggested a significant degree of glutamatergic plasticity occurs under pathophysiological conditions as a potentially important mechanism by which homeostasis can be maintained (17–20). It should be noted that glutamatergic synapses have been implicated in the regulation of physiological pancreatic (21) and hepatic (15, 16) functions, however, suggesting the possibility of target organ specificity within the excitatory-inhibitory balance of vagal neurocircuit pathways. The purpose of this review is to discuss the current literature exploring the role of glutamatergic transmission in the DVC in the regulation of GI functions.

DVC GLUTAMATERGIC SIGNALING UNDER PHYSIOLOGICAL CONDITIONS

Glutamatergic Transmission at the Vagal Afferent-NTS Synapse

As sensory neurons responsible for the transmission of signals from many autonomic systems, vagal afferent neurons must rapidly and reliably transmit information to the brainstem. Despite displaying distinct neurochemical phenotypes and containing an array of potential neurotransmitters and neuromodulators (22), glutamate appears the primary, if not sole, neurotransmitter used at the central terminals of sensory vagal afferent neurons (23). Both the cell bodies of vagal afferent neurons within the nodose and jugular ganglion as well as their central terminals that impinge upon NTS neurons display dense immunoreactivity for vesicular glutamate transporters (VGLUT1 and VGLUT2) confirming their glutamatergic phenotype (24, 25). Microdialysis measurements within the NTS found that glutamate levels increase significantly following electrical and mechanical stimulation of vagal afferent fibers (26, 27). Furthermore, mechanical and chemical stimulation of the upper GI tract increases NTS neuronal activity in a glutamate and non-NMDA receptor-dependent manner (28). Electrophysiological recordings from NTS neurons have shown that stimulation of the TS induces monosynaptic excitatory events that are blocked following the application of glutamatergic antagonists (23, 29). Finally, immunohistochemical studies have identified ionotropic (AMPA, kainate, and NMDA) and metabotropic (groups I, II, and III) glutamate receptors (23, 30, 31) within the brainstem confirming the critical role of glutamatergic signaling in relaying visceral sensory information from the periphery to the brainstem.

Significantly, glutamate is released from vagal afferent terminals by at least three different mechanisms: synchronous, asynchronous, and spontaneous. Synchronous release, in which an action potential evokes the coordinated release of glutamatergic vesicles, is important in ensuring the precise fidelity and temporal patterning of transmission from vagal afferent terminals. Asynchronous release, in contrast, occurs when neurotransmitter release is less tightly coupled to

action potential firing, and transmitter release is more prolonged and less coordinated [reviewed in Ref. (32)]. This appears particularly important under conditions of repetitive or higher frequency afferent signaling, when activation of NMDA receptors is important to allow continued synaptic throughput when AMPA receptors are desensitized (20).

Electrophysiological studies have shown, however, that the principle means by which vagal sensory information is relayed centrally is via spontaneous release of glutamate from their central terminals (33). Thermosensitive transient receptor potential (TRP) channels present on central afferent terminals contribute to the "tone" of spontaneous glutamate release and physiological temperatures drive TRPV1-dependent glutamate release, particularly from cardiovascular C-type (unmyelinated) afferents (33, 34). The heterogenous distribution of GI afferents within the NTS has restricted detailed characterization of their release properties, but recordings from NTS subnucleus centralis neurons, which receive inputs exclusively from subdiaphragmatic esophageal afferents (35), suggests visceral afferents are nonuniform. GABAergic NTS subnucleus centralis neurons, for example, receive glutamatergic inputs with a lower release probability and lower maximal glutamate release (36), implying that afferent-NTS pathways may display activity and functional specificity.

It is also clear, however, that glutamate release from the central terminals of vagal afferents is regulated and modulated by an array of neuropeptides and neurotransmitters, such that synaptic transmission can be up- or downregulated in response to ongoing physiological demands [reviewed in Ref. (22)]. The ability of endocrine "feeding" peptides to modulate vagal afferent transmission is of particular interest in the control of vagally dependent GI functions, particularly when considering the circumventricular nature of the brainstem DVC (37). Indeed, previous studies have shown that NTS neurons are still activated following peripheral administration of cholecystokinin (CCK) in rats that previously underwent vagal deafferentation, implying direct central actions of circulating peptides (38). The ability of neuroendocrine hormones and neuromodulatory transmitters, including CCK, ghrelin, glucagon-like peptide 1 (GLP-1), and 5-hydroxytryptamine (5-HT, serotonin), to modulate the excitability and glutamate-releasing ability of central vagal afferent terminals, has been described by several groups (38–43).

Of note, the "phenotype" of vagal afferent neurons switches from orexigenic to anorexigenic depending upon the feeding status-dependent internalization/externalization of neuropeptide receptors, with concomitant effects on the responsiveness of neurons and afferents to feeding-related peptides and hormones [reviewed in Ref. (44)]. It remains to be determined whether the central terminals of these afferents display a similar degree of phenotypic "switching," which may be reasonably expected to affect glutamate release and the throughput of vagal afferent transmission. The ability of glucose, for example, to modulate spontaneous glutamate release from vagal afferent terminals in a $5-HT_3$-receptor-dependent manner suggests that vagal activation of NTS neurons may be finely attuned to ongoing physiological conditions (43, 45, 46).

Similarly, recent studies have highlighted profound circadian rhythmicity within peripheral vagal afferents (47), with

the result being a decrease in sensitivity of mechanosensitive gastric afferents during the dark period. This results in a larger gastric distention (hence increased meal size) being required to signal satiation compared to the light period, when afferent sensitivity increases and food intake is reduced. Although it remains to be determined whether a similar circadian pattern underlies the "tone" of glutamate release from their central terminals, given the identification of clock genes within the brainstem (48), it appears likely that vagal afferent responses are also under profound circadian control. Not only does this raise some interesting questions regarding the potential for significant periodicity within autonomic reflexes and the potential for differential sensitivity of vagal afferents to neuromodulation but reinforces the critical need for rigor and consistency in the planning and timing of experiments involving the vagal brainstem.

