Glucose increases synaptic transmission from vagal afferent central nerve terminals via modulation of 5-HT\textsubscript{3} receptors

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Submitted 14 April 2008; accepted in final form 12 September 2008

Wan S, Browning KN. Glucose increases synaptic transmission from vagal afferent central nerve terminals via modulation of 5-HT\textsubscript{3} receptors. Am J Physiol Gastrointest Liver Physiol 295: G1050–G1057, 2008. First published September 18, 2008; doi:10.1152/ajpgi.90288.2008.—Acute hyperglycemia has profound effects on vagally mediated gastrointestinal functions. We have reported recently that the release of glutamate from the central terminals of vagal afferent neurons is correlated directly with the extracellular glucose concentration. The present study was designed to test the hypothesis that 5-HT\textsubscript{3} receptors present on vagal afferent nerve terminals are involved in this glucose-dependent modulation of glutamatergic synaptic transmission. Whole-cell patch-clamp recordings were made from neurons of the nucleus tractus solitarius (NTS) in thin rat brainstem slices. Spontaneous and evoked glutamate release was decreased in a concentration-dependent manner by the 5-HT\textsubscript{3} receptor selective antagonist, ondansetron. Alterations in the extracellular glucose concentration induced parallel shifts in the ondansetron-mediated inhibition of glutamate release. The changes in excitatory synaptic transmission induced by extracellular glucose concentration were mimicked by the serotonin uptake inhibitor, fenfluramine. These data suggest that glucose alters excitatory synaptic transmission within the rat brainstem via actions on tonically active 5-HT\textsubscript{3} receptors, and the number of 5-HT\textsubscript{3} receptors on vagal afferent nerve terminals is positively correlated with the extracellular glucose concentration. These data indicate that the 5-HT\textsubscript{3} receptors present on synaptic connections between vagal afferent nerve terminals and NTS neurons are a strong candidate for consideration as one of the sites where glucose acts to modulate vagovagal reflexes.

brainstem; electrophysiology

ALTERATIONS IN BLOOD GLUCOSE levels have profound effects on gastrointestinal functions (12, 23, 34, 57, 72). Gastric emptying is delayed by physiological hyperglycemia, for example, but accelerated by hypoglycemia (12, 44, 57). Several lines of experimental evidence suggest that these glucose-induced alterations in gastric functions occur, at least in part, via modulation of the vagovagal reflexes controlling the stomach (24, 61). The vagus nerve provides the parasympathetic motor and sensory innervation to the stomach and, at their most basic, vagovagal reflexes consist of three components. Sensory information from the viscera is relayed to the central nervous system via chemo- and mechanosensory vagal afferent fibers that terminate within the brainstem at the level of the nucleus of the tractus solitarius (NTS) using glutamate as their principal neurotransmitter (3, 9, 26), resulting in the excitation of NTS neurons. These NTS neurons then project to, among other areas, the adjacent dorsal motor nucleus of the vagus (DMV), which contains the preganglionic parasympathetic neurons that provide the motor output to the GI tract via the efferent vagus (70).

Glucose is known to exert prominent excitatory effects on vagal afferent neurons and nerve terminals both centrally and peripherally. At the central level, microinjection of glucose into either the DMV or the NTS decreases gastric motility and secretion (24, 58, 61) although a recent study did not observe any effects on gastric relaxation following mild hyperglycemia due to intracisternal application of dextrose (79). Several studies have demonstrated that subpopulations of NTS and DMV neurons respond to alterations in glucose by either increasing or decreasing their activity (1, 6, 7, 18, 19, 48, 73, 77, 78), and we have demonstrated recently that synaptic transmission from the central nerve terminals of vagal afferent neurons is dependent upon glucose concentration (73), suggesting that the synaptic connections between vagal afferent fibers and NTS neurons are a probable site of action of glucose to modulate vagovagal reflexes.

