D-Glucose modulates synaptic transmission from the central terminals of vagal afferent fibers

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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. First published January 17, 2008; doi:10.1152/ajpgi.00576.2007.—Experimental evidence suggests that glucose modulates gastric functions via vagally mediated effects. It is unclear whether glucose affects only peripheral vagal nerve activity or whether glucose also modulates vagal circuitry at the level of the brain stem. This study used whole cell patch-clamp recordings from neurons of the nucleus of the tractus solitarius (NTS) to assess whether acute variations in glucose modulates vagal brain stem neurocircuitry. Increasing D-glucose concentration induced a postsynaptic response in 54% of neurons; neither the response type (inward vs. outward current) nor response magnitude was altered in the presence of tetrodotoxin suggesting direct effects on the NTS neuronal membrane. In contrast, reducing D-glucose concentration induced a postsynaptic response (inward or outward current) in 54% of NTS neurons; tetrodotoxin abolished these responses, suggesting indirect sites of action. The frequency, but not amplitude, of spontaneous and miniature excitatory postsynaptic currents (EPSCs) was correlated with D-glucose concentration in 79% of neurons tested (n = 48). Prior surgical afferent rhizotomy abolished the ability of D-glucose to modulate spontaneous EPSC frequency, suggesting presynaptic actions at vagal afferent nerve terminals to modulate glutamatergic synaptic transmission. In experiments in which EPSCs were evoked via electrical stimulation of the tractus solitarius, EPSC amplitude correlated with D-glucose concentration. These effects were not mimicked by L-glucose, suggesting the involvement of glucose metabolism, not uptake, in the nerve terminal. These data suggest that the synaptic connections between vagal afferent nerve terminals and NTS neurons are a strong candidate for consideration as one of the sites where glucose-evoked changes in vagovagal reflexes occurs.

brain stem; electrophysiology; vagus

DELAYED GASTRIC EMPTYING, or gastroparesis (diabetic gastropathy) in its extreme state, is reported in ~35–50% of patients with Type 1 or Type 2 diabetes (17, 25, 44, 52) and is associated with early satiety, nausea, vomiting, and abdominal pain. Autonomic nerve dysfunction(s) undoubtedly contribute to the development of this syndrome (52), but reports that physiological hyperglycemia delays gastric emptying have led to the understanding that poor glycemic control per se may be responsible for at least some of these symptoms (25, 26, 37, 38, 45). Acute changes in blood glucose concentration, even within the physiological range, have profound effects on gastrointestinal functions, including gastric emptying. In healthy subjects, gastric emptying of both solids and liquids is slower at a blood glucose concentration of 8 mM than at 4 mM, and profound hyperglycemia (15 mM) causes a clear relaxation of the proximal stomach (29, 37). Hypoglycemia, in contrast, accelerates gastric emptying markedly (7, 37).

Experimental evidence suggests the actions of glucose to alter gastric function involve vagovagal reflexes (18, 41). These reflexes consist of three components, the first of which is a sensory limb comprising chemo- and mechanosensory elements linked to vagal afferent fibers (49). Sensory information from the viscera are transmitted via a glutamatergic synapse into the brain stem at the level of the nucleus tractus solitarius (NTS) (2, 24, 27, 49). The NTS, in turn, sends projections to, among other areas, the efferent vagal neurons in the dorsal motor nucleus of the vagus (DMV), which provides the preganglionic parasympathetic fibers innervating the digestive tract (49).

It is well accepted that glucose has pronounced effects both on peripheral vagal sensory fibers and on central components of vagovagal reflexes (3, 18, 20, 20, 32, 35, 36, 48). In fact, ingestion of glucose increases vagal afferent fiber discharge (20, 30, 31) and increases c-Fos expression in the dorsal vagal complex (53, 57). Furthermore, hyperglycemia enhances vagal afferent gastrointestinal sensory perception (37). It is unclear, however, whether this augmentation occurs at the level of sensory transduction within peripheral vagal afferent nerve terminals, at the level the vagal afferent neurons themselves, or within the brain stem at the level of synaptic transmission from vagal afferent central nerve terminals. To start elucidating the site(s) responsible for glucose modulation of vagovagal reflexes, we aimed to assess whether acute variations of extracellular glucose concentration modulate the vagal brain stem neurocircuitry via actions on the synaptic connections between the tractus solitarius and NTS neurons.

