Abstract—The nucleus of the solitary tract (NTS) is the central site of termination of baroreceptor afferents. We hypothesize that changes occur in voltage-gated calcium channels (VGCCs) within NTS neurons as a consequence of hypertension. Whole-cell patch-clamp recordings were obtained from adult normotensive (109±2 mm Hg; n=6 from 6 sham-operated and 31 nonsurgically treated) and hypertensive (158±6 mm Hg; n=24) rats. In some experiments, 4-(4-[dihexadecylamino]styryl)-N-methylpyridinium iodide was applied to the aortic nerve to visualize NTS neurons receiving baroreceptor synaptic contacts. Ba2+ currents (500 ms; −80 mV prepotential; 500 ms voltage steps in 5-mV increments to +15 mV) peaked between −20 and −10 mV and were blocked by 100 μM of Cd2+. Peak VGCCs were not different comparing non-4-(4-[dihexadecylamino]styryl)-N-methylpyridinium iodide-labeled and 4-(4-[dihexadecylamino]styryl)-N-methylpyridinium iodide-labeled NTS neurons in hypertensive and normotensive rats. The peak VGCC was significantly greater in cells from hypertensive compared with normotensive rats for both non-DiA-labeled (P=0.02) and DiA-labeled (P=0.04) neurons. To separate high-voltage activated (HVA) and low-voltage activated (LVA) components of VGCCs, voltage ramps (−110 mV to +30 mV over 50 ms) were applied from a holding potential of −60 mV (LVA channels inactivated) and a holding potential of −100 mV (both LVA and HVA currents activated). HVA currents were subtracted from HVA+LVA currents to yield the LVA current. Peak LVA currents were not different between hypertensive (8.9±0.8 pA/pF) and normotensive (7.8±0.6 pA/pF) groups of NTS neurons (P=0.27). These results demonstrate that 4 weeks of renal wrap hypertension induce an increase in Ca2+ influx through HVA VGCCs in NTS neurons receiving arterial baroreceptor inputs. (Hypertension. 2007;49:1163-1169.)

Key Words: baroreflex ■ nucleus of the solitary tract ■ calcium channels ■ ion channels ■ central nervous system ■ arterial hypertension

The arterial baroreceptor reflex plays an indispensable role in integrated cardiovascular regulation. Baroreceptors are stretch receptors located in systemic arteries, and they transmit information to the central nervous system regarding the level of blood pressure. The central nervous system integrates this information and initiates changes in heart rate and peripheral resistance in an attempt to maintain blood pressure within normal limits. The first central synapse of the baroreflex arc is in the medullary nucleus of the solitary tract (NTS); therefore, NTS neurons play a key role in cardiovascular regulation.

We have reported previously that ligand-gated and voltage-gated ion channels in NTS neurons receiving arterial baroreceptor afferent inputs undergo adaptive changes in chronic hypertension. In renal wrap hypertension, NTS neuronal sensitivity to activation of γ-aminobutyric acid type A receptors is reduced,1,2 whereas sensitivity to activation of γ-aminobutyric acid type B receptors is enhanced.3 Voltage-gated, transient outward potassium currents are reduced in NTS neurons in chronic renal wrap hypertension.3 These alterations are viewed as adaptations in response to hypertension and could modify baroreflex regulation of sympathetic nerve discharge and heart rate in hypertension.4

Other factors of potential importance in determining neuronal function are mechanisms related to neuronal calcium homeostasis. Increases in cytosolic calcium may be achieved by calcium influx through voltage-gated calcium channels (VGCCs) and ligand-gated calcium channels or by release from intracellular calcium stores. VGCCs provide the primary mechanism for Ca2+ influx in excitable cells5 and mediate Ca2+ influx in response to action potentials and subthreshold depolarizing signals. Previous studies have identified all of these mechanisms in NTS neurons; however, information on calcium homeostasis in NTS neurons during hypertension is lacking. Alterations in VGCCs in NTS neurons in hypertension could lead to changes in neuronal excitability, gene transcription, intracellular enzymes, and neurotransmitter receptors.6 Changes in any of these param-
ers could modify the ability of the baroreflex to stabilize blood pressure in hypertension. The goal of this study was to determine whether alterations in Ca\(^{2+}\) influx via VGCCs occur in NTS neurons receiving arterial baroreceptor inputs during hypertension.