Glutamate released from vagal afferent terminals activates principally non-NMDA (AMPA and kainate) receptors on NTS neurons, which appears sufficient to maintain synaptic efficacy at low stimulation frequencies. Electrophysiological studies suggest AMPA receptors are activated at basal activity levels, but NMDA receptors are recruited at higher (>5 Hz) afferent firing frequencies and can contribute as much as 70% of the total charge transferred across the synapse (20). Such frequency-dependent facilitation allows for a high fidelity of synaptic transmission and the maintenance of action potential firing even at moderate–high stimulation frequencies (20). NMDA receptors have, however, been shown to have a role in the physiological regulation of caloric intake and meal size. Fourth ventricular application of NMDA receptor antagonists increases food intake following fasting and abolishes the satiating effects of peripheral CCK administration (49). Curiously, despite electrophysiological studies demonstrating NMDA receptors are not activated under basal conditions (10, 19), fourth ventricular application of NMDA receptor antagonists increases basal food intake (49), suggesting that food intake per se may be sufficient to increase afferent firing frequency enough to require recruitment of NMDA receptors.

In addition to ionotropic receptors, multiple metabotropic glutamate receptors (mGluR) are present within the brainstem and play diverse roles within the regulation of brainstem glutamatergic transmission. Presynaptic groups II and III mGluRs decrease (50), whereas presynaptic mGluRI receptors increase, spontaneous glutamate release (51), and attenuate the frequency-dependent depression of afferent transmission (52). It should be noted, however, that heterosynaptic crossover and mGluR-mediated alterations in GABA release, as well a subsequent effects on the activation of presynaptic inhibitory GABA$_B$ receptors, also appears important in this regard. Indeed, the excitatory-inhibitory balance appears shifted in favor of mGluRI activation on GABAergic nerve terminals, which increases the GABA$_B$ inhibition of glutamate release (53). Thus, afferent glutamate release exerts multiple coordinated effects on selective postsynaptic NTS neurons, as well as presynaptic activation/inhibition of mGluR and GABA$_B$ receptors which, in turn, regulate and modulate glutamate release.

Glutamate in the NTS-DMV Synapse

Unlike glutamatergic signaling from vagal afferent fibers to NTS neurons, which is critically important for physiological signaling, the influence of glutamate release at the NTS-DMV synapse may be dependent upon the efferent target organ. With regard to the control of GI functions, for example, glutamatergic transmission does not appear to have a strong influence on vagal efferent activity (8, 12, 19). Studies from several groups have demonstrated that the primary synaptic input regulating the activity of GI-related DMV neurons is inhibitory GABAergic signaling from the presynaptic NTS (8–10, 12). Indeed, although DMV neurons express both NMDA and non-NMDA receptors, synaptic NMDA receptors are not active under physiological conditions (10, 19) and antagonism of AMPA receptors has little effect on vagal efferent control of gastric functions unless ionotropic GABA receptors are also blocked (11). Inhibitory GABAergic inputs to DMV neurons do, however, express group II and group III metabotropic glutamate receptors, with group II receptors being activated tonically by glutamate released from monosynaptic vagal afferent inputs (54). By consequence, this GABAergic synapse, which is critical to the regulation of gastric vagal efferent motoneuron activity, is unable to be modulated by a variety of neurotransmitters and neuromodulators until the influence of presynaptic mGluR activation is overcome (7). Vagal afferent-release of glutamate could be considered, therefore, to play a significant, albeit indirect, role in modulating the excitatory-inhibitory balance of synaptic inputs to DMV neurons. In contrast to their apparently minor role in regulating gastric functions directly, glutamatergic synapses appear to play a more prominent role in the regulation of vagal efferent control of pancreatic functions (21), suggesting the potential for neurocircuit specificity according to efferent pathway and target organ.

The concept of a synapse comprising simple pre- and postsynaptic elements is clearly outdated, however, and a tri- or even tetrapartite synapse encompassing astrocytes and/or microglia, which modulate synaptic efficacy and responsiveness is a more integrated and holistic approach to brainstem synaptic function. Originally described as merely passive, support cells, astroglia have recently been shown to fulfill many critical roles in the function of the CNS (55). Microglia are the resident immune cells of the central nervous system and astrocytes are responsible for maintaining the blood-brain barrier, promoting neuronal survival, and the formation and maintenance of the synapse [reviewed in Ref. (55)]. In addition, astroglia have been shown to be intrinsically involved in the regulation of synaptic transmission through several different mechanisms including neurotransmitter reuptake as well as the release of essential cofactors required for the activation of ionotropic glutamate receptors such as D-serine and glycine that subsequently modulate the probability of receptor activation and total glutamatergic drive to postsynaptic neurons (56–58). It is important to note that while the role of gliotransmission under normal, physiological conditions is still open to debate (59), astroglia can nevertheless modulate synaptic transmission and neuronal activity through the regulation of the extracellular ionic environment and neurotransmitter reuptake and turnover [see Ref. (60)].

The role of astrocytes in the regulation of vagal neurocircuitry within the brainstem has been the subject of renewed attention (61). Indeed, blockade of NTS astrocytic glutamate transporters increases neuronal action potential firing and spontaneous excitatory synaptic currents but decreases evoked synaptic currents, possibly due to loss of presynaptic glutamate uptake/recycling (62). A critical role for astrocytes in the regulation of vagal afferent-NTS synaptic activity is further suggested by studies demonstrating that the saporin-mediated loss of NTS astrocytes decreased baroreflex, chemoreflex, and cardiorespiratory reflex responsiveness and decreased the response to glutamate agonists even in the absence of changes to NMDA or AMPA receptor density (63). Brainstem astrocytes have also been implicated in feeding-related neurocircuits, including important roles in glucoregulation, particularly in response to hypoglycemia (64), food intake (41), and the regulation of gastric motility (65), suggesting a widespread role in the regulation of GI and autonomic reflexes.

MODULATION OF GLUTAMATERGIC SIGNALING IN PATHOPHYSIOLOGICAL CONDITIONS

While the role of brainstem glutamatergic transmission in the regulation of basal physiological GI conditions has still to be defined completely, derangement of glutamatergic neurotransmission is observed rapidly in pathophysiological states (17, 19, 66, 67), suggesting a critical role for glutamate neuroplasticity in the regulation of visceral reflexes under pathophysiological conditions.

Hyperglycemia and Diabetes

Glucose modulates vagal neurocircuitry at multiple peripheral and central sites (68) to coordinate a range of GI responses (69, 70). While glucose levels within the brain parenchyma are undoubtedly lower than that of circulating plasma and are likely to have a much narrower concentration range, CSF glucose levels are approximately two-thirds that of blood concentrations (71) and vary over a wider dynamic range (72). The circumventricular nature of the DVC implies that brainstem afferent terminals and neurons may be exposed to higher glucose levels than many other central neurons and glycemic levels have been shown to modulate glutamatergic signaling from central afferent terminals in a very dynamic manner, with glutamate release being modulated in an almost linear fashion across a wide range of glucose levels (43).

