Secretin depolarizes nucleus tractus solitarius neurons through activation of a nonselective cationic conductance

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Yang, Bo, Martin Goulet, Richard Boismenu, and Alastair V. Ferguson. Secretin depolarizes nucleus tractus solitarius neurons through activation of a nonselective cationic conductance. Am J Physiol Regul Integr Comp Physiol 286: R927–R934, 2004.—The recent suggestion that secretin may be useful in treating autism and schizophrenia has begun to focus attention on the mechanisms underlying this gut-brain peptide’s actions in the central nervous system (CNS). In vitro autoradiographic localization of $^{125}$I-secretin binding sites in rat brain shows the highest binding density in the nucleus tractus solitarius (NTS). Recent evidence suggests that intravenous infusion of secretin causes fos activation in NTS, a relay station playing important roles in the central regulation of autonomic functions. In this study, whole cell patch-clamp recordings were obtained from 127 NTS neurons in rat medullary slices. The mean resting membrane potential of these neurons was $\sim 54.7 \pm 0.3$ mV, the mean input resistance was $3.7 \pm 0.2$ GΩ, and the action potential amplitude of these neurons was always $>70$ mV. Current-clamp studies showed that bath application of secretin depolarized the majority (80.8%; 42/52) of NTS neurons tested. The depolarizing effects were maintained in the presence of 5 μM TTX and found to be concentration dependent from $10^{-12}$ to $10^{-7}$ M. Using voltage-clamp techniques, we also identified modulatory actions of secretin on specific ion channels. Our results demonstrate that while secretin is without effect on net whole cell potassium currents, it activates a nonselective cationic conductance (NSCC). These results show that NTS neurons are activated by secretin as a consequence of activation of a NSCC and support the emerging view that secretin can act as a neuromodulator within the CNS.

SECRETIN, a 27-amino acid peptide, was the first hormone identified. In a series of experiments conducted in early 1900s, Bayliss and Starling (3, 4) showed that intravenous injection of a mucosal extract from the duodenum induced release of bicarbonate and water from the pancreas. Therefore this chemical messenger was named “secretin.” Secretin actions in the digestive system have been well documented (17, 19, 27, 28, 33, 38, 47). Recent reports suggesting a potential therapeutic application for secretin in treating autistic children (15, 24) and schizophrenia patients (40) have begun to focus attention on the mechanisms underlying this gut-brain peptide’s actions in the central nervous system (CNS).

The native peptide secretin, its receptors (8, 16, 21, 30, 48), secretin-like immunoreactivity, and bioactivity (29, 32) have all been detected in the brain. Intracerebroventricular administration of secretin upregulates dopamine turnover and tyrosine hydroxylase activity in the hypothalamus and inhibits prolactin release (1, 10, 39). In addition, recent evidence has suggested that after intravenous infusion, secretin can cross the blood-brain barrier to reach many brain regions (2). Intravenous secretin activates fos expression in several brain regions, including the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus (DMNV) (11). Stimulation of cAMP production by secretin was observed in cultured brain cells and in brain slice preparations (9, 37, 44). Moreover, secretin was found to facilitate evoked, spontaneous, and miniature inhibitory postsynaptic currents (IPSCs) in Purkinje cells in rat cerebellum (53). While highly suggestive of secretin actions in NTS, this literature does not definitively identify the source of secretin as peripheral or central.

In vitro autoradiographic localization of $^{125}$I-secretin receptor binding sites in rat brain shows the highest binding in the NTS (31). Located in the dorsomedial medulla oblongata, NTS is widely accepted as a pivotal brain region involved in the integration of cardiovascular, respiratory, gustatory, hepatic, and renal control mechanisms (25). NTS receives afferent input from and sends efferent output to many CNS areas, including essential autonomic control centers in the hypothalamus, midbrain, and spinal cord (52).