**Methods**

**General**

The study was approved by the Institutional Animal Care and Use Committee and was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animals were housed in specific pathogen-free conditions in the Institutional Animal Care facility, which is Association for Assessment and Accreditation of Laboratory Animal Care Internationally accredited. All of the experiments were conducted on adult male (1 to 3 months) Sprague-Dawley rats (300 to 500 g, Charles River Laboratories). Chronic hypertension was induced using a 1-kidney renal wrap procedure as described previously. Briefly, rats were anesthetized with medetomidine (0.5 mg/kg IP; Pfizer) and ketamine (75 mg/kg IP; Fort Dodge Laboratory), and a figure-8 renal wrap and contralateral nephrectomy were performed (n = 24). Control animals (n = 37) consisted of sham-operated rats that were similarly anesthetized and received a unilateral nephrectomy but no wrap of the contralateral kidney (n = 6) or rats with no surgical procedures before the day of the experiment (n = 31). Because the responses of both groups of control rats were identical, they were grouped together for analysis. At the conclusion of the surgical procedures, anesthesia was terminated by atipamezole (1 mg/kg IP; Pfizer). Rarely, a renal-wrap rat does not present with hypertension because of loosening of the figure-8 ligature around the kidney. Therefore, to verify that renal wrap rats were indeed hypertensive, 2 to 4 days before study, all of the renal-wrap rats were anesthetized with isoflurane, and an arterial catheter was placed in the femoral artery. The catheter was plugged with heparin (1000 U/mL), subcutaneously tunneled to the nape of the neck, and secured. After recovery from surgery, the animals were returned to their cages. Surgical wounds were treated with a topical antibiotic. Two days later, the rat was brought into the laboratory, and after a 1- to 2-hour acclimatization period, arterial pressure was measured in the conscious rat for 1 hour. We have never observed a sham operated or nonoperated rat present with hypertension; therefore, blood pressures were only measured in 6 of the 37 control rats.

**Aortic Nerve and 4-(4-[dihexadecylamino]styryl)-N-Methylpyridinium Iodide Application**

Two weeks after renal or sham surgery, crystals of the fluorescent tracer 4-(4-[dihexadecylamino]styryl)-N-methylpyridinium iodide ([DiA] Molecular Probes, Invitrogen) were applied to the aortic nerve under aseptic conditions and isoflurane anesthesia. The lipophilic DiA dissolves in and diffuses along the length of the axons and has been used to identify NTS neurons receivingafferent synaptic contacts from arterial baroreceptors and chemoreceptors. There is no processing of the tissue required to visualize the DiA; the fairly weak fluorescence was visualized 7 to 14 days after surgery using appropriate bandpass filters (fluorescein isothiocyanate). Surgical wounds were treated with a topical antibiotic and postoperative analgesics (Nubaine, 10 mg IM) were provided for 3 days postsurgery.

**Dispersion of NTS Neurons**

As described previously, rats were anesthetized with isoflurane, and the brain stem was rapidly removed and placed in ice-cold Krebs buffer. The brain stem was cut into three 440-mm-thick transversal sections caudal to calamus using a vibratome (Warner Instrument Corp). The sections were incubated in the piperazine-N,N'-bis(ethanesulfonic acid) (PIPES) buffer with trypsin (Sigma type XI; 3 to 7 mg/10 mL) for 60 minutes at 34°C. After the enzyme treatment, slices were rinsed 3 times with incubation solution and were maintained at room temperature (22 to 25°C) in the continuously oxygenated jar with PIPES buffer. Before dissociation, brain stem slices were placed on a glass slide, and the NTS region was identified and excised using a scalpel blade. The excised NTS region was gently triturated in a Dulbecco’s modified eagle’s medium (DMEM) buffer using a series of fire-polished pipettes. After trituration, an aliquot of the DMEM/neuron suspension was placed in the perfusion bath and neurons allowed to settle to the bottom of the bath for 5 minutes, after which superfusion of the cells began with a normal physiological solution. All of the neurons were studied within 10 hours of dispersion.

**Drug Application**

Solutions were applied by gravity flow to isolated cells via multibarrel square glass pipettes using a fast-step perfusion apparatus (Warner Instrument Corp). Each pipette was attached via tubing to the valve connecting it to 1 of the solution jars. The first pipette was positioned adjacent to and as close as possible to the target cell. A steady stream of drug-free solution protected the neuron from effluent from the solution in the second pipette which was downstream to the first pipette. To apply drugs, a digital signal was sent to the Warner Perfusion Fast-Step and the pipette assembly was rapidly moved so that the second, drug-ejecting pipette was adjacent to the cell. After drug application, the pipette assembly was returned to the starting position.