As demonstrated for nodose ganglion neurons, glucose also alters 5-HT$_3$ receptor levels on the central terminals of vagal afferents, externalizing receptors as glucose levels increase (43). The DVC receives a dense serotonergic innervation from dorsal raphe neurons (73), and 5-HT$_3$ receptors appear tonically active in vitro (40, 43), suggesting that spontaneous glutamate release is regulated dynamically by circulating glycemic levels (17, 67, 69, 74). It is also clear that brainstem glutamatergic neurocircuits undergo a significant degree of neuroplasticity in response to more prolonged alterations in glucose levels; in a streptozotocin-induced mouse model of diabetes, for example, glutamatergic transmission to DMV neurons is increased significantly while glutamate-dependent heterosynaptic facilitation of GABAergic neurotransmission is also upregulated (66, 67). Thus, the excitatory-inhibitory balance of synaptic inputs to DMV neurons may be altered dramatically by glycemic levels, although it remains to be determined whether the neurons involved in specific vagal efferent functions are affected predominately in one direction or the other, whether such modulation occurs in an attempt to maintain or restore homeostasis, or whether it contributes materially to exacerbated dysfunction.

Circulating insulin levels also affect the excitability of DVC neurocircuits, further illustrating the close relationship between glycemic regulation and central vagal signaling. Insulin decreases glutamatergic signaling to DMV neurons in a PI3K and K$_{ATP}$ channel-dependent manner (18), effects that would be expected to decrease vagal efferent excitability, hence gastric motility and tone. Dysregulated response to insulin as a result of diabetes, therefore, may exert profound effects on gastric functions, including food intake, and may exacerbate energy dysregulation and the development of obesity.

Diet-Induced Obesity

High-fat diet (HFD) exposure and diet-induced obesity (DIO) have been linked to the dysregulation of vagal neurocircuits (75–78). Certainly, a large body of evidence supports the decreased excitability and responsiveness of vagal afferent neurons in response to prolonged HFD exposure, which is also likely to contribute to disrupted glutamatergic signaling at the vagal afferent-NTS synapse and the consequent dysregulation of vagal motoneuron excitability (75). Of note, the tonic activation of presynaptic group II mGluR on inhibitory GABAergic NTS-DMV synapses was also reduced in DIO, suggestive of a decrease in tonic vagal afferent activity. Together with the findings that prolonged HFD exposure attenuated the ability of circulating GI neurohormones such as CCK to increase glutamate release at the NTS-DMV synapse, it appears that diet-induced alterations in central glutamatergic signaling may dramatically alter the excitatory-inhibitory balance centrally, with consequent effects on vagal motoneuron activity and vagal efferent output (79).

Recent studies from our laboratory (19) have examined the changes within DVC neurocircuits during an acute (3–5 days) period of HFD exposure, a time period of particular interest because of its association with the restoration of caloric intake that follows a brief, 24 h, period of hyperphagia. This period of caloric regulation is maintained for 12–14 days before energy intake is disrupted, food intake is increased, and the development of obesity is exacerbated (80). We have shown the restoration of caloric balance is associated with an increase in glutamatergic signaling to DMV motoneurons (19). Specifically, acute HFD exposure induces the activation of synaptic NMDA receptors, in addition to AMPA receptors, on DMV neurons, increasing vagal motoneuron excitability, efferent control of gastric motility and tone, and contributing to the regulation of food intake and energy balance.

Inflammation

Within the brainstem, astroglia appear to be critical to the control of glutamatergic signaling in physiological, as well as pathophysiological, states (81). Central neuroinflammation is characterized by the activation of local astrocytes and microglia, which is associated with altered astroglial morphology and neurochemical phenotype (82). Astroglia within vagal neurocircuits appear particularly sensitive to dietary modulation; as little as 12–24 h of HFD exposure increases mRNA levels of inflammatory markers within the nodose ganglion, altering the membrane properties and excitability of visceral afferent neurons through altered ion channel function (83), which may be reasonably expected to alter glutamatergic transmission central from vagal afferent terminals independent of any potential alterations centrally. Activation of central astroglia has been observed as soon as 3–5 days following HFD exposure, however (84). Notably, the timescale of this astroglial activation is similar to the temporal pattern of NMDA receptor activation on DMV

neurons and associated with the restoration of caloric balance (19), suggesting a possible mechanistic role for astroglial activation in this particular form of glutamatergic neuroplasticity. Recent studies have also indicated that astrocytes undergo significant morphological changes following dark-phase HFD feedings and that chemogenetic activation of brainstem astrocytes modifies feeding behaviors and caloric intake (61), although the mechanism of action remains to be investigated.

More prolonged pathophysiological changes are also associated with changes in brainstem astroglial activity, which may subsequently impact vagal efferent control of GI functions. Indeed, astrocyte inflammatory signaling pathways, specifically both the inhibitor of κ B kinase β (IKKβ) and nuclear factor κ B (NFκB), are required for the development of diet-induced hyperphagia and DIO susceptibility (85). DIO is also associated with leptin resistance in astrocytes, suggesting a critical role for astrocytes in the faithful transmission of neuroendocrine signaling within the DVC (86). Interestingly, hypothalamic inflammation appears to decline
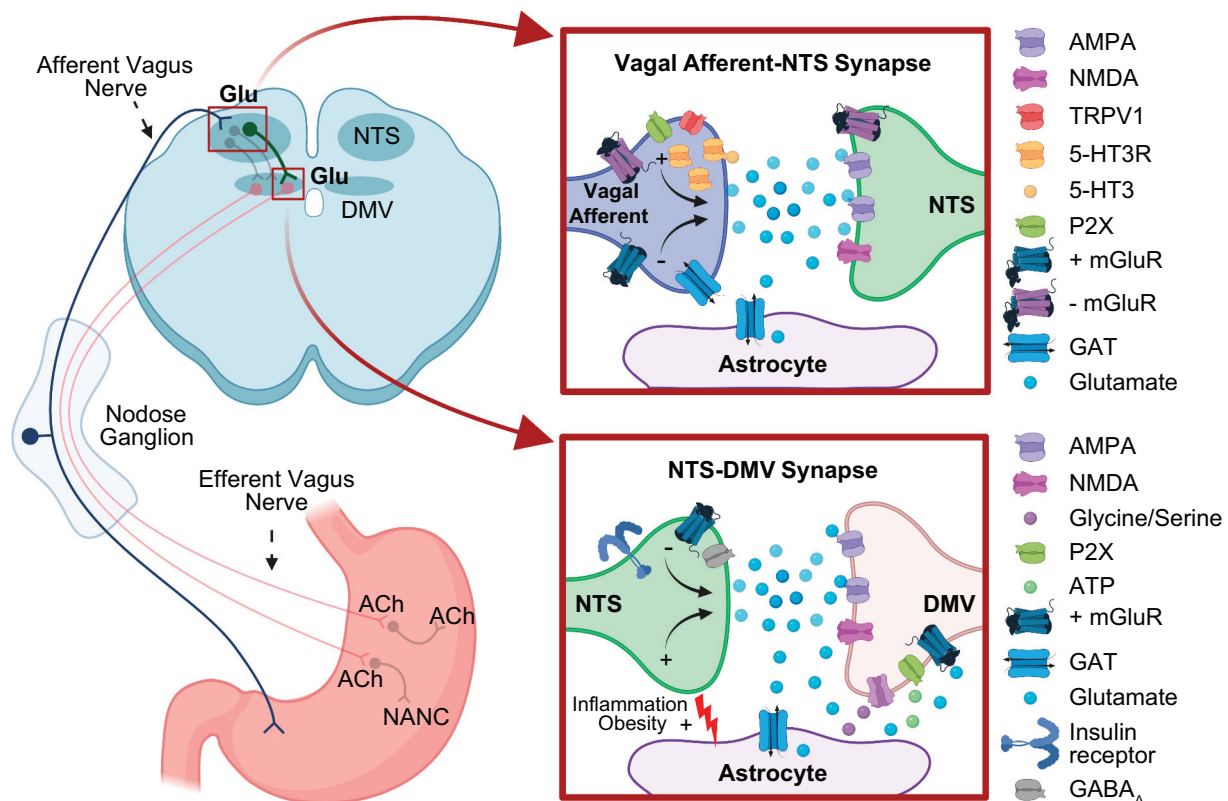