Collectively these observations support the hypothesis that NTS represents an important CNS site where endogenous and/or infused secretin could act to influence central autonomic regulation as well as other brain-mediated activities. The present electrophysiological study was designed to test the hypothesis that secretin exerts direct effects on the excitability of NTS neurons. Having identified such effects, our studies were extended to describe the modulatory roles of secretin on specific ion channels of NTS neurons.

MATERIALS AND METHODS

Medullary slice preparation. Male Sprague-Dawley rats (110–140 g, Charles River, PQ, Canada) were decapitated, and the brain stem was quickly removed from the skull and immersed in cold (0–2°C) artificial cerebrospinal fluid (ACSF). Four-hundred-micrometer-thick medullary slices including NTS were cut using a vibratome (Leica VT1000S, Leica Microsystems, Nussloch, Germany) and incubated in oxygenated ACSF (95% O$_2$-5% CO$_2$) for at least 90 min at room temperature. Before recording, slices were transferred into an interface-type recording chamber and continuously perfused with oxygenated ACSF through a gravity pressure perfusion system. The ACSF flow rate was adjusted to $\sim 1.5$ ml/min and maintained constant throughout the entire recording period. All experiments were performed in the dark.

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formed at room temperature (21–22°C). All procedures conformed to the standards outlined by the Canadian Council on Animal Care, and protocols were approved by the Queen’s University Animal Care Committee.

**Electrophysiological methods.** Whole cell patch recordings were obtained using the whole cell configuration of the blind gigascale patch-clamp technique to record from NTS neurons (50, 51), most of which were located in the commissural region of the nucleus. Electrodes of 4- to 7-MΩ resistance were pulled from TW150F-6 glass micropipettes (Wald Precision Instruments, Sarasota, FL) on a Narishige Flaming/Brown micropipette puller (model P-97, Sutter Instrument, Novato, CA) and were filled with the appropriate filling solution (see Experimental solutions). After establishment of >1-GΩ seal, a brief suction pulse was applied to rupture the membrane and achieve whole cell configuration. Signals were amplified and processed using an AxoClamp 2B (Axon Instruments, Union City, CA) amplifier. Series resistance (<15 MΩ) was not compensated. An Ag–AgCl electrode connected to the bath solution via a KCl-agar bridge served as reference. After recording from each NTS neuron, the pipette was withdrawn from the cell membrane, the remaining junction potential was measured (4–8 mV), and the appropriate correction was applied to all data. Drugs were applied by switching perfusion from ACSF to a solution containing the desired drug(s). In addition, the concentration of EGTA in the pipette solution was increased from 1.1 to 10 mM to decrease the Ca²⁺ concentration in the internal solution in one set of experiments. EGTA is a rather slow Ca²⁺ buffer; consequently, a faster buffer such as BAPTA might reveal a calcium contribution that EGTA fails to show. All signals were filtered at 3 kHz, digitized using the CED 1401 plus interface [Cambridge Electronic Design (CED), Cambridge, UK] at 5 kHz, and stored on computer for offline analysis. Data were collected using the Signal (episode-based capture) or Spike2 (continuous recording) packages (CED). Leak current was routinely subtracted using the option offered by the Signal program (CED).

Cells were defined as neurons by the presence of at least 70-mV action potentials (current-clamp recordings) or by the presence of large rapid voltage-activated inward currents, which were blocked by TTX (voltage-clamp recordings).

**Experimental solutions.** The standard internal pipette solution contained (in mM) 140 K-gluconate, 0.1 CaCl₂, 2 MgCl₂, 1.1 EGTA, 10 HEPES, and 2 Na₂ATP and was adjusted to pH 7.25 with KOH. In experiments examining the role of Ca²⁺ in activating the NSCC, the concentration of EGTA in the pipette solution was increased from 1.1 to 10 mM to decrease the Ca²⁺ concentration in the internal solution in one set of experiments. EGTA is a rather slow Ca²⁺ buffer; consequently, a faster buffer such as BAPTA might reveal a calcium contribution that EGTA fails to show. All signals were filtered at 3 kHz, digitized using the CED 1401 plus interface [Cambridge Electronic Design (CED), Cambridge, UK] at 5 kHz, and stored on computer for offline analysis. Data were collected using the Signal (episode-based capture) or Spike2 (continuous recording) packages (CED). Leak current was routinely subtracted using the option offered by the Signal program (CED).