**Electrophysiology**

Whole-cell patch-clamp recordings were performed on acutely dissociated NTS neurons from normotensive (NT) and hypertensive (HT) rats. Electrodes were formed from thin-walled quartz glass with a laser-based P-2000 puller (Sutter Instrument Co) to resistances of 3 to 9 MΩ. To investigate changes in Ca\(^{2+}\) influx during depolarization in neurons receiving baroreceptor synaptic contacts in NT versus HT rats, voltage step square pulse and ramp protocols were applied. Neurons were bathed in an external solution consisting of, in mM: NaCl, 140; D-glucose, 33; HEPES, 10; KCl, 3; CaCl\(_2\), 1.5; and MgCl\(_2\), 1.2 (pH 7.4 with NaOH; osmolality 315 to 330 milliosmols). Electrodes were filled with a solution that contained, in mM: CsCl, 120; MgCl\(_2\), 2; TEA-Cl, 20; EGTA, 10; GTP, 0.1; ATP, 4; and HEPES, 10 (pH 7.2 with CsOH; osmolality 280 to 300 milliosmols). The presence of ATP in the pipette solution minimized “rundown” of VGCC currents. To maximize Ba\(^{2+}\) currents through VGCCs and reduce sodium and potassium currents, a modified external solution was used that contained, in mM: NaCl, 132; BaCl\(_2\), 2; MgCl\(_2\), 2; D-glucose, 33; TEA-Cl, 10; HEPES, 10; and tetrodotoxin, 0.5 mM/L. During periods of recording, the external solution was switched to the modified external solution. Cd\(^{2+}\) and nickel were applied using a fast-step perfusion apparatus before initiating a ramp or voltage step protocol. Cells were voltage clamped using an Axopatch 200B amplifier (Molecular Devices). Currents were low-pass filtered at 1 kHz, sampled at 10 kHz, and analyzed using the pCLAMP8.1 software suite (Molecular Devices). Changes in standing leak current were corrected to the initial baseline, and if leak was more than ~100 pA, data were excluded from the analysis. At the amplifier, 40% to 80% series resistance compensation was applied. At the initiation of each recording, we used Membrane Test (Molecular Devices) to monitor the possibility that access resistance changed over time or during different experimental conditions.

**Fura-2 Ca\(^{2+}\) Imaging**

NTS neurons were dispersed from NT and HT rats and then placed in the bath loaded with fura-2 (2 µmol/L) in the presence of pluronic acid (0.01%) and stored in an incubator at 37°C. After 30 minutes, fluorescent microscopy was performed with an inverted Nikon Eclipse TE300 microscope in differential interference contrast configuration with an oil immersion ×40/1.30 numerical aperture objective. A Polychrome IV monochromator (T.I.L.L. Photonics) and FURA2 71000 filter set were used for fura-2 imaging. Cells were excited alternatively at 340 and 380 nm (50 to 200 ms every 2 s), and the fluorescent emission was collected by an IMAGO 12-bit cooled...
charge-coupled device camera. Images were saved and analyzed with TILLvisION 4.0 software.

Data Analysis

Plots of the currents versus test potential (I-V curves) were generated during voltage step square pulse and ramp protocols. Peak currents were expressed as pA/pF to normalize for cells of different sizes. I-V curves generated by ramps at holding potential (V_h) −60 mV were used to calculate relative membrane permeabilities using the Goldman–Hodgkin–Katz current equation:

\[
P = \frac{p_{\text{exp}} V F T}{RT} \left[ \frac{[\text{Ca}^{2+}]_o - [\text{Ba}^{2+}]_o}{1 - \exp(-zF V_m / RT)} \right]
\]

where \(P\) is membrane permeability to \(\text{Ba}^{2+}\), \(p_{\text{exp}}\) is current density normalized to membrane capacitance, \(V_m\) is membrane potential (\(z=2; F=9.648 \times 10^4\) Cmol\(^{-1}\); \(R=8.315\) VCK\(^{-1}\) mol\(^{-1}\); and \(T=273.16+25\) K). The resting calcium concentrations ([Ca\(^{2+}\)]\(_o\)) was 2 mmol/L. Permeabilities were normalized (\(P \times 100/P_{\text{max}}\)) and plotted over membrane potential from −50 to 5 mV. Activation curves were fit by a single Boltzmann relationship to reveal half-activation voltage and slope factor for NT and HT groups of experiments.