Figure 1. Schematic diagram summarizing glutamate transmission within central vagal brainstem neurocircuits regulating GI functions. Vagal afferent signals are relayed centrally via the afferent (sensory) vagus and enter the brainstem via the tractus solitarius, releasing glutamate (Glu) to activate neurons of the nucleus of the tractus solitarius (NTS; upper right). Glutamate released from vagal afferents activates postsynaptic NTS ionotropic glutamate receptors (AMPA and, at higher frequencies of stimulation, NMDA receptors) as well as metabotropic glutamate receptors (mGluR). Glutamate release from vagal afferent terminals is modulated by a variety of presynaptic receptors including 5-HT3, TRPV1, and mGluR. Synaptic glutamate levels are regulated by glutamate transporters (GAT) present on astrocytes and presynaptic afferent terminals. NTS neurons integrate vagal afferent inputs with those from brainstem, midbrain, and higher CNS centers involved in autonomic homeostasis and transmit the integrated signal to the adjacent dorsal motor nucleus of the vagus (DMV) using norepinephrine, GABA, and glutamate as neurotransmitters. Glutamate released from NTS neurons activates postsynaptic DMV ionotropic glutamate receptors (AMPA and, following acute high fat diet exposure, NMDA receptors) as well as postsynaptic mGluR. Glutamate release from NTS terminals is modulated by a variety of presynaptic receptors including mGluR, insulin, and GABA$_A$ receptors, in addition to other metabotropic and ionotropic receptors not listed. Astrocytes play a significant role in regulating synaptic glutamate levels via GAT, as well as via release of gliotransmitters following insult or injury such as inflammation and obesity. Ach, acetylcholine; NANC, non-adrenergic, non-cholinergic; P2X, ATP-gated P2X receptor.

progressively following Roux-en-Y gastric bypass surgery (87), again implicating central inflammation with the disruption of energy balance.

Rodent models of neurodegeneration, including the well-recognized model of parkinsonism, in which 6-hydroxydopamine (6OHDA) microinjection into the striatum induces degeneration of catecholaminergic neurons, are associated with the long-term activation of brainstem astrocytes (88). The recently described monosynaptic connection between the substantia nigra pars compacta and the DVC (89) certainly provides a physiological and anatomical basis for the alterations in GI functions observed in Parkinson's disease (6). While recent studies have suggested these changes may be due, at least in part, to altered dopaminergic signaling within the DVC, the potential involvement of altered astroglial regulation of brainstem synaptic excitatory efficacy cannot be discounted. In fact, many neurological disorders are associated with disrupted GI functions and brainstem astroglial activation, including Alzheimer's disease (90) and autism spectrum disorder (91), suggesting this may be a common mechanism by which autonomic reflexes in general, and GI functions in particular, are dysregulated.

CONCLUSIONS

The precise regulation of glutamatergic signaling within the DVC is critical for the regulation and coordination GI and metabolic functions. The faithful and rapid transmission of information from sensory afferent vagal neurons to second-order neurons of the NTS and vagal efferent motoneurons of the DMV requires precise control over glutamatergic synapses that are susceptible to fine-tuning from a wide range of signaling factors (Fig. 1). While this rapid modulation of glutamatergic signaling is an adaptive responsive for the reliable transmission of information, a variety of pathological states result in persistent changes in synaptic efficacy. Such alterations in glutamatergic signaling may have many negative outcomes, including altered vagal motoneuron excitability and a subsequent disruption to parasympathetic control of several GI functions, including gastric motility, tone, and emptying, as well as intestinal motility and transit. Given the increasing recognition of the importance of DVC glutamatergic transmission in the regulation of visceral functions, understanding neuroplasticity within these synapses may uncover the mechanistic basis for GI dysfunction in a variety of pathophysiological states.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.C. and K.N.B. drafted manuscript; C.C. and K.N.B. edited and revised manuscript; C.C. and K.N.B. approved final version of manuscript.

REFERENCES

1. **Cummings DE, Overduin J.** Gastrointestinal regulation of food intake. *J Clin Invest* 117: 13–23, 2007. doi:10.1172/JCI30227.

2. **Janssen P, Vanden Berghe P, Verschueren S, Lehmann A, Depoortere I, Tack J.** Review article: the role of gastric motility in the control of food intake. *Aliment Pharmacol Ther* 33: 880–894, 2011. doi:10.1111/j.1365-2036.2011.04609.x.

3. **Hunt RH, Camilleri M, Crowe SE, El-Omar EM, Fox JG, Kuipers EJ, Malfertheiner P, McColl KE, Pritchard DM, Rugge M, Sonnenberg A, Sugano K, Tack J.** The stomach in health and disease. *Gut* 64: 1650–1668, 2015. doi:10.1136/gutjnl-2014-307595.