**Peptides and drugs.** Secretin and [β-Asp³]secretin (Repligen, Waltham, MA) were prepared on the day of experiment by diluting 50-μl aliquots of 10⁻⁵ M stock solution stored at −70°C to concentrations ranging from 10⁻⁷ to 10⁻⁵ M in ACSF. In experiments where synaptic transmission was blocked, TTX (5 μM) was added to external solutions, and blockade of Na⁺ channels was confirmed when either depolarizing current pulses to 0 mV failed to elicit fast spikes (current-clamp recordings) and/or the large rapid voltage-activated inward currents were abolished (voltage-clamp recordings). In voltage-clamp experiments where K⁺ channel activities were examined, TTX (5 μM) was added to external solutions to block the Na⁺ channels. All of these drugs were prepared on the day of experiment by diluting stock solutions stored at appropriate temperatures into ACSF. All chemicals, unless otherwise stated, were obtained from Sigma Chemical (St. Louis, MO).

**Definition of response.** A series of hyperpolarizing current pulses were applied to determine the identity of each neuron as a delayed excitation (DE), postinhibitory rebound (PIR), or neither DE nor PIR (NON) cell based on its electrophysiological fingerprint (45). Neurons were required to maintain a stable baseline for at least 2 min before application of test agents. A response to secretin was arbitrarily defined as a sustained change in membrane potential of >3 mV. In those spontaneously firing neurons, we evaluated this in time-expanded traces by looking at membrane potential between spikes, which still made up most of the recording time as peak frequency even during excitatory effects seldom exceeded 10 Hz.

**Statistical analysis.** For statistical analysis of effects of secretin on NTS neurons under various conditions, means were calculated from cells that were determined to have been affected using the above criteria. Changes in membrane potentials and net whole cell K⁺ conductances in response to secretin were compared using the Student’s t-test. A minimum probability value of P < 0.05 was selected to determine significance. All values are plotted as means ± SE.

**RESULTS**

Whole cell recordings were obtained from a total of 127 NTS neurons. All of these cells demonstrated action potentials with amplitude of >70 mV (arbitrary minimum cutoff for inclusion), and they had a mean resting membrane potential of −54.7 ± 0.3 mV and a mean input resistance (IR) of 3.7 ± 0.2 GΩ.

**Secretin depolarizes NTS neurons.** Current-clamp recordings from a total of 52 NTS cells showed that 82.7% (43 of 52) of this population responded to bath perfusion of secretin (see the criteria established in MATERIALS AND METHODS), whereas the remainder of neurons tested did not respond in a sustained manner and were therefore classified as nonresponders. Depolarization was the predominant effect caused by secretin exposure (42 of 52 cells, 80.8%). Similar proportions of DE (77.8%; 14 of 18), PIR (82.4%; 14 of 17), and NON (82.4%; 14 of 17) cells were found to be responsive to 10⁻⁸ M secretin. Responses were also quantitatively similar [mean depolarization for each group was 9.7 ± 0.9 mV (DE cells), 9.8 ± 0.8 mV (PIR cells), and 10.5 ± 3.8 mV (NON cells)], and therefore these cell types were grouped together for all subsequent analysis.