At a peripheral level, both vagal afferent neurons and nerve terminals are excited by glucose in a concentration-dependent manner (29, 46, 47). Although glucose appears capable of exciting vagal afferent neurons directly (29), at least part of the glucose-induced excitation of vagal afferent nerves is indirect, or paracrine, in nature. In particular, glucose within the intestinal tract induces the release of 5-HT from enteroendocrine cells. 5-HT then activates 5-HT\textsubscript{3} receptors on vagal afferent nerve terminals, and this signal is then translated centrally (32, 43, 53–56, 80).

5-HT\textsubscript{3} receptors are ubiquitous throughout the central and peripheral nervous systems, and the highest density of these receptors in the central nervous system is found within the dorsal vagal complex (21, 66). Many of these 5-HT\textsubscript{3} receptors are located on the nerve terminals of vagal afferent neurons since vagotomy was found to decrease 5-HT\textsubscript{3} receptor binding dramatically (41, 42, 51). The NTS receives a prominent serotonergic innervation from other brainstem nuclei, mostly notable the medullary raphe nuclei (64, 65, 69), although vagal afferent neurons themselves contain 5-HT (49, 67).

It has been recognized for several years that, at least with respect to cardiovascular vagal circuits, 5-HT modulates synaptic transmission at this first central vagal synapse via activation of 5-HT\textsubscript{3} receptors on vagal afferent nerve terminals (28, 35, 37, 38, 52, 74). Activation of 5-HT\textsubscript{3} receptors within
5-HT3 antagonists have been used clinically to treat the gastroparesis associated with diabetes (45). Although a large proportion of gastric afferent nerve terminals are involved in the ability of perfusion chamber (volume 500 ml; 120 NaCl, 26 NaHCO3, 3.75 KCl, 1 MgCl2, 2 CaCl2, and 10 mM glucose, maintained at pH 7.4 with 95% O2-5% CO2) at 25°C for at least 90 min before use. A single slice was placed in a custom-made mEPSCs, respectively), neurons were voltage clamped at 60 mV, to block sodium currents and prevent action potential-mediated synaptic transmission, respectively.

Data were acquired with the use of a single electrode voltage clamp amplifier (Axopatch 200B or 1D, Axon Instruments, Foster City, CA; acquisition rate of 10 kHz, filtered at 2 kHz, and digitized via a Digidata 1320 interface) before being stored and analyzed on a personal computer utilizing pClamp software (Axon Instruments) or Mini Analysis software (Jaejin Software, Leonia, NJ). Only record-ings with a series resistance (i.e., access + pipette resistance) <15 MΩ were used.

Electrical stimulation. Tungsten bipolar stimulating electrodes (tip size 1–5 μm, electrode tip separation ~125 μm; World Precision Instruments, Sarasota, FL) placed in the tractus solitarius (TS) were used to evoke synaptic currents in the recorded cNTS or mNTS neurons. Pairs of stimuli (0.05–1.0 ms, 10–500 μA, 35–400 ms apart) were applied every 20 s to evoke submaximal EPSCs. The stimulus interval was altered to allow the first stimulated current to decay completely before the second stimulus was applied but was kept constant throughout each neuronal recording. The paired-pulse ratio was calculated as the amplitude of the second current relative to that of the first; alterations in the paired-pulse ratio are suggestive of a presynaptic site of action (14, 20, 40, 71, 81).

Equiosmolar Krebs solutions containing 5, 10, or 20 mM glucose (295–305 mosmol/kgH2O, balanced by adjusting the NaCl concentration) were applied by superfusion, through a series of manually operated valves, for periods of time sufficient for the response to reach plateau. Each neuron served as its own control; that is, the neuronal response was assessed before and after exchanging the glucose concentration (or before and after drug application, respectively). Each neuron was tested with more than one concentration of glucose (or drug), and the results were normalized to the effects of 10 mM glucose or the response in the absence of drug to reduce interneuronal variation. Results were compared using the ANOVA (single factor) or the Students t-test with statistical significance set at 5%. Only responding neurons were included in the statistical analysis, and results expressed as means ± SE.