4. **Furness JB.** The enteric nervous system and neurogastroenterology. *Nat Rev Gastroenterol Hepatol* 9: 286–294, 2012. doi:10.1038/nrgastro.2012.32.

5. **Browning KN, Travagli RA.** Central control of gastrointestinal motility. *Curr Opin Endocrinol Diabetes Obes* 26: 11–16, 2019. doi:10.1097/MED.0000000000000449.

6. **Travagli RA, Anselmi L.** Vagal neurocircuitry and its influence on gastric motility. *Nat Rev Gastroenterol Hepatol* 13: 389–401, 2016. doi:10.1038/nrgastro.2016.76.

7. **Browning KN, Travagli RA.** Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Compr Physiol* 4: 1339–1368, 2014. doi:10.1002/cphy.c130055.

8. **Babic T, Browning KN, Travagli RA.** Differential organization of excitatory and inhibitory synapses within the rat dorsal vagal complex. *Am J Physiol Gastrointest Liver Physiol* 300: G21–G32, 2011. doi:10.1152/ajpgi.00363.2010.

9. **Davis SF, Derbenev AV, Williams KW, Glatzer NR, Smith BN.** Excitatory and inhibitory local circuit input to the rat dorsal motor nucleus of the vagus originating from the nucleus tractus solitarius. *Brain Res* 1017: 208–217, 2004. doi:10.1016/j.brainres.2004.05.049.

10. **Travagli RA, Gillis RA, Rossiter CD, Vicini S.** Glutamate and GABA-mediated synaptic currents in neurons of the rat dorsal motor nucleus of the vagus. *Am J Physiol Gastrointest Liver Physiol* 260: G531–G536, 1991. doi:10.1152/ajpgi.1991.260.3.G531.

11. **Sivarao DV, Krowicki ZK, Abrahams TP, Hornby PJ.** Vagally-regulated gastric motor activity: evidence for kainate and NMDA receptor mediation. *Eur J Pharmacol* 368: 173–182, 1999. doi:10.1016/s0014-2999(99)00015-1.

12. **Sivarao DV, Krowicki ZK, Hornby PJ.** Role of GABA$_A$ receptors in rat hindbrain nuclei controlling gastric motor function. *Neurogastroenterol Motility* 10: 305–313, 1998. doi:10.1046/j.1365-2982.1998.00110.x.

13. **Berthoud HR, Powley TL.** Morphology and distribution of efferent vagal innervation of rat pancreas as revealed with anterograde transport of DiI. *Brain Res* 553: 336–341, 1991. doi:10.1016/0006-8993(91)90846-n.

14. **Mussa BM, Verberne AJ.** Activation of the dorsal vagal nucleus increases pancreatic exocrine secretion in the rat. *Neurosci Lett* 433: 71–76, 2008. doi:10.1016/j.neulet.2007.12.048.

15. **Boychuk CR, Smith KC, Peterson LE, Boychuk JA, Butler CR, Derera ID, McCarthy JJ, Smith BN.** A hindbrain inhibitory microcircuit mediates vagally-coordinated glucose regulation. *Sci Rep* 9: 2722, 2019. doi:10.1038/s41598-019-39490-x.

16. **Kwon E, Joung HY, Liu SM, Chua SC Jr, Schwartz GJ, Jo YH.** Optogenetic stimulation of the liver-projecting melanocortinergic pathway promotes hepatic glucose production. *Nat Commun* 11: 6295, 2020. doi:10.1038/s41467-020-20160-w.

17. **Bach EC, Halmos KC, Smith BN.** Enhanced NMDA receptor-mediated modulation of excitatory neurotransmission in the dorsal vagal complex of streptozotocin-treated, chronically hyperglycemic mice. *PLoS One* 10: e0121022, 2015. doi:10.1371/journal.pone.0121022.

18. **Blake CB, Smith BN.** Insulin reduces excitation in gastric-related neurons of the dorsal motor nucleus of the vagus. *Am J Physiol Regul Integr Comp Physiol* 303: R807–R814, 2012. doi:10.1152/ajpregu.00276.2012.

19. **Clyburn C**, **Travagli RA**, **Browning KN.** Acute high-fat diet upregulates glutamatergic signaling in the dorsal motor nucleus of the vagus. *Am J Physiol Gastrointest Liver Physiol* 314: G623–G634, 2018. doi:10.1152/ajpgi.00395.2017.

20. **Zhao H**, **Peters JH**, **Zhu M**, **Page SJ**, **Ritter RC**, **Appleyard SM.** Frequency-dependent facilitation of synaptic throughput via postsynaptic NMDA receptors in the nucleus of the solitary tract. *J Physiol* 593: 111–125, 2015. doi:10.1113/jphysiol.2013.258103.

21. **Babic T**, **Travagli RA.** Acute pancreatitis decreases the sensitivity of pancreas-projecting dorsal motor nucleus of the vagus neurones to group II metabotropic glutamate receptor agonists in rats. *J Physiol* 592: 1411–1421, 2014. doi:10.1113/jphysiol.2013.270108.

22. **de Lartigue G.** Putative roles of neuropeptides in vagal afferent signaling. *Physiol Behav* 136: 155–169, 2014. doi:10.1016/j.physbeh.2014.03.011.

23. **Andresen MC**, **Yang M.** Non-NMDA receptors mediate sensory afferent synaptic transmission in medial nucleus tractus solitarius. *Am J Physiol Heart Circ Physiol* 259: H1307–H1311, 1990. doi:10.1152/ajpheart.1990.259.4.H1307.

24. **Lin LH**, **Talman WT.** Vesicular glutamate transporters and neuronal nitric oxide synthase colocalize in aortic depressor afferent neurons. *J Chem Neuroanat* 32: 54–64, 2006. doi:10.1016/j.jchemneu.2006.04.004.

25. **Saha S**, **Batten TF**, **McWilliam PN.** Glutamate-immunoreactivity in identified vagal afferent terminals of the cat: a study combining horseradish peroxidase tracing and postembedding electron microscopic immunogold staining. *Exp Physiol* 80: 193–202, 1995. doi:10.1113/expphysiol.1995.sp003839.

26. **Allchin RE**, **Batten TF**, **McWilliam PN**, **Vaughan PF.** Electrical stimulation of the vagus increases extracellular glutamate recovered from the nucleus tractus solitarii of the cat by in vivo microdialysis. *Exp Physiol* 79: 265–268, 1994. doi:10.1113/expphysiol.1994.sp003761.