Depolarizations usually occurred within 2 min of secretin reaching the slice and were normally accompanied by a rapid increase in firing frequency of action potentials. Effects of secretin lasted for 7–12 min, and after washout of secretin, membrane potential and action potential frequency returned to/toward control levels as shown in Fig. 1A. Figure 1A, bottom, shows expanded time scales from the same recording (before, during, and after bath application of secretin) illustrating action potentials (truncated) and postsynaptic potentials (of up to 10 mV) with baseline noise <1 mV. In 12 cells excited by 10⁻⁸ M secretin, the mean depolarization was 9.9 ± 0.9 mV. Secretin-induced depolarizations were accompanied by a significant decrease in IR as measured by the voltage responses to hyperpolarizing current pulses [control (4.0 ± 0.3 GΩ) vs. 10⁻⁸ M secretin (3.0 ± 0.4 GΩ), P < 0.05, n = 8; Fig. 1, B and C], effects that were still observed when membrane potential was returned to baseline with injection of hyperpolarizing current before assessment of input resistance.

To determine if the observed actions of secretin were due to direct effects on NTS neurons, six neurons that responded to 10⁻⁸ M secretin were tested with a second application of secretin during the blockade of action potentials by bath administration of TTX (5 μM) (Fig. 2, A and B). After treatment with TTX, bath administration of secretin elicited a similar depolarizing response in all six cells tested (8.9 ± 0.7 vs. 9.9 ± 0.9 mV without TTX, n = 12, P = 0.43) (Fig. 2C).

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Similar reversible depolarizing responses, normally accompanied by increases in spike frequency, were also recorded from NTS neurons in response to exposure to $10^{-7}$, $10^{-9}$, and $10^{-11}$ M secretin as illustrated in Fig. 3A. These effects of secretin were repeatable as a second bath application of the peptide resulted in similar changes in membrane potential. Analysis of group mean depolarization recorded from NTS neurons in response to secretin concentrations ranging from $10^{-12}$ to $10^{-7}$ M demonstrated these effects were concentration dependent as illustrated in Fig. 3B ($EC_{50} = 8.2 \times 10^{-10}$ M). Although NTS neurons did not depolarize significantly (<3 mV, see the criteria established in MATERIALS AND METHODS) in response to $10^{-12}$ M secretin, all neurons tested with this concentration were included as a group to complete the concentration-response curve.

Fig. 2. Secretin depolarizes NTS neurons in the presence of TTX. A: current-clamp recordings illustrate the responses of a single NTS neuron to bath administration of 10 M secretin (represented in this and other figures by the horizontal bar above each trace) resulted in rapid sustained depolarization accompanied in most cases by a rapid increase in firing frequency of action potentials. After washout of secretin, the membrane potential and action potential frequency returned to control levels. Scale bars represent 60 s (horizontal) and 10 mV (vertical). The dashed line indicates baseline membrane potential. A, bottom: expanded time scales from the same recording (before, during, and after bath application of secretin). These traces illustrate action potentials (truncated) and postsynaptic potentials (of up to 10 mV) with baseline noise <1 mV. Scale bars, 0.5 s (horizontal) and 10 mV (vertical). B: secretin also caused consistent decreases in input resistance as shown in the current-voltage relationships obtained from this NTS neuron during application of control artificial cerebrospinal fluid (ACSF; ■) and ACSF containing $10^{-8}$ M secretin (○). Successive hyperpolarizing pulses (-1 to -6 pA) were delivered and the peak changes in membrane potential were measured. C: bar chart shows summary data illustrating statistically significant effects of secretin on input resistance in NTS cells: control (4.0 ± 0.3 GΩ) vs. $10^{-8}$ M secretin (3.0 ± 0.4 GΩ), *$P < 0.05$, $n = 8$.
In view of the present lack of high-affinity specific secretin receptor antagonists (54), we used the nonfunctional analog [β-Asp]secretin (5, 46) as a control to look at the interaction between secretin and its receptor. Similar current-clamp recordings from a total of eight NTS neurons showed that only two cells were slightly depolarized (<3 mV, see the criteria established in MATERIALS AND METHODS) by bath application of [β-Asp]secretin (10^{-8} M), while the remaining six cells did not respond. Summary data show a statistically significant difference between effects of 10^{-8} M secretin and 10^{-8} M [β-Asp]secretin on membrane potential of NTS cells [9.9 ± 0.9 mV (n = 12) vs. 1.3 ± 0.6 mV (n = 8), P < 0.05].