Vagal deafferentation. A unilateral vagal nerve deafferentation was performed in 4 rats, as described previously (8, 13, 14). Rats were anesthetized with a mixture of ketamine/acepromazine/xylazine in saline (80/1.6/5.0 mg/kg, respectively) and were placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA) once a deep level of anesthesia was obtained. A dorso-lateral incision was made at the level of the occipital bone, and the muscle tissue was blunt dissected to expose the cervical vertebrae and the occipital bone. The occipital bone was “shaved” to reveal all three supranodose vagal dorsal afferent rootlets on one vagal trunk that were then sectioned under microscopic guidance using a 27-gauge needle. The incision was closed with 5/0 suture, and the rats were allowed to recover for 4–5 days before experimentation. Hereafter, these rats will be referred to as “deafferented.” Although we realize that, in cutting the brainstem slices to perform electrophysiological recordings implies that the vagus nerve trunks are also sectioned, we refer to these rats as “vagally intact” since vagal afferent fibers are still viable in the slice preparation. In each rat, the veracity of the deafferentation was confirmed by the inability of electrical stimulation of the TS to evoke EPSCs in NTS neurons, even at current intensities one order of magnitude greater than that required in vagally intact NTS neurons (8).

Drugs and chemicals. TTX was purchased from Alomone Laboratories (Jerusalem, Israel); all other chemicals were purchased from Sigma (St. Louis, MO).

RESULTS

Whole-cell patch-clamp recordings were made from a total of 93 neurons from 25 rats. Eighteen of these neurons (19%) showed no change in measured response (spontaneous, miniature, or evoked EPSCs) following an alteration in extracellular glucose solution, hence, were classified as glucose unresponsive neurons. Recordings were made from 4 rats that had undergone a unilateral surgical deafferentation, 4–5 days before experimentation. The accuracy of the deafferentation was checked in each rat by recording from neurons in both the deafferented (n = 9) as well as the contralateral vagally intact side (n = 9). Differences were not observed between neurons recorded from the contralateral side of deafferented rats and from vagally intact rats, and, as a result, we assume compensatory responses do not occur within the timeframe of these experiments. Since the NTS is a heterogenous nucleus receiving sensory inputs from cardiovascular, respiratory, and as subdiaphragmatic organs, recordings were restricted to the centralis (c) subnucleus of the NTS. The cNTS receives inputs...
The glucose-dependent modulation of glutamate release is dependent upon 5-HT3 receptors. When voltage was clamped at −60 mV, the frequency of sEPSCs in control (10 mM) glucose Krebs solution was 2.4 ± 0.69 events/s (n = 6). The glutamatergic nature of these currents was confirmed by their complete abolition following perfusion with the nonselective ionotropic glutamate receptor antagonist, kynurenic acid (1 mM, data not shown). As demonstrated previously (64), sEPSC frequency was dependent upon the concentration of the perfusing glucose solution, decreasing to 1.6 ± 0.71 events/s within 5 min of perfusion with 5 mM glucose (P < 0.05, n = 6). In 20 mM glucose, the frequency of sEPSCs was 2.7 ± 0.80 events/s (P > 0.05, n = 4). The 5-HT3 receptor selective antagonist, ondansetron (0.1 μM), inhibited the frequency of sEPSCs reversibly in all 14 neurons tested, by 64 ± 1.8%, 66.4 ± 6.2%, and 35.3 ± 4.4%, in 5, 10, and 20 mM glucose, respectively (N = 6, 6, 4, respectively; P < 0.05 vs. control). In contrast, the amplitude of sEPSCs was unaffected by ondansetron (97 ± 5%, 99 ± 3.5%, and 97 ± 2.7% of control, respectively, P > 0.05).

These data confirm that the extracellular glucose concentration regulates glutamatergic synaptic transmission to NTS neurons. The ability of the receptor antagonist, ondansetron, to inhibit glutamate release suggests that tonically active 5-HT3 receptors increase synaptic transmission to NTS neurons.