METHODS

All animal protocols employed in the present study were approved by the Institutional Animal Care and Use Committee of the Pennington Biomedical Research Center-LSU System and conform fully to the National Institute of Health guidelines.

Rat brain stem slices comprising the NTS were prepared as described previously (4, 5). In brief, rats 25–35 days old were anesthetized with isoflurane before removal of the brain stem, which was placed immediately in oxygenated chilled Krebs solution (see below for composition). A vibratome was used to cut four to six coronal slices (300 μm) that were incubated in Krebs solution at 25°C for at least 90 min before recording. A single slice was placed in a custom-
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made perfusion chamber (volume 500 μl; Michigan Precision Instruments, Parma, MI) on the stage of a Nikon E600FN microscope and perfused constantly with Krebs solution (2.5–3 ml/min). Electrophysiological recordings were made at room temperature from neurons of the subnuclei centralis (cNTS) and medialis (mNTS) under brightfield illumination using Nomarski optics.

Whole cell patch-clamp recordings were made by using pipettes of 4–7 MΩ resistance when filled with K-glucuronate. When recording spontaneous or miniature excitatory postsynaptic currents (EPSCs; sEPSCs or mEPSCs, respectively), neurons were voltage clamped at −60 mV, and all recordings were carried in the presence of bicuculline (50 μM) to prevent GABAergic currents or bicuculline and TTX (1 μM) to block sodium currents and prevent action potential-mediated synaptic transmission. The recording pipette solution contained lidocaine N-ethyl bromide (0.5 μM) to prevent antidromically activated action potentials. Recordings were conducted at −60 mV.

Data were acquired by using 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 pClamp9 software (Axon Instruments) or Mini Analysis software (Jaejin Software, Leonia, NJ). Only recordings 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; WPI, Sarasota, FL) placed in the tractus solitarii 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 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 (9, 15, 28, 50, 58).

Equimolar solutions (295–305 mOsm; balanced by adjusting the NaCl concentration) were applied by superfusion through a series of manually operated valves, and glucose concentrations were applied for sufficient periods of time for the response to reach plateau. Each neuron served as its own control; that is, the neuronal response was assessed before and after exchange of the glucose concentration. Results were compared using the ANOVA (single factor) or Student’s t-test with statistical significance set at 5%. Only responding neurons were included in the statistical analysis, and results are expressed as means ± SE.

Vagal deafferentation. A unilateral vagal nerve deafferentation was performed in three rats, as described previously (4, 8, 9). Briefly, rats were anesthetized with a mixture of ketamine-acepromazine-xylazine in saline (80:1.6:5.0 mg/kg, respectively). After a deep level of anesthesia was obtained (abolition of the foot-pinch withdrawal reflex), rats were placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA). A dorsolateral 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. After “shaving” of the occipital bone, all three supraneurodinal vagal dorsal afferent rootlets on one vagal trunk were sectioned under microscopic guidance by use of a 27-gauge needle. The incision was closed with 5-0 thread, 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 cutting the brain stem 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.

Solution composition. Krebs solution consisted of (in mM) 120 NaCl, 26 NaHCO3, 3.75 KCl, 1 MgCl2, 2 CaCl2, and 10 D-glucose, maintained at pH 7.4 with O2-CO2 (95%-5%). Potassium gluconate intracellular solution consisted of (in mM) 128 K-glucuronate, 10 KCl, 0.3 CaCl2, 1 MgCl2, 10 HEPES, 1 EGTA, 2 ATP, 0.25 GTP, adjusted to pH 7.35 with KOH.

Drugs and chemicals. Tetrodotoxin (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 84 NTS neurons from 25 rats. In three of these rats, a surgical deafferentation was carried out 4–5 days prior to experimentation. The veracity of the deafferentation procedure was checked in every rat by recording both from neurons from the “deafferented” brain stem as well as from the contralateral “vagally intact” side. Differences were not observed between neurons from the contralateral side of deafferented rats and from “vagally intact” rats and, as a result, we assume that compensatory responses do not occur, at least within the short time period following deafferentation (4 days). Furthermore, differences were not observed in the type or magnitude of neuronal response throughout the rostrocaudal extent of the brain stem.