Secretin is without effect on whole cell K^+ currents in NTS neurons. Multiple ion channels are known to be involved in the regulation of neuronal excitability (13, 26). Our previous work demonstrated that orexin-A inhibits a specific potassium conductance (the sustained K^+ current, I_k) in NTS neurons (50, 51). We therefore used voltage-clamp techniques (49–51) to examine the effects of secretin on net whole cell K^+ currents (measured at both the peak and the sustained values) evoked in response to 20-mV depolarizing voltage steps (0.5 s) applied from holding potentials of −100 mV (with 5 μM TTX in ACSF) before and after bath application of secretin. A typical response of an NTS neuron to secretin (10^{-8} M) illustrated in Fig. 4A shows no change of the net whole cell K^+ currents induced by secretin. The summary data presented in Fig. 4B support the conclusion that NTS neurons (n = 13) exhibit no change in whole cell K^+ currents during exposure to secretin (10^{-8} M). Figure 4B, inset, shows summary data of peak and sustained K^+ currents evoked by the +40-mV voltage step from a holding potential of −100 mV before and during bath application of 10^{-8} M secretin (n = 13), illustrating secretin does not affect these currents.

Secretin activates NSCC of NTS neurons. In view of the considerable literature demonstrating peptidergic effects on neuronal excitability occurring as a consequence of the modulation of nonselective cationic conductances (14, 18) as well as our own recent studies identifying NSCC in area postrema (49) and NTS (50, 51) neurons as mediators of orexin-A actions, we next used slow voltage ramps (−100 to 0 mV in 10 s) after a prepulse to −100 mV (0.5 s) to determine if secretin influenced NTS neurons as a consequence of activation of such conductances. The data presented in Fig. 5A show average currents recorded from an NTS neuron in response to such ramps (each trace is the mean of 5 ramps) recorded before, during, and after bath administration of secretin (10^{-8} M). Figure 5A, inset, illustrates the difference current (i.e., secretin-induced current) obtained by subtracting control ramps from those obtained during secretin. Application of secretin (10^{-8} M) caused a clear change in this ramp-evoked current, and ~6–11 min after replacement of secretin with ACSF, the current recovered toward control levels. Similar effects of secretin (10^{-8} M) were observed in 13 of 16 (81.3%) cells tested, a proportion that closely matches the proportion (80.8%) of NTS neurons depolarized by secretin in our current-clamp experiments. The mean secretin-evoked current for this
A group of responsive neurons is shown in Fig. 5B (closed squares) and was found to be linear throughout the voltage range tested ($r^2 = 0.98$), indicating a lack of voltage dependence. This conductance is voltage independent across the voltage scale of the slow ramp, which indicates that it is a NSCC (6, 14, 18). The mean reversal potential of the secretin (10^-8 M)-sensitive current was $-45.6 \pm 2.1$ mV (such values were obtained after subtraction of junction potentials), and the mean conductance of this NSCC is $0.33 \pm 0.02$ nS ($n = 13$).