Glucose regulates 5-HT3 receptors present on presynaptic nerve terminals. Ondansetron inhibited the frequency, but not the amplitude, of sEPSCs, which is suggestive of a presynaptic, rather than a postsynaptic, site of action (13, 39, 71). To confirm a presynaptic site of action, we conducted a series of experiments in the presence of TTX (1 μM) to block action potential-dependent synaptic transmission. Under these conditions, in the absence of stimulation, neurotransmitter is released from the nerve terminal at random intervals. The frequency of release can be altered by depolarizing or hyperpolarizing the nerve terminal, but the size of the mEPSC is unaltered since neurotransmitter is released in fixed quantal amounts. Similar to sEPSCs (see above), in the presence of TTX, the ability of ondansetron to decrease mEPSC frequency was dependent upon the glucose concentration of the perfusate. In the presence of 10 mM glucose, ondansetron decreased mEPSC frequency by 49 ± 9.2% (P < 0.05, n = 4). In the presence of 5 mM glucose, the ondansetron-induced inhibition of mEPSC frequency increased to 60 ± 4.0% (P < 0.05, N = 4) but decreased to 35 ± 4.2% in 20 mM glucose (P < 0.05, N = 6; see Fig. 1). Regardless of the concentration of glucose, ondansetron never altered mEPSC amplitude (99 ± 3.5%, 101 ± 3.5%, and 91 ± 3.5% of control in 5, 10, and 20 mM glucose, respectively, P > 0.05 vs. mEPSC amplitude in the absence of ondansetron). The lack of effect of ondansetron on mEPSC amplitude is again indicative of a presynaptic site of action.

These data confirm our earlier demonstration that glucose acts at presynaptic nerve terminals to modulate glutamatergic synaptic transmission (73) and indicate that the effects of ondansetron to inhibit glutamate release are dependent upon the extracellular glucose concentration.

Since vagal afferent fibers provide the majority of glutamatergic input into the NTS, and we have demonstrated previously that glucose modulates glutamate release from these nerve terminals (73), we conducted a series of experiments in which the effects of ondansetron to modulate sEPSCs were assessed in rats that had previously undergone a unilateral selective vagal deafferentation. Ondansetron (0.1 μM) had no effect on either the frequency or amplitude of sEPSCs in these neurons (93 ± 8.6% and 100 ± 2.8%, respectively, n = 9, P > 0.05 vs. control). This suggests that the 5-HT3 receptors affected by extracellular glucose concentration are present on vagal afferent terminals, rather than on terminals of nonvagal origin.

Glucose modulates evoked synaptic currents via actions on presynaptic 5-HT3 receptors. The ability of ondansetron to inhibit synaptic transmission was assessed in 35 further NTS neurons in which EPSCs were evoked by electrical stimulation of the TS. Neurons were perfused with Krebs solution containing 5, 10, or 20 mM glucose and the effects of exposure to ondansetron (0.1–10 μM) on evoked EPSCs amplitude measured. Although the maximum inhibition of EPSC amplitude induced by ondansetron was not altered by the perfusing...
glucose concentration (37.5 ± 1.8%, 39.7 ± 5.4%, and 39.1 ± 4.4% at 5, 10, and 20 mM glucose, respectively, \(P > 0.05\)), the efficacy of ondansetron was dependent upon the glucose concentration of the perfusate. In fact, the estimated IC50 for the efficacy of ondansetron was dependent upon the glucose concentration (37.5 ± 4.4% at 5, 10, and 20 mM glucose, respectively, \(P > 0.05\)).

The facilitatory effects on endogenous 5-HT is dependent upon the glucose concentration. The ability of the antagonist, ondansetron, to inhibit glutamate release was dependent upon the glucose concentration of the perfusing medium, these data suggest that glucose modulates synaptic transmission via alterations in the number of 5-HT3 receptors present on presynaptic nerve terminals.