27. **Granata AR**, **Sved AF**, **Reis DJ.** In vivo release by vagal stimulation of L-[^{3}H] glutamic acid in the nucleus tractus solitarius preloaded with L-[^{3}H] glutamine. *Brain Res Bull* 12: 5–9, 1984. doi:10.1016/0361-9230(84)90207-7.

28. **Zhang X**, **Fogel R.** Involvement of glutamate in gastrointestinal vago-vagal reflexes initiated by gastrointestinal distention in the rat. *Auton Neurosci* 103: 19–37, 2003. doi:10.1016/S1566-0702(02)00145-5.

29. **Doyle MW**, **Andresen MC.** Reliability of monosynaptic sensory transmission in brain stem neurons in vitro. *J Neurophysiol* 85: 2213–2223, 2001. doi:10.1152/jn.2001.85.5.2213.

30. **Hay M**, **McKenzie H**, **Lindsley K**, **Dietz N**, **Bradley SR**, **Conn PJ**, **Hasser EM.** Heterogeneity of metabotropic glutamate receptors in autonomic cell groups of the medulla oblongata of the rat. *J Comp Neurol* 403: 486–501, 1999.

31. **Kessler J-P**, **Baude A.** Distribution of AMPA receptor subunits GluR1-4 in the dorsal vagal complex of the rat: a light and electron microscope immunocytochemical study. *Synapse* 34: 55–67, 1999. doi:10.1002/(SICI)1098-2396(199910)34:1<55::AID-SYN7>3.0.CO;2-B.

32. **Kaeser PS**, **Regehr WG.** Molecular mechanisms for synchronous, asynchronous, and spontaneous neurotransmitter release. *Annu Rev Physiol* 76: 333–363, 2014. doi:10.1146/annurev-physiol-021113-170338.

33. **Fenwick AJ**, **Wu SW**, **Peters JH.** Isolation of TRPV1 independent mechanisms of spontaneous and asynchronous glutamate release at primary afferent to NTS synapses. *Front Neurosci* 8: 6, 2014. doi:10.3389/fnins.2014.00006.

34. **Peters JH**, **McDougall SJ**, **Fawley JA**, **Smith SM**, **Andresen MC.** Primary afferent activation of thermosensitive TRPV1 triggers asynchronous glutamate release at central neurons. *Neuron* 65: 657–669, 2010. doi:10.1016/j.neuron.2010.02.017.

35. **Altschuler SM**, **Bao X**, **Bieger D**, **Hopkins DA**, **Miselis RR.** Viscerotopic representation of the upper alimentary tract in the rat: sensory ganglia and nuclei of the solitary and spinal trigeminal tracts. *J Comp Neurol* 283: 248–268, 1989. doi:10.1002/cne.902830207.

36. **Babic T**, **Ambler J**, **Browning KN**, **Travagli RA.** Characterization of synapses in the rat subnucleus centralis of the nucleus tractus solitarius. *J Neurophysiol* 113: 466–474, 2015. doi:10.1152/jn.00598.2014.

37. **Fry M**, **Ferguson AV.** The sensory circumventricular organs: brain targets for circulating signals controlling ingestive behavior. *Physiol Behav* 91: 413–423, 2007. doi:10.1016/j.physbeh.2007.04.003.

38. **Baptista V**, **Zheng ZL**, **Coleman FH**, **Rogers RC**, **Travagli RA.** Cholecystokinin octapeptide increases spontaneous glutamatergic synaptic transmission to neurons of the nucleus tractus solitarius centralis. *J Neurophysiol* 94: 2763–2771, 2005. doi:10.1152/jn.00351.2005.

39. **Appleyard SM**, **Bailey TW**, **Doyle MW**, **Jin YH**, **Smart JL**, **Low MJ**, **Andresen MC.** Proopiomelanocortin neurons in nucleus tractus solitarius are activated by visceral afferents: regulation by cholecystokinin and opioids. *J Neurosci* 25: 3578–3585, 2005. doi:10.1523/JNEUROSCI.4177-04.2005.

40. **Hosford PS**, **Mifflin SW**, **Ramage AG.** 5-Hydroxytryptamine-mediated neurotransmission modulates spontaneous and vagal-evoked glutamate release in the nucleus of the solitary tract effect of uptake blockade. *J Pharmacol Exp Ther* 349: 288–296, 2014. doi:10.1124/jpet.113.211334.

41. **Reiner DJ**, **Mietlicki-Baase EG**, **McGrath LE**, **Zimmer DJ**, **Bence KK**, **Sousa GL**, **Konanur VR**, **Krawczyk J**, **Burk DH**, **Kanoski SE**, **Hermann GE**, **Rogers RC**, **Hayes MR.** Astrocytes regulate GLP-1 receptor-mediated effects on energy balance. *J Neurosci* 36: 3531–3540, 2016. doi:10.1523/JNEUROSCI.3579-15.2016.

42. **Swartz EM**, **Browning KN**, **Travagli RA**, **Holmes GM.** Ghrelin increases vagally mediated gastric activity by central sites of action. *Neurogastroenterol Motil* 26: 272–282, 2014. doi:10.1111/nmo.12261.

43. **Wan S**, **Browning KN.** Glucose increases synaptic transmission from vagal afferent central nerve terminals via modulation of 5HT3 receptors. *Am J Physiol Gastrointest Liver Physiol* 295: G1050–G1057, 2008. doi:10.1152/ajpgi.90288.2008.

44. **Dockray GJ.** Gastrointestinal hormones and the dialogue between gut and brain. *J Physiol* 592: 2927–2941, 2014. doi:10.1113/jphysiol.2014.270850.

45. **Roberts BL**, **Zhu M**, **Zhao H**, **Dillon C**, **Appleyard SM.** High glucose increases action potential firing of catecholamine neurons in the nucleus of the solitary tract by increasing spontaneous glutamate inputs. *Am J Physiol Regul Integr Comp Physiol* 313: R229–R239, 2017. doi:10.1152/ajpregu.00413.2016.

46. **Wan S**, **Browning KN.** D-Glucose modulates synaptic transmission from the central terminals of vagal afferent fibers. *Am J Physiol Gastrointest Liver Physiol* 294: G757–G763, 2008. doi:10.1152/ajpgi.00576.2007.

47. **Kentish SJ**, **Frisby CL**, **Kennaway DJ**, **Wittert GA**, **Page AJ.** Circadian variation in gastric vagal afferent mechanosensitivity. *J Neurosci* 33: 19238–19242, 2013. doi:10.1523/JNEUROSCI.3846-13.2013.