We also examined the role of intracellular Ca^{2+} in activating this NSCC in experiments where we decreased the theoretical concentration of free intracellular Ca^{2+} to 10% of its normal values by increasing EGTA in the pipette solution from 1.1 mM (standard) to 10 mM. Of 13 NTS neurons recorded with this high EGTA pipette solution, 10 (76.9%) showed activation of the NSCC in response to secretin ($r^2 = 0.98$, mean reversal potential $=-44.9 \pm 1.6$ mV and the mean conductance $=0.37 \pm 0.02$ nS), which was quite similar to that observed in cells recorded with standard internal pipette solution.
We usually held NTS neurons between −52 and −53 mV before secretin (10^{-8} M) administration in our current-clamp recordings. At these baseline membrane potentials, secretin would be expected to activate the NSCC as a 2.3- to 2.7-pA inward current (see Fig. 5B), which we calculate to evoke an 8.5- to 10.0-mV depolarization (average input resistance of NTS neurons is 3.7 MΩ). This predicted depolarization is fairly close to the average depolarization (9.9 ± 0.9 mV) caused by 10^{-8} M secretin application that we recorded in current-clamp experiments. Additional experiments were performed while the baseline membrane potentials of NTS neurons were held at −45 mV (close to the reversal potential of this NSCC) and approximately −60 mV, before bath application of secretin. None of four neurons held at −45 mV was depolarized by secretin (10^{-8} M), and the depolarization of cells held at approximately −60 mV was potentiated (13.4 ± 2.3 mV, n = 4), observations further supporting the conclusion that such effects were the result of activation of this NSCC. Finally, Fig. 5B (open squares) demonstrates that bath application of [β-Asp]secretin (10^{-8} M) did not activate this NSCC in eight of eight NTS neurons, supporting the observations of considerable loss of potency with modification of secretin NH₂ terminus (5, 12, 46).

DISCUSSION

In vitro autoradiographic localization of 125I-secretin binding sites in rat brain shows the highest binding density in the NTS (31). Secretin appears to be widely expressed within the CNS (8, 16, 21, 30, 48) where it may act as an endogenous neuropeptide. Recent evidence showed that intravenous infusion of secretin to rats leads to fos activation in several brain regions, including the NTS and DMNV (11). Secretin was reported to cross the blood-brain barrier as an intact peptide (2). Therefore, it is a possibility that peripherally administered secretin activates secretin-responsive neurons in the NTS and/or other regions. The NTS is a relay station that plays important roles in the central regulation of autonomic functions (25, 52), which were reported to be altered in autism (20, 35, 36).

Previous studies reporting electrophysiological properties and subtypes of NTS neurons in slice preparations have suggested lower input resistances for these cells (45) than we have recorded in the current study (3.7 ± 0.2 MΩ, n = 127) and previous reports (50, 51). These differences are most likely the result of differences in the techniques for slice preparation [we recorded in room temperature (21–22°C) vs. 31–32°C] or the exceptionally high resistance seals obtained in the present studies (often >4 MΩ).

Our results are the first to demonstrate that secretin influences the excitability of NTS neurons. The only previous electrophysiological study investigating secretin’s actions on CNS neurons reported that secretin facilitated GABA release from presynaptic terminals contacting Purkinje cells but was without effect on membrane potential of these neurons (53). To determine if the observed depolarizing actions of secretin were due to similar presynaptic effects (53), six secretin-responsive neurons were tested with a second application of secretin during the blockade of action potentials by bath administration of TTX. The fact that these depolarizing effects were observed in the presence of TTX suggests that they are the result of direct actions on each recorded NTS neuron. The present lack of high-affinity specific secretin receptor antagonists (54) precluded a definitive identification of the secretin receptor as the mediator of these effects. However, the clear reversibility and concentration dependence of these effects and the lack of similar effects of the nonfunctional analog [β-Asp]secretin argue strongly that they are receptor mediated. The EC₅₀ (8.2 × 10^{−10} M) obtained in this study is also consistent with the literature describing secretin actions (6, 8, 12, 23, 34, 41, 42).

Multiple ion channels are known to be involved in the regulation of neuronal excitability (13, 26). Our previous work demonstrated that orexin-A inhibits a specific potassium conductance (the sustained K⁺ current Iₖ) in NTS neurons (50, 51). We therefore examined the effects of secretin on voltage-gated K⁺ currents of NTS neurons using voltage-clamp techniques. However, our data demonstrated that secretin did not affect whole cell voltage-dependent K⁺ currents. In view of the clear lack of effects of the peptide on these mixed K⁺ currents, they were not further dissected for the current analysis, although separate experiments have shown that Iₖ, I₅, and I₇ all likely contribute to the total current we examined, and we would thus conclude that secretin is without effect on any of these currents.