Since the ability of the receptor antagonist, ondansetron, to inhibit glutamate release was dependent upon the glucose concentration of the perfusing medium, these data suggest that glucose modulates synaptic transmission via alterations in the number of 5-HT3 receptors present on presynaptic nerve terminals.

The facilitatory effects on endogenous 5-HT is dependent upon the glucose concentration. The ability of the antagonist, ondansetron, to alter glutamatergic synaptic transmission suggests that these 5-HT3 receptors are activated tonically. As further confirmation, the ability of the serotonin uptake inhibitor, fenfluramine (10 \(\mu\)M) to facilitate glutamatergic synaptic transmission was assessed in 16 NTS neurons. Specifically, fenfluramine increased the amplitude of EPSCs evoked via electrical stimulation of the TS, and the magnitude of this fenfluramine-induced increase was dependent upon the perfusing glucose concentration increasing from 112 ± 5.2% to 139 ± 4.6% and 160 ± 6.2% of control in 5, 10, and 20 mM glucose, respectively (\(P < 0.05\); Fig. 3). The effect of fenfluramine to increase EPSC amplitude was, indeed, due to its action to prevent serotonin uptake, since, in 6 further neurons (recorded in 10 mM glucose Krebs solution), the ability of fenfluramine to increase eEPSC amplitude was prevented by ondansetron (0.1 \(\mu\)M). Specifically, fenfluramine increased eEPSC amplitude to 141 ± 8.9% of control (\(P < 0.05\)), whereas, in the presence of ondansetron, fenfluramine had no effect (106 ± 2.6% of control; \(P > 0.05\) vs. control). These

![Figure 2](http://ajpgi.physiology.org/)

**Fig. 2.** The inhibition in evoked excitatory postsynaptic current (EPSC) amplitude in response to the 5-HT3 receptor antagonist, ondansetron, is dependent upon the glucose concentration. A: representative traces of paired evoked EPSCs (C1 and C2) from an NTS neuron voltage clamped at −60 mV perfused with 10 mM glucose Krebs solution. The amplitude of the evoked EPSCs was inhibited by perfusion with the 5-HT3 receptor selective antagonist, ondansetron, in a concentration-dependent manner. B: representative traces from an NTS neuron voltage clamped at −60 mV. In the presence of 5 mM glucose Krebs solution, 5-min perfusion with ondansetron (0.1 \(\mu\)M) inhibited EPSC amplitude (left). In the presence of 20 mM glucose, however, the same concentration of ondansetron had little effect on EPSC amplitude (right). C: graphical representation of the concentration-dependent inhibition in EPSC amplitude induced by ondansetron. Note that the maximum inhibition of EPSC amplitude induced by ondansetron was similar at different glucose concentrations. In contrast, increasing the glucose concentration induced a rightwards shift in the ondansetron concentration-response curve i.e., the estimated IC50 was −0.1, 0.4, and 1 \(\mu\)M at 5, 10, and 20 mM glucose.
data suggest that blocking serotonin uptake with fenfluramine increases glutamatergic synaptic transmission to NTS neurons and that glucose modulates the magnitude of this fenfluramine-induced effect, possibly via alterations in the number of 5-HT₃ receptors present on vagal afferent nerve terminals.

**DISCUSSION**

In the present study, we report that acute variations in extracellular glucose concentrations alter the glutamate released from vagal afferent fiber terminals via actions involving presynaptic 5-HT₃ receptors. We have shown that 1) the frequency of spontaneous and miniature EPSCs recorded from NTS neurons was decreased by the 5-HT₃ receptor antagonist, ondansetron, in a glucose-dependent manner; 2) the ability of ondansetron to decrease synaptic event frequency was abolished following selective vagal deafferentation; 3) the amplitude of EPSCs evoked by electrical stimulation of the TS was decreased by ondansetron in a concentration-dependent manner; 4) the estimated IC₅₀ of the ondansetron-induced inhibition was dependent upon the glucose-concentration; and 5) the serotonin-reuptake inhibitor, fenfluramine, increased amplitude of evoked EPSCs in a glucose-dependent manner.