48. **Kaneko K**, **Yamada T**, **Tsukita S**, **Takahashi K**, **Ishigaki Y**, **Oka Y**, **Katagiri H.** Obesity alters circadian expressions of molecular clock genes in the brainstem. *Brain Res* 1263: 58–68, 2009. doi:10.1016/j.brainres.2008.12.071.

49. **Guard DB**, **Swartz TD**, **Ritter RC**, **Burns GA**, **Covasa M.** NMDA NR2 receptors participate in CCK-induced reduction of food intake and hindbrain neuronal activation. *Brain Res* 1266: 37–44, 2009. doi:10.1016/j.brainres.2009.02.003.

50. **Glaum SR**, **Miller RJ.** Metabotropic glutamate receptors depress afferent excitatory transmission in the rat nucleus tractus solitarii. *J Neurophysiol* 70: 2669–2672, 1993. doi:10.1152/jn.1993.70.6.2669.

51. **Ohi Y**, **Kimura S**, **Haji A.** Modulation of glutamatergic transmission by presynaptic N-methyl-D-aspartate mechanisms in second-order neurons of the rat nucleus tractus solitarius. *Neurosci Lett* 587: 62–67, 2015. doi:10.1016/j.neulet.2014.12.031.

52. **Chen C-Y**, **Ling E-h**, **Horowitz JM**, **Bonham AC.** Synaptic transmission in nucleus tractus solitarius is depressed by Group II and III but not Group I presynaptic metabotropic glutamate receptors in rats. *J Physiol* 538: 773–786, 2002. doi:10.1113/jphysiol.2001.012948.

53. **Fernandes LG**, **Jin YH**, **Andresen MC.** Heterosynaptic crosstalk: GABA-glutamate metabotropic receptors interactively control glutamate release in solitary tract nucleus. *Neuroscience* 174: 1–9, 2011. doi:10.1016/j.neuroscience.2010.11.053.

54. **Browning KN**, **Travagli RA.** Functional organization of presynaptic metabotropic glutamate receptors in vagal brainstem circuits. *J Neurosci* 27: 8979–8988, 2007. doi:10.1523/JNEUROSCI.1105-07.2007.

55. **Chowen JA**, **Argente J**, **Horvath TL.** Uncovering novel roles of nonneuronal cells in body weight homeostasis and obesity. *Endocrinology* 154: 3001–3007, 2013. doi:10.1210/en.2013-1303.

56. **Bonansco C**, **Couve A**, **Perea G**, **Ferradas CA**, **Roncagliolo M**, **Fuenzalida M.** Glutamate released spontaneously from astrocytes sets the threshold for synaptic plasticity. *Eur J Neurosci* 33: 1483–1492, 2011. doi:10.1111/j.1460-9568.2011.07631.x.

57. **Jourdain P**, **Bergersen LH**, **Bhaukaurally K**, **Bezzi P**, **Santello M**, **Domercq M**, **Matute C**, **Tonello F**, **Gundersen V**, **Volterra A.** Glutamate exocytosis from astrocytes controls synaptic strength. *Nat Neurosci* 10: 331–339, 2007. doi:10.1038/nn1849.

58. **Pascual O**, **Ben Achour S**, **Rostaing P**, **Triller A**, **Bessis A.** Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. *Proc Natl Acad Sci USA* 109: E197–E205, 2012. doi:10.1073/pnas.1111098109.

59. **Fiacco TA**, **Agulhon C**, **Taves SR**, **Petravicz J**, **Casper KB**, **Dong X**, **Chen J**, **McCarthy KD.** Selective stimulation of astrocyte calcium in situ does not affect neuronal excitatory synaptic activity. *Neuron* 54: 611–626, 2007. doi:10.1016/j.neuron.2007.04.032.

60. **Fellin T**, **Carmignoto G.** Neurone-to-astrocyte signalling in the brain represents a distinct multifunctional unit. *J Physiol* 559: 3–15, 2004. doi:10.1113/jphysiol.2004.063214.

61. **MacDonald AJ**, **Holmes FE**, **Beall C**, **Pickering AE**, **Ellacott KLJ.** Regulation of food intake by astrocytes in the brainstem dorsal vagal complex. *Glia* 68: 1241–1254, 2020. doi:10.1002/glia.23774.

62. **Matott MP**, **Kline DD**, **Hasser EM.** Glial EAAT2 regulation of extracellular nTS glutamate critically controls neuronal activity and cardiorespiratory reflexes. *J Physiol* 595: 6045–6063, 2017. doi:10.1113/JP274620.

63. **Talman WT**, **Dragon DN**, **Lin L-H.** Reduced responses to glutamate receptor agonists follow loss of astrocytes and astroglial glutamate markers in the nucleus tractus solitarii. *Physiol Rep* 5: e13158, 2017. doi:10.14814/phy2.13158.

64. **Rogers RC**, **McDougal DH**, **Ritter S**, **Qualls-Creekmore E**, **Hermann GE.** Response of catecholaminergic neurons in the mouse hindbrain to glucoprivic stimuli is astrocyte dependent. *Am J Physiol Regul Integr Comp Physiol* 315: R153–R164, 2018. doi:10.1152/ajpregu.00368.2017.

65. **Hermann GE**, **Viard E**, **Rogers RC.** Hindbrain glucoprivation effects on gastric vagal reflex circuits and gastric motility in the rat are suppressed by the astrocyte inhibitor fluorocitrate. *J Neurosci* 34: 10488–10496, 2014. doi:10.1523/JNEUROSCI.1406-14.2014.

66. **Boychuk CR**, **Halmos KC**, **Smith BN.** Diabetes induces GABA receptor plasticity in murine vagal motor neurons. *J Neurophysiol* 114: 698–706, 2015. doi:10.1152/jn.00209.2015.

67. **Boychuk CR**, **Smith BN.** Glutamatergic drive facilitates synaptic inhibition of dorsal vagal motor neurons after experimentally induced diabetes in mice. *J Neurophysiol* 116: 1498–1506, 2016. doi:10.1152/jn.00325.2016.

68. **Pitra MS**, **Smith BN.** Musings on the wanderer: what's new in our understanding of vago-vagal reflexes? VI. Central vagal circuits that control glucose metabolism. *Am J Physiol Gastrointest Liver Physiol* 320: G175–G182, 2021. doi:10.1152/ajpgi.00368.2020.

69. **Ferreira M Jr**, **Browning KN**, **Sahibzada N**, **Verbalis JG**, **Gillis RA**, **Travagli RA.** Glucose effects on gastric motility and tone evoked from the rat dorsal vagal complex. *J Physiol* 536: 141–152, 2001. doi:10.1111/j.1469-7793.2001.t01-1-00141.x.