NSCs are voltage-independent membrane channels, which allow passage of cations (Na⁺, K⁺, or Ca²⁺) in varying proportions (22). These channels have been shown to participate in controlling neuronal excitability in many systems, including generation of the depolarizing phase of bursting pacemaker activity in Aplysia burst-firing neurons (22) and in the intrinsic activation of rat supraoptic neurons by hyperosmotic stimuli (6), neurotensin (18), and P₂ purinoceptor agonists (14). In addition, our previous work has demonstrated that orexin-A depolarizes rat area postrema and NTS neurons through activation of NSCC (49, 50, 51). The results from the current study illustrate direct reversible effects of secretin on a NSCC (voltage-clamp experiments) in a proportion of NTS neurons similar to that depolarized by the peptide (current-clamp experiments). Such effects of secretin on this NSCC likely explain the depolarization of NTS neurons in response to the peptide, especially in view of the close correlation between the predicted (obtained by calculation using biophysical features of cells and conductance) and recorded potential changes. Our data suggest that this NSCC is not activated by cytoplasmic Ca²⁺. These data suggest the involvement of alternative second messenger system(s) such as activation of adenyl cyclase and a rise in intracellular cAMP in mediating secretin effects as already demonstrated in nonneuronal target tissues (27, 43) as well as neuronal tissues (9, 44, 53). However, given the small size of these NTS neurons, it seems likely that small molecules like cAMP might be completely diazylated thru the patch pipette. Therefore, it is quite possible that other signal transduction mechanism(s) might also be involved. In fact, our own recent work (50, 51) identified that orexin-A depolarizes NTS neurons through effects on nonselective cationic and K⁺ conductances, and these excitatory effects are mediated by phospholipase C and protein kinase C pathways. This study and our previous papers demonstrating orexin-A effects on a NSCC in rat NTS neurons (50, 51) suggest that the modulation...
of this conductance by different neuropeptides may represent a common mechanism through which they exert control over neuronal excitability in NTS. The signal transduction mechanisms underlying secretin’s modulation of the NSCC in NTS neurons have not been examined in the present study.

Although the electrophysiological consequences of secretin actions on NTS neurons in increasing their excitability are clear, the question still arises as to the physiological implications and the potential therapeutic benefits of such effects in autism and schizophrenia. Studies have demonstrated important roles for these neurons in cardiovascular, respiratory, neuroendocrine, and gastrointestinal control, although in our slice recordings we are unable to identify the specific output of individual neurons from which we record. The homogeneity of the observed responses of NTS neurons to secretin suggests it unlikely that the physiological consequences of this peptide’s action in NTS would be limited to one or another of these specific autonomic outputs. These broad excitatory actions of secretin characterized here for NTS neurons may possibly contribute to the reported beneficial therapeutic effects of this peptide in autism and schizophrenia (15, 24, 40) by modifying autonomic and/or other responses.

It should be noted that our results presented in this paper do not exclude other possible influences of secretin in the NTS. It remains possible that in addition to the direct effects on the NSCC that we have observed here, secretin may also influence other ionic conductances in NTS neurons and/or synaptic transmission in this nucleus (similar to Ref. 53). Future studies are needed to further explore these possibilities.

In conclusion, this study provides the first evidence that secretin exerts direct effects on the excitability of NTS neurons. In addition, our studies provide description of secretin’s ability to directly modulate specific ion channels in NTS neurons, suggesting potential neuroregulatory roles for this gut-brain peptide. Thus the findings presented here add to an emerging electrophysiological framework for understanding the effect of endogenous secretin on neuronal activity. This knowledge may help to clarify the role of this peptide when used in the clinic to treat neuropsychiatric disease states.

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DISCLOSURES

R. Boismenu and M. Goulet are employed by Repligen Corp., a for-profit pharmaceutical company.

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