Postsynaptic effects of alterations in glucose concentration. The postsynaptic effects on NTS neurons following alterations in extracellular glucose concentration were assessed in 55 of these neurons (Table 1). Increasing the D-glucose concentration from 10 to 20 mM induced a postsynaptic response in 40% of NTS neurons (n = 22). The majority of these neurons (n = 15, 68%) responded with an outward current (19 ± 4 pA) whereas the remaining 32% of neurons (n = 7) responded with an inward current (22 ± 6 pA). Superfusion with the action potential-dependent synaptic transmission blocker TTX (1 μM) did not alter the proportion of responding neurons (36%, n = 22), the proportion of neurons responding with an outward or inward current (75 and 25%, respectively), nor the magnitude of the induced current (20 ± 3 and 27 ± 4 pA, respectively; P > 0.05 for all parameters).

In contrast, decreasing the concentration of D-glucose in the extracellular perfusing medium, from 10 mM to either 5 or 2.5 mM, induced a postsynaptic response in 54% of NTS neurons (n = 22). Of the 12 responding neurons, 6 displayed an inward current (50%, 31 ± 4 pA) and the remaining 6 neurons displayed an outward current (50%, 27 ± 5 pA). In the presence of TTX, however, only 1 of 11 NTS neurons responded (i.e., 10%; P < 0.05) with an inward current of 17 pA.

Table 1. Postsynaptic effects of D-glucose on NTS neurons

<table>
<thead>
<tr>
<th>Change in Glucose Concentration</th>
<th>Responsive Neurons</th>
<th>Inward Current</th>
<th>Outward Current</th>
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<tbody>
<tr>
<td>Increase (10 to 20 mM)</td>
<td>40% (22 of 55 neurons)</td>
<td>32% (7 of 22) 22 ± 6 pA</td>
<td>68% (15 of 22) 19 ± 4 pA</td>
</tr>
<tr>
<td>+ TTX</td>
<td>36% (8 of 22 neurons)</td>
<td>25% (2 of 8) 27 ± 4 pA</td>
<td>75% (6 of 8) 20 ± 3 pA</td>
</tr>
<tr>
<td>Decrease (10 to 5 mM; 10 to 2.5 mM)</td>
<td>54% (12 of 22 neurons)</td>
<td>50% (6 of 12) 31 ± 4 pA</td>
<td>50% (6 of 12) 27 ± 5 pA</td>
</tr>
<tr>
<td>+ TTX</td>
<td>10%* (1 of 11 neurons)</td>
<td>100% (1 of 1) 17 pA</td>
<td>0%*</td>
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NTS, nucleus of the tractus solitarius. *P < 0.05 vs. response in the absence of TTX.
These results suggest that NTS neuronal membranes respond directly to increasing levels of d-glucose but that decreasing d-glucose levels induces responses predominantly via actions at presynaptic sites.

Presynaptic effects of alterations in glucose concentration. When voltage clamped at −60 mV in 10 mM d-glucose, spontaneous inward currents had a frequency of 2.6 ± 0.38 events/s and amplitude of 31.9 ± 0.73 pA (n = 53). These currents were abolished completely by perfusion with the nonselective ionotropic glutamate antagonist kynurenic acid (1 mM; n = 3; data not shown), confirming their glutamatergic nature.

In 48 of the neurons in which spontaneous glutamatergic events (sEPSCs), were measured, the d-glucose concentration was changed from 10 mM (i.e., control) to 2.5 mM (n = 9), 5 mM (n = 9), or 20 mM (n = 35) (NB: some neurons were exposed to more than one concentration of d-glucose). Changing the extracellular d-glucose concentration altered the frequency of the sEPSCs in 38 of these neurons (i.e., 79%). In particular, the frequency of sEPSCs was augmented in a concentration-dependent manner with increasing concentrations of extracellular glucose. When normalized with respect to the frequency at 10 mM glucose (i.e., 100%), the frequency was 44 ± 7.1, 48 ± 6.0, and 186 ± 9.9% at 2.5, 5, and 20 mM, respectively (P < 0.05) and returned to baseline values upon perfusion with 10 mM glucose. The amplitude of the spontaneous events was unaffected by variations of the extracellular glucose concentration. When normalized with respect to the frequency at 10 mM glucose (i.e., 100%), the amplitude was 95 ± 5.4, 96 ± 1.8, and 105 ± 1.8% of control at 2.5, 5, and 20 mM, respectively (P > 0.05).