Statistical significance of differences between NTS neurons obtained from NT and HT rats was determined by the Student 2-tail t-test. All of the values were expressed as mean ±SEM, and significance was accepted at \(P \leq 0.05\).

Results

Whole-cell patch-clamp recordings were obtained from adult NT (109±2 mm Hg, measured in 6 of 37) and HT (158±6 mm Hg measured in 24 of 24) rats. Cell size, estimated by membrane capacitance, was the same comparing neurons from NT (7.6±.5 pF; \(n=36\)), NT DiA (9±1.9 pF; \(n=7\)), HT (8.9±0.7 pF; \(n=35\)), HT DiA (10.5±2 pF; \(n=9\)) rats.

Voltage ramps from −110 to 30 mV after a V_h of −100 mV activated both low-voltage activated (LVA) and high-voltage activated (HVA) \(\text{Ba}^{2+}\) currents (Figure 1A). Voltage ramps after a prepotential of −50 mV revealed only HVA currents (Figure 1B), which were blocked by cadmium (\(\text{Cd}^{2+}\); 100 \(\mu\)mol/L), indicating that the currents were carried through VGCCs (Figure 1C).

To compare voltage dependence of activation in HVA and LVA components of VGCC conductances separately, 3 fast (50-ms) voltage ramps were applied to NTS neurons from the NT (\(n=28\)) and HT (\(n=26\)) group (Figure 1D and 1E). Voltage ramps from −110 to +30 mV activated an inward current near −50 mV and reached the maximum between −20 and −10 mV. The protocol started with a \(V_h\) of −60 mV, which was decreased at the end of successive ramps to −80 mV and −100 mV (Figure 1D). From \(V_h\) of −100 mV, both LVA and HVA currents were activated, and the I-V curve displayed a deflection in the negative activation range (Figure 1E). From a \(V_h\) of −60 mV, LVA channels were inactivated, so the HVA currents could be subtracted from combined HVA and LVA currents to yield the approximate LVA current (Figure 1E).

From a −80 mV prepotential, voltage steps of 500-ms duration were made in 5-mV increments to +15 mV to construct I-V curves (Figure 2). The peak amplitude of \(\text{Ba}^{2+}\) currents was measured (10 to 15 ms after the onset of depolarizing pulses) to minimize the influence of time- and voltage-dependent inactivation of VGCCs. Very little fast inactivation component was observed during the depolarizing pulses (Figure 2). The I-V curve was maximal at −15 mV (Figure 3A). The amplitude of \(\text{Ba}^{2+}\) currents was not different between DiA-labeled and non-DiA-labeled NTS neurons within either the NT or HT group. The normalized peak current was significantly greater in cells from HT (46.5±2.9 pA/pF; \(n=36\)) and HT DiA (45.3±3.8 pA/pF; \(n=9\)) compared with NT (35.2±3.0 pA/pF; \(n=35\); \(P=0.009\)) and NT DiA (34.4±3.1 pA/pF; \(n=7\); \(P=0.04\); Figure 3B). A total of 70% of NT neurons had current density <35 pA/pF; conversely, 23% of cells from the HT group were represented in this population. (Figure 3C and 3D).