70. **Grabauskas G**, **Song I**, **Zhou SY**, **Owyang C.** Electrophysiological identifications of glucose-sensing neurons in the rat nodose ganglia. *J Physiol* 588: 617–632, 2010. doi:10.1113/jphysiol.2009.182147.

71. **Nigrovic LE**, **Kimia AA**, **Shah SS**, **Neuman MI.** Relationship between cerebrospinal fluid glucose and serum glucose. *N Engl J Med* 366: 576–578, 2012. doi:10.1056/NEJMc1111080.

72. **Verbeek MM**, **Leen WG**, **Willemsen MA**, **Slats D**, **Claassen JA.** Hourly analysis of cerebrospinal fluid glucose shows large diurnal fluctuations. *J Cereb Blood Flow Metab* 36: 899–902, 2016. doi:10.1177/0271678X16637612.

73. **Thor KB**, **Helke CJ.** Serotonin and substance P colocalization in medullary projections to the nucleus tractus solitarius: dual-colour immunohistochemistry combined with retrograde tracing. *J Chem Neuroanat* 2: 139–148, 1989.

74. **Balfour RH**, **Hansen AM**, **Trapp S.** Neuronal responses to transient hypoglycaemia in the dorsal vagal complex of the rat brainstem. *J Physiol* 570: 469–484, 2006. doi:10.1113/jphysiol.2005.098822.

75. **de Lartigue G**, **de La Serre CB**, **Raybould HE.** Vagal afferent neurons in high fat diet-induced obesity; intestinal microflora, gut inflammation and cholecystokinin. *Physiol Behav* 105: 100–105, 2011. doi:10.1016/j.physbeh.2011.02.040.

76. **Kentish S**, **Li H**, **Philp LK**, **O'donnell TA**, **Isaacs NJ**, **Young RL**, **Wittert GA**, **Blackshaw LA**, **Page AJ.** Diet-induced adaptation of vagal afferent function. *J Physiol* 590: 209–221, 2012. doi:10.1113/jphysiol.2011.222158.

77. **McMenamin CA**, **Travagli RA**, **Browning KN.** Perinatal high fat diet increases inhibition of dorsal motor nucleus of the vagus neurons regulating gastric functions. *Neurogastroenterol Motil* 30: e13150, 2018. doi:10.1111/nmo.13150.

78. **Troy AE**, **Simmonds SS**, **Stocker SD**, **Browning KN.** High fat diet attenuates glucose-dependent facilitation of 5-HT$_3$ -mediated responses in rat gastric vagal afferents. *J Physiol* 594: 99–114, 2016. doi:10.1113/JP271558.

79. **Bhagat R**, **Fortna SR**, **Browning KN.** Exposure to a high fat diet during the perinatal period alters vagal motoneurone excitability, even in the absence of obesity. *J Physiol* 593: 285–303, 2015. doi:10.1113/jphysiol.2014.282806.

80. **Woods SC**, **D'Alessio DA.** Central control of body weight and appetite. *J Clin Endocrinol Metab* 93: S37–50, 2008. doi:10.1210/jc.2008-1630.

81. **MacDonald AJ**, **Ellacott KLJ.** Astrocytes in the nucleus of the solitary tract: contributions to neural circuits controlling physiology. *Physiol Behav* 223: 112982, 2020. doi:10.1016/j.physbeh.2020.112982.

82. **Langle SL**, **Poulain DA**, **Theodosis DT.** Neuronal-glial remodeling: a structural basis for neuronal-glial interactions in the adult hypothalamus. *J Physiol Paris* 96: 169–175, 2002. doi:10.1016/s0928-4257(02)00003-7.

83. **Waise TM**, **Toshinai K**, **Naznin F**, **NamKoong C**, **Md Moin AS**, **Sakoda H**, **Nakazato M.** One-day high-fat diet induces inflammation in the nodose ganglion and hypothalamus of mice. *Biochem Biophys Res Commun* 464: 1157–1162, 2015. doi:10.1016/j.bbrc.2015.07.097.

84. **Dalvi PS**, **Chalmers JA**, **Luo V**, **Han D-Y**, **Wellhauser L**, **Liu Y**, **Tran DQ**, **Castel J**, **Luquet S**, **Wheeler MB**, **Belsham DD.** High fat induces acute and chronic inflammation in the hypothalamus: effect of high-fat diet, palmitate and TNF-alpha on appetite-regulating NPY neurons. *Int J Obes* 41: 149–158, 2017. doi:10.1038/ijo.2016.183.

85. **Douglass JD**, **Dorfman MD**, **Fasnacht R**, **Shaffer LD**, **Thaler JP.** Astrocyte IKKβ/NF-κB signaling is required for diet-induced obesity and hypothalamic inflammation. *Mol Metab* 6: 366–373, 2017. doi:10.1016/j.molmet.2017.01.010.

86. **Jayaram B**, **Khan RS**, **Kastin AJ**, **Hsuchou H**, **Wu X**, **Pan W.** Protective role of astrocytic leptin signaling against excitotoxicity. *J Mol Neurosci* 49: 523–530, 2013. doi:10.1007/s12031-012-9924-0.

87. **Camilleri M**, **Bharucha AE**, **Farrugia G.** Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 9: 5–12, 2011. doi:10.1016/j.cgh.2010.09.022.

88. **Henning J**, **Strauss U**, **Wree A**, **Gimsa J**, **Rolfs A**, **Benecke R**, **Gimsa U.** Differential astroglial activation in 6-hydroxydopamine models of Parkinson's disease. *Neurosci Res* 62: 246–253, 2008. doi:10.1016/j.neures.2008.09.001.

89. **Anselmi L**, **Toti L**, **Bove C**, **Hampton J**, **Travagli RA.** A nigro-vagal pathway controls gastric motility and is affected in a rat model of parkinsonism. *Gastroenterology* 153: 1581–1593, 2017. doi:10.1053/j.gastro.2017.08.069.

90. **Femminella GD**, **Rengo G**, **Komici K**, **Iacotucci P**, **Petraglia L**, **Pagano G**, **de Lucia C**, **Canonico V**, **Bonaduce D**, **Leosco D**, **Ferrara N.** Autonomic dysfunction in Alzheimer's disease: tools for assessment and review of the literature. *J Alzheimers Dis* 42: 369–377, 2014. doi:10.3233/JAD-140513.

91. **Kang V**, **Wagner GC**, **Ming X.** Gastrointestinal dysfunction in children with autism spectrum disorders. *Autism Res* 7: 501–506, 2014. doi:10.1002/aur.1386.