Since varying extracellular glucose concentration increased the frequency but not the amplitude of sEPSCs, these data suggest an effect on pre- but not postsynaptic sites. To confirm the frequency but not the amplitude of sEPSCs, these data exposed to more than one concentration of d-glucose). Chang-
Effects of glucose on electrically evoked synaptic currents.
To further confirm that D-glucose modulates synaptic transmission via actions at the level of vagal afferent terminals, we made recordings from NTS neurons in which EPSCs were evoked following electrical stimulation of the tractus solitarius. As with the responses observed when recording mEPSCs, the amplitude of the evoked EPSC (eEPSC) was proportional to the D-glucose concentration. When normalized with respect to eEPSC amplitude at 10 mM glucose (i.e., 100%), varying the D-glucose concentration to 2.5, 5, or 20 mM altered eEPSC amplitude to 60 ± 7.1, 77 ± 4.1, and 125 ± 3.0% of control, respectively (n = 5, 6, 6, respectively; P < 0.05; Fig. 3). Furthermore, these D-glucose-induced modulations of evoked EPSC amplitude were accompanied by alterations in the paired pulse ratio; increasing the concentration of D-glucose from 10 to 20 mM increased the paired pulse ratio from 0.45 ± 0.08 to 0.62 ± 0.09 (P < 0.05) whereas decreasing the concentration of D-glucose increased the paired pulse ratio to 0.70 ± 0.14 (P < 0.05; Fig. 3). These data further confirm that D-glucose modulates glutamatergic synaptic transmission from vagal sensory fibers to NTS neurons via actions at presynaptic sites.

Effects of L-glucose on glutamatergic synaptic transmission.
To verify whether the effect of extracellular D-glucose to increase the frequency of sEPSCs required glucose metabolism rather than simply glucose uptake, a series of experiments were conducted in which we increased the total glucose concentration by adding the equiosmotic but nonmetabolizable isomer L-glucose. In 15 neurons, perfusion with 20 mM D-glucose increased the spontaneous EPSC event frequency from 0.9 ± 0.14 to 1.5 ± 0.23 events/s (i.e., 186 ± 12.2% of control; P < 0.05); the EPSC frequency returned to 0.8 ± 0.10 events/s upon perfusion with control Krebs (i.e., 10 mM D-glucose). The neurons were then perfused for 10 min with a Krebs solution containing 10 mM D-glucose + 10 mM L-glucose. Under these conditions, the event frequency was 0.8 ± 0.12 events/s (P > 0.05 vs. control; Fig. 4).

Similarly, in a further four neurons, EPSCs were evoked in NTS neurons following electrical stimulation of the tractus solitarius. In these neurons, perfusion with 20 mM D-glucose increased the amplitude of the evoked EPSC to 133 ± 2.7% of control (P < 0.05); the EPSC amplitude returned to baseline upon perfusion with control (10 mM D-glucose) Krebs solution. Subsequent perfusion for 10 min with Krebs solution containing 10 mM D-glucose + 10 mM L-glucose did not alter EPSC amplitude (92 ± 3.2% of control; P > 0.05; Fig. 4), confirming that the modulation of spontaneous and evoked EPSCs by alterations of extracellular D-glucose concentration is due to glucose metabolism rather than glucose uptake.