**Figure 1.** Responses to ramp increases in current of an NTS neuron isolated from an NT rat. A, From a preholding potential of −100 mV, both LVA and HVA VGCCs are activated. Arrow denotes inflection on current trace indicative of LVA. B, From a preholding potential of −50 mV, only HVA VGCCs are activated. C, Application of 100 \(\mu\)mol/L cadmium abolishes HVA VGCCs. D, Fast (50 ms) voltage ramps applied to an NTS neuron from NT rat starting at 3 different holding potentials to separate LVA from HVA VGCCs. E, To isolate LVAs, the current response to ramp 1 was subtracted from the current response to ramp 3. Voltage ramps from −110 to +30 mV activated an inward current near −50 mV and reached maximum between −20 and −10 mV. With change of \(V_h\) to −80, −100 mV, the peak of the current-voltage relationship was increased.
As in the voltage step experiments, membrane capacitance of the cells was no different comparing NT (7.48 ± 0.5 pF) and HT (8.43 ± 0.8 pF) neurons. Both NT and HT groups had the same voltage dependence of activation, and with changes of V_h to −80 and −100 mV, the peak of the I-V relationship was increased (Figure 4). The peak current densities were significantly greater in cells from HT (36.9 ± 3.6 pA/pF at V_h = 60 mV; 38.8 ± 3.7 pA/pF at V_h = 80 mV; 43.7 ± 4 pA/pF at V_h = 100 mV) compared with NT (26.6 ± 2.6 pA/pF at V_h = −60 mV; 27.8 ± 2.7 pA/pF at V_h = −80 mV; 32.3 ± 2.8 pA/pF at V_h = −100 mV; P < 0.02). The isolated LVA currents were not different comparing HT (8.9 ± 0.8 pA/pF) and NT (7.8 ± 0.6 pA/pF) groups of NTS neurons (Figure 4).

To calculate membrane permeability, I-V curves from a V_h of −60 mV were generated by ramp increases in voltage from −110 to 30 mV to isolate HVA currents. Peak currents were significantly greater in HT compared with NT neurons (Figure 5A). The resting calcium concentrations ([Ca^{2+}]_i) in neurons from NT 75 ± 2 nM (n = 16) and HT 70 ± 2 nM (n = 16) rats were obtained using Fura-2 measurements and were not significantly different. These measurements were used to construct permeability curves, which were not different comparing NT and HT rats (Figure 5B). Voltage at half activation was −16.08 ± 0.1 mV and −14.83 ± 0.04 mV for the NT and HT group, respectively.

Changes in LVA current inactivation kinetics could lead to changes in LVA current independent of changes in the peak current. To examine time-dependent recovery from inactivation of LVA currents in isolation from HVA currents, a series of −100 mV prepulses of different durations were applied from a V_h = −60 mV, to remove inactivation of the LVA, before application of test pulses of −40 mV (Figure 6A1). By varying the duration of the −100 mV conditioning pulse, the time-dependent recovery from inactivation of the LVA current could be observed (Figure 6A2). The current evoked by this protocol was further established as an LVA current, because it was blocked by the addition of 200 μmol/L of nickel (Figure 6A3). No change in time-dependent recovery...
from inactivation was seen for the LVA between the NT (n=34) and HT (n=21) groups of neurons (Figure 6B).

**Discussion**

These results demonstrate that hypertension is associated with an increase in Ca\(^{2+}\) influx through VGCCs in NTS neurons receiving baroreceptor afferent inputs, and this influx appears to be because of an increased HVA current. Virtually identical increases in HVA current were observed in ventricular myocytes isolated from rats in heart failure.\(^{16}\) In the absence of a change in membrane permeability, possible explanations for the increased HVA current include alterations in the number of VGCCs and/or modulation of the channel by intracellular signal transduction pathways.

The increased HVA current was not associated with any change in voltage dependence of activation. A recent report\(^{3}\) in NTS neurons isolated from renal wrap HT rats found that transient voltage-dependent potassium currents were reduced in hypertension with no change in voltage-dependent activation or inactivation kinetics. These findings indicate that renal wrap hypertension can induce either upregulation and down-regulation of specific voltage-gated channels in NTS neurons.

However, the number of channels could be unchanged and persistent changes in ion channel function mediated by activation of intracellular signal transduction pathways that outlast the presence of the stimulus. For example, exposures to angiotensin II (Ang II)\(^{17,18}\) and corticosterone\(^{19}\) influence intracellular signal transduction pathways and gene transcription for hours beyond the period of exposure.

Several studies have identified stimuli that enhance VGCC function. The increased HVA current observed in ventricular myocytes isolated from rats in heart failure mentioned above depends on membrane depolarization. Increased baroreceptor afferent input or other synaptic inputs to NTS neurons could provide a depolarization that induces a persistent change in VGCC function. NO could also alter VGCCs, because NO facilitates excitatory amino acid transmission in NTS neurons\(^{20}\) and enhances N-type calcium currents in rat sympathetic neurons.\(^{21}\) Reactive oxygen species modulate calcium influx via VGCCs in neuronal cultures\(^{22}\) and in NTS neurons.\(^{23}\) The role of afferent inputs as an initiator of the observed changes is difficult to determine experimentally, as any intervention that would eliminate peripheral afferent inputs (eg, aortic nerve section) will likely alter the hemodynamic profile and circulating hormone levels associated with the hypertension.