The central terminals of vagal afferent nodose ganglion neurons use glutamate as their principal neurotransmitter (3, 33, 36, 70). We have demonstrated previously that d-glucose modulates neurotransmission from vagal afferent terminals to NTS neurons in a concentration-dependent manner (73), suggesting that this synapse may be one of the sites where glucose acts to modulate vagovagal reflex control of the stomach. A central site of action of glucose in the modulation of gastrointestinal functions still appears to arouse controversy. Several studies have demonstrated profound alterations in gastric tone and motility in response to microinjection of glucose directly into the NTS or the DMV (24, 58, 61), whereas other studies did not observe any noticeable effect following intracerebral application of glucose (79). It is unlikely that these differences can be explained entirely through the disparities in experimental techniques although the latter study used relatively modest alterations in central glucose levels. Although glucose levels of both cerebrospinal fluid and brain parenchyma are consistently 10–30% lower than those of plasma, they are subject to fluctuation in parallel with changes in peripheral glucose levels (62, 63). It is important to recognize that the dorsal vagal complex is essentially a circumventricular organ with large areas being either entirely outside the blood-brain barrier (e.g., the area postrema) or having a “leaky” blood-brain barrier because of the presence of fenestrated capillaries [e.g., NTS and DMV (17, 30)]. Thus neurons within the dorsal vagal complex, including the NTS, are more accessible to circulating factors, including glucose and peripherally administered drugs. This implies that the glucose concentration in the dorsal vagal complex may be greater than in CSF and may approach that of blood glucose levels (63).

Synaptic transmission from vagal afferent terminals to second-order NTS neurons is subject to modulation by a wide variety of neurotransmitters and neuromodulators (4, 10, 11, 22, 27, 37) including glucose (73). Several studies have demonstrated that 5-HT is able to modulate synaptic transmission at this first central vagal synapse via 5-HT₃ receptors present on vagal afferent terminals (28, 37, 75). In the rat, vagal afferent terminals within the NTS display some of the highest densities of 5-HT₃ receptors and play a prominent role in cardiovascular regulation (38, 42, 51, 75). Activation of 5-HT₃ receptors within the NTS results in a rise in blood pressure (37, 38) and inhibition of the bradycardia evoked by chemoreceptor activation (38, 59) as well as inhibition of the Bezold-Jarisch reflex (50, 60). Activation of 5-HT₃ receptors may also play a critical role in gastrointestinal function. Gastric emptying is delayed by 5-HT₃ receptor selective agonists via relaxation of the proximal stomach (16, 31), whereas receptor selective antagonists accelerate gastric transit (25, 56, 76). Indeed, 5-HT₃ antagonists have been used clinically to treat the gastroparesis associated with diabetes (45). Previous studies have also indicated that higher doses of 5-HT₃ antagonists are required to induce the same degree of gastric emptying during conditions of hyperglycemia, such as diabetes (68, 76). The need for increased doses of 5-HT₃ receptor antagonists in hyperglycemic states suggests that these receptors play a relevant role in hyperglycemia-induced alterations in gastric functioning. The site of action of these 5-HT₃ antagonists (central vs. peripheral receptors) remains to be determined. Peripheral autonomic neuropahties characteristic of prolonged diabetes...
may play a role in the resultant need for increased agonist doses; however, we cannot exclude the possibility that the requirement of higher doses of 5-HT₃ antagonists may also be due, in part, to an increase in 5-HT₃ receptor number and/or function (see below).