DISCUSSION

The results of the present study indicate that acute variations in extracellular glucose levels can modulate vagal brain stem neurocircuitry via actions on the synaptic connections from vagal afferent nerve terminals to NTS neurons. A summary of our evidence is the following: 1) the frequency of spontaneous and miniature EPSCs recorded from NTS neurons was correlated with the concentration of D-glucose in the perfusing solution; 2) the correlation between the synaptic event fre-
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Fig. 4. D-Glucose modulates glutamatergic synaptic transmission via metabolic mechanisms. A: in a neuron voltage clamped at −60 mV, perfusion with Krebs solution containing 20 mM D-glucose increased the frequency of sEPSCs (left top traces). Upon washout and recovery, perfusion with Krebs solution containing 10 mM D-glucose + 10 mM L-glucose had no effect on sEPSC frequency, suggesting that the actions of D-glucose and L-glucose on sEPSC frequency are compared graphically (right). B: representative traces from an NTS neuron voltage clamped at −60 mV. Electrical stimulation of the tractus solitarius was used to evoke a glutamatergic EPSC in the recorded neuron. The amplitude of the EPSC was increased, reversibly, upon perfusion with Krebs solution containing 20 mM glucose. In contrast, perfusion with Krebs solution containing 10 mM D-glucose + 10 mM L-glucose had no effect on EPSC amplitude, again suggestive of actions dependent on glucose metabolism, not uptake. The effects of D-glucose and L-glucose on evoked EPSC amplitude are compared graphically (right). *P < 0.05 vs. 10 mM D-glucose.

Effects of glucose on central neurons. The ability of glucose to alter the activity of brain stem neurons has been well documented; NTS neurons respond to glucose with either a decrease in activity (glucose-sensitive or glucose-inhibited neurons) or an increase in activity (glucose-responsive or glucose-excited neurons) (1, 13, 14, 32, 55, 56). Thus NTS neurons appear to differ from other central nuclei where generally either only glucose-inhibited neurons or only glucose-excited neurons were identified, e.g., lateral hypothalamus or ventromedial hypothalamus and arcuate nucleus, respectively (19, 34, 39). Some studies raised the possibility that the response of glucose-inhibited neurons may be due partially to indirect actions via impinging inhibitory nerve terminals (39, 46). Since the effect of glucose to inhibit NTS neurons persisted in the conditions of synaptic blockade, however, this effect has been proposed to be an intrinsic neuronal property (32). Although the mechanism responsible for neuronal inhibition by glucose still remains to be elucidated fully, studies in hypothalamic neurons have suggested that glucose may reduce the activity of the depolarizing electrogenic sodium-potassium pump (34). More recently, glucose has also been proposed to activate an inhibitory chloride conductance (39, 46). The mechanism of neuronal excitation by glucose has been studied more thoroughly and several studies have demonstrated that glucose induces closure of ATP-sensitive potassium channels in a manner similar to that of pancreatic β cells (3, 10, 14, 39). Other excitatory mechanisms independent of ATP-sensitive potassium channels may exist, however (19), including electrogenic glucose entry, where entry of glucose into a neuron is directly coupled to the movement of ions such as sodium (10, 54).

The present study confirms these results in so far as NTS neurons appeared to respond directly to elevations in D-glucose levels with either an inward or an outward current. These responses were presumably due to direct actions of glucose on the neuronal membrane since they were unaffected by TTX. In contrast, perfusion with Krebs solution containing 10 mM D-glucose + 10 mM L-glucose had no effect on sEPSC amplitude, again suggestive of actions dependent on glucose metabolism, not uptake. The effects of D-glucose and L-glucose on evoked EPSC amplitude are compared graphically (right). *P < 0.05 vs. 10 mM D-glucose.

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Imminently activated under the electrophysiological conditions used in the present study (10 mM D-glucose).

Presynaptic effects of glucose. The results of the present study demonstrate that, as in the ventromedial hypothalamus (46), the substantia nigra (16) and the DMV (18), the extracellular level of D-glucose modulates presynaptic neurotransmission in a concentration-dependent manner that is independent of the postsynaptic effects. Specifically, glucose modulates excitatory glutamnergic synaptic transmission via actions at the level of vagal afferent nerve terminals. Furthermore, vagal afferent nerve terminals appear responsive to glucose over a wide range of glucose concentrations (i.e., 2.5–20 mM), in contrast to nonvagal inputs that appear to be maximally activated at 10 mM glucose (see Fig. 2). Glucose-sensitive neurons have also been identified within the area postrema (1, 21), a nucleus that is known to send projections to the NTS (33, 40, 51). In the present study, however, the ability of glucose to modulate glutamnergic synaptic transmission to neurons of the NTS was abolished following vagal deafferentation, suggesting that glucose-sensitive neurons of the area postrema do not play a major role in the modulation of vagal afferent neurotransmission.