Another factor of potential importance is Ang II. Circulating or tissue Ang II systems are important in the development of renal wrap HT, because blockade of Ang II type 1 receptors with losartan\(^{24}\) or ZD7155 (JR Haywood, unpub-
and consequent activation of VGCC. Sumners et al. demonstrated that Ang II elicits an ATR1 receptor-mediated increase in voltage-gated Ca\(^{2+}\) current in neurons cultured from rat brain stem. Therefore, it is possible that Ang II mediates the changes that we report. Whatever mediates the increased VGCC current, it results in an effect that persists in the absence of the initiating stimulus. If Ang II initiates the changes that we observed, it must induce a change in VGCC function that persists in the absence of angiotensin for a time period at least as long as our dispersion and recording protocols, typically 10 to 12 hours.

Enhanced calcium influx during depolarization of NTS neurons in HT rats could initiate a number of changes in neuronal function. Excitability could be either increased because of depolarizing calcium influx, or excitability could be decreased via activation of calcium-activated potassium conductances. Our previous current clamp study of NTS neurons in renal wrap HT rats found that responses to depolarizing current pulses initiated from the resting membrane potential were not different in NT compared with HT rats, nor were there any differences in the amplitude or duration of the action potential and after hyperpolarization. These observations suggest that, within the parameters of this previous study, enhanced current flow through VGCCs has no obvious effect on neuronal excitability. Changes in intracellular calcium, either as a direct result of VGCCs or because of release from intracellular stores, can also mediate alterations in gene transcription, and enhanced expression of γ-aminobutyric acid type B receptor mRNA has been reported in the NTS of renal wrap HT rats. Finally, increased intracellular calcium can alter the phosphorylation status and activity of a variety of intracellular enzymes and neurotransmitter receptors.

**Perspectives**

The observation that enhanced current flow through VGCCs was observed in neurons from HT rats, regardless of whether or not they possessed somatic DiA labeling, and, therefore, a presumptive baroreceptor afferent input, suggests that the consequences of the finding are not specific for or restricted to NTS neurons involved in baroreflex pathways. As a caveat, not all of the NTS neurons receiving baroreceptor inputs will be labeled by application of DiA to the aortic nerve. For example, neurons receiving carotid sinus baroreceptor inputs will not be labeled using this approach. It is important to keep in mind that HVA VGCCs will only be functionally significant if the neuron is sufficiently depolarized to activate the channels. This may only occur in NTS neurons receiving increased excitatory baroreceptor afferent inputs and, therefore, synaptic depolarization. The number of baroreceptor afferent fibers discharging action potentials is increased in renal wrap HT, and this could translate into sufficient depolarization in those cells receiving baroreceptor afferent inputs to activate HVA VGCCs. Therefore, changes induced in VGCC function in most NTS neurons by tissue-generated and/or circulating Ang II might only be of functional significance in those cells in which there is also an elevated afferent, depolarizing input. This afferent input need not only be from peripheral sources, because projections to NTS from

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**Figure 6.** Time-dependent recovery from inactivation. LVA currents were isolated by stepping from a conditioning potential of \(-100\) and stepping to \(-40\) mV (subthreshold for activation of HVA currents) followed by a return to \(-60\) mV (A1). By varying the duration of the \(-100\)-mV conditioning potential, the time-dependent recovery from inactivation of the LVA current could be observed (A2). In A3, application of nickel during the period indicated by the horizontal line abolished the evoked current, further establishing it as an LVA current. B, Mean data of peak current densities as a function of the duration of the conditioning potential. Note that there is no difference in the peak LVA current density between NT and HT neurons as in Figure 5 and that the time course of recovery from inactivation also did not differ in NT \((n=34)\) compared with HT neurons \((n=21)\).
other central sites could also mediate or contribute to the synaptic depolarization.

Source of Funding
This work was supported by National Institutes of Health grant HL-56637.

Disclosures
None.

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Gleb Tolstykh, Patricia M. de Paula and Steve Mifflin

Hypertension. 2007;49:1163-1169; originally published online March 19, 2007;
doi: 10.1161/HYPERTENSIONAHA.106.084004
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
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