The present study demonstrates that the 5-HT₃ receptor-mediated modulation of glutamate release between vagal afferent terminals and cNTS neurons was dependent upon the concentration of glucose in the perfusing medium. Indeed, the efficacy of ondansetron to inhibit glutamate release was inversely correlated with the glucose concentration; i.e., in the presence of higher concentrations of glucose, ondansetron was less effective at inhibiting glutamate release (in 20 mM glucose, the estimated IC₅₀ for ondansetron was ~1 μM). Conversely, ondansetron was more effective at inhibiting glutamate release at lower concentrations of glucose (in 5 and 10 mM glucose, the estimated IC₅₀ for ondansetron was ~0.1 and ~0.4 μM, respectively). Similarly, the ability of the serotonin uptake inhibitor, fenfluramine, to facilitate glutamate release was also dependent upon the perfusing glucose concentration. In contrast, however, the facilitatory effect of fenfluramine increased in parallel with the perfusing glucose concentration. That is, at lower concentration of glucose, fenfluramine was less able to increase glutamate release than it was at higher concentrations of glucose. The results of the present study suggest that the glucose-induced modulation of synaptic transmission from vagal afferent nerve terminals occurs via alterations in the number of presynaptic 5-HT₃ receptors. Specifically, as the extracellular glucose concentration increases, the number of 5-HT₃ receptors present on vagal afferent nerve terminals also increases.

At any given concentration, an antagonist is expected to occupy a defined number of receptors. As the number of receptors increases, however, the number of receptors occupied by the same concentration of antagonist will comprise a smaller proportion of the total receptor population. As a result, the antagonist becomes less effective; indeed our data demonstrate that ondansetron is less effective at inhibiting glutamate release at higher glucose concentrations. Conversely, the serotonin uptake inhibitor, fenfluramine, is more effective as the concentration of perfusing glucose increases since the resulting increase of 5-HT present in the synaptic cleft has a larger pool of presynaptic 5-HT₃ receptors upon which it can act.

The rapid time course of the glucose-mediated effects (within 5 min) suggests that the glucose-mediated increase in 5-HT₃ receptors on vagal afferent nerve terminals does not involve de novo receptor synthesis but rather involves alterations in receptor trafficking or vesicular recycling.

The present study also suggested that 5-HT₃ receptors on vagal afferent nerve terminals are activated tonically since the receptor agonist, per se, was able to inhibit synaptic transmission. This is similar to some previous reports demonstrating a decrease in NTS neuronal activity in a small population of neurons following administration of the 5-HT₃ receptor-selective agonist, granisetron (5, 37). Some controversy arises, however, since other reports using anesthetized rat preparations showed that 5-HT₃ receptor antagonists had little, if any, effect (15, 50, 60). Although Jeggo et al. (37) reported effects of 5-HT₃ receptor antagonists in some neurons, this certainly may be due to differences in neuronal preparations (anesthetized in vivo rat models vs. in vitro brainstem slice preparations used in the present study) although it may also represent another potentially relevant difference in the role of 5-HT₃ receptors in cardiovascular and gastrointestinal NTS circuits.

Because of their widespread location, 5-HT₃ receptors are ideally situated to modulate both the peripheral and central processing and modulation of the visceral vagal response to glucose. The present study suggests that the 5-HT₃ receptors present on synaptic connections between vagal afferent nerve terminals and NTS neurons are a strong candidate for consideration as one of the sites where glucose acts to modulate vagovagal reflexes and that glucose modulates the number of these 5-HT₃ receptors on a rapid (minute-to-minute) timescale. This type of adaptation presents a new and intriguing model of sensory neuronal plasticity; glucose is sensed in the GI tract primarily indirectly via a paracrine action to release 5-HT from enteroeンドocrine cells. By also controlling the density and function of 5-HT₃ receptors, glucose appears to also be capable of modulating the neuronal response to the released 5-HT, amplifying or reducing neuronal signaling rapidly as physiological demands dictate.

ACKNOWLEDGMENTS

We thank Dr. R. Alberto Travagli for comments on earlier versions of this manuscript. We also thank W. Nairn Browning for support and encouragement.

GRANTS

This work was supported by a Louisiana Experimental Program to Stimulate Competitive Research grant to K. Browning.

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