In the present study, the D-glucose-induced effects were not mimicked by the nonmetabolizable isomer L-glucose, suggesting that the effects are dependent on glucose metabolism within the nerve terminal, rather than glucose uptake. Unlike the ventromedial hypothalamus, however, we never observed synaptic inputs that were excited by a decrease in glucose concentration, nor did we observe synaptic inputs that were inhibited by an increase in glucose concentration (46). This may reflect a fundamental difference between the glucose sensing of vagal afferent nerve terminals and nerve terminals within the hypothalamus. Since vagal afferent nerves are tonically active, even within the slice preparation (2, 6), a range of glucose concentrations can be transduced and signaled solely via alterations in their basal activity.

Despite being consistently 10–30% lower than those of plasma, glucose levels within both cerebrospinal fluid (CSF) and brain parenchyma are subject to fluctuation in concert with changes in peripheral glucose levels. In the CSF, glucose levels as low as 3.2 mM were measured after 24-h food deprivation, rising to 6.6 mM following peripheral glucose infusion (47); similarly in the brain parenchyma, insulin-induced hypoglycemia decreased glucose levels to 0.16 mM whereas peripheral glucose administration increased levels to 4.5 mM (42). Regardless of the lower central levels of glucose, one important qualification must be reinforced: neurons of a circumventricular organ or in a region lacking a blood-brain barrier (such as the NTS; Refs. 12, 23, 49) may be exposed to levels of glucose that are much higher than the rest of the central nervous system and closer to that of plasma (10, 19, 39). Because of technical considerations, in most brain slice preparations the concentration of glucose in the perfusing medium is ~10 mM and some preparations require levels as high as 30 mM (22), far in excess of that measured either in plasma (~5–8 mM), CSF (~5.2 mM), or extracellular brain parenchyma (2.5 mM) (42, 47). In the present study, marked pre- and postsynaptic modulation of NTS neurons were observed even within glucose concentrations of 2.5–10 mM (the normal range of plasma glucose concentration), making it all the more likely the present results represent a physiological phenomenon.

Central effects of glucose on gastric functions. Gastric motility is controlled by two opposing parasympathetic pathways originating from the preganglionic motoneurons of the DMV: a tonic cholinergic (excitatory) pathway and a nonadrenergic, noncholinergic (NANC, inhibitory) pathway. Neurons of the DMV receive glutamergic, catecholaminergic, and, predominantly, GABAAergic inputs from NTS neurons (49). Given the importance of these GABAAergic inputs from NTS to DMV in the control of gastric functions (43), a decrease in gastric motility may result either from a reduced activity of GABAAergic neurons projecting on DMV neurons involved in the NANC inhibitory pathway or an increased activity of GABAAergic neurons projecting to DMV neurons involved in the cholinergic excitatory pathway (reviewed in Ref. 49).

Both clinical and animal studies have shown that glucose levels modulate gastric motility and tone (7, 18, 25, 29, 37, 41). A central site of action was suggested following studies demonstrating that, when injected into the dorsal vagal complex of anesthetized rats, glucose decreases gastric motility and increases both gastric tone and intragastric pressure; more recent studies have indicated that these effects are due to actions of glucose on NTS, rather than DMV, neurons (18, 41). This finding is in general agreement with earlier studies demonstrating pronounced effects of glucose on vagal sensory nerves and central components of vagovagal reflexes rather than on vagal efferent outflow. Here we demonstrate a prominent action of glucose to increase vagal afferent excitatory synaptic transmission to NTS neurons. Since glucose acts centrally to decrease gastric motility and tone, we would suggest that the NTS neurons excited by glucose are GABAAergic neurons involved in the excitatory cholinergic vagal pathway. Activation of these neurons would, therefore, increase the inhibitory drive to DMV preganglionic excitatory motoneurons resulting in decreased gastric functions via a withdrawal of cholinergic tone. By regulating the ability of vagal afferent sensory nerve terminals to release glutamate, glucose may act as a rapid and tonic modulator of visceral afferent activity, and alterations in glucose levels, even within physiological limits, may exert profound effects on central vagal brain stem circuits.

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GRANTS

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