Chronic Intermittent Hypoxia and Hypercapnia Inhibit the Hypothalamic Paraventricular Nucleus Neurotransmission to Parasympathetic Cardiac Neurons in the Brain Stem

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Abstract—Obstructive sleep apnea is associated with chronic intermittent hypoxia/hypercapnia (CIHH) episodes during sleep that heighten sympathetic and diminish parasympathetic activity to the heart. Although one population of neurons in the paraventricular nucleus of the hypothalamus strongly influences sympathetic tone and has increased activity after CIHH, little is known about the role of this pathway to parasympathetic neurons and how this network is altered in CIHH. We hypothesized that CIHH inhibits the excitatory pathway from the paraventricular nucleus of the hypothalamus to parasympathetic cardiac vagal neurons in the brain stem. To test this hypothesis, channelrhodopsin was selectively expressed, using viral vectors, in neurons in the paraventricular nucleus of the hypothalamus and channelrhodopsin-expressing fibers were photoactivated to evoke postsynaptic currents in cardiac vagal neurons in brain stem slices. Excitatory postsynaptic currents were diminished in animals exposed to CIHH. The paired-pulse and prolonged facilitation of the postsynaptic current amplitudes and frequencies evoked by paired and bursts of photoactivation of channelrhodopsin fibers, respectively, occurred in unexposed rats but were blunted in CIHH animals. In response to an acute challenge of hypoxia/hypercapnia, the amplitude of postsynaptic events was unchanged during, but increased after hypoxia/hypercapnia in unexposed animals. In contrast, postsynaptic currents were inhibited during hypoxia/hypercapnia in rats exposed to CIHH. In conclusion, the excitatory pathway to cardiac vagal neurons is diminished in response to both acute and chronic exposures to hypoxia/hypercapnia. This could elicit a reduced cardioprotective parasympathetic activity and an enhanced risk of adverse cardiovascular events in episodes of apnea and chronic obstructive sleep apnea. (Hypertension. 2014;64:597-603.)

Key Words: anoxia ■ hypercapnia ■ hypothalamus

Obstructive sleep apnea (OSA) is a significant health risk occurring in as many as 24% of adult males and 9% of adult females within the US population.1,2 Patients with OSA experience chronic nocturnal recurrent apneas resulting in intermittent periods of hypoxia and hypercapnia (H/H) that increase the risk of sudden cardiac death, hypertension, arrhythmias, myocardial ischemia, and stroke.2-4 However, the mechanisms that enable OSA to initiate or maintain cardiovascular diseases or both are poorly understood.

Chronic exposure to intermittent hypoxia (CIH) or hypoxia/hypercapnia (CIHH) during the inactive sleeping period in animals mimics the repetitive episodes of apneas that occur in humans with OSA. Both patients with OSA and animals exposed to CIH or CIHH have an altered balance of autonomic activity with elevated sympathetic and reduced parasympathetic activity to the heart with resulting tachycardia, decreased baroreflex sensitivity, and elevated blood pressure often to hypertensive levels.3,5-10 Neurons in the paraventricular nucleus (PVN) of the hypothalamus are critical in setting autonomic tone.11,12 The maintenance of both heightened sympathetic activity and hypertension after CIH is dependent on ongoing activity of sympathoexcitatory neurons in the PVN.11,12 Although the role of PVN neurons that project to sympathetic targets has been well studied, little is known about the role of different neurons in the PVN in controlling parasympathetic activity and how this network is altered in CIHH. The results from animal studies indicate that the mechanisms for decreased baroreflex control of heart rate and diminished parasympathetic activity to the heart that occurs with CIH include central autonomic dysregulation and, in particular, altered function of cardiac vagal neurons (CVNs) in the brain stem.10,13 Parasympathetic cardiac vagal activity is typically cardio-protective14,15 while diminished parasympathetic activity to the heart is associated with cardiovascular diseases such as heart failure.16,17 It has been postulated that increasing and restoring cardiac vagal function would play a beneficial role and increase survival in individuals with cardiovascular diseases.15

Previous work, using optogenetic techniques, has established a monosynaptic glutamatergic pathway from the PVN
to CVNs in the dorsal motor nucleus of the vagus (DMV). However, the alterations that occur with CIHH in this neurotransmission are unknown. In addition, the results from recent studies have demonstrated that the excitatory neurotransmission to CVNs are very sensitive to acute H/H exposures. Accordingly, in this study we tested the hypothesis that CIHH impairs activation of CVNs and diminishes the excitatory glutamatergic pathway from the PVN to CVNs under both normoxic conditions and during acute H/H challenges.

**Materials and Methods**

Experiments were conducted on Sprague–Dawley rats of both sexes. All animal procedures were performed in compliance with the institutional guidelines at George Washington University and are in accordance with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association and the National Institutes of Health publication Guide for the Care and Use of Laboratory Animals.

**PVN Lentiviral Injections and CVN Labeling**

A lentiviral vector that drives channelrhodopsin-2 (ChR2)–enhanced yellow fluorescent protein expression was synthesized and stereotactically injected into the PVN as performed across all experiments as recently described. Rat pups (4–5 days old) were anesthetized by hypothermia and maintained in a stereotactic apparatus with a neonatal adapter (Stoelting, Wood Dale, IL). The skull was exposed and a small burr hole was made to position a pulled calibrated pipette (WVR, Radnor, PA) containing viral vector at the following coordinates: 1.5–1.95 mm posterior (depending on the distance between bregma and lambda) and 0.3 mm lateral relative to bregma. The pipette tip was lowered 4.80 mm from the dorsal surface of the brain and 75 nl of viral vector was injected at a visually monitored rate of 60 nl per minute. The pipette was left in place for 5 minutes, before careful and slow retraction. We examined the expression of ChR2 in all of the animals used in this study, and only those animals in which the expression of ChR2 was limited to the PVN were included for analysis. Animals with ChR2 expression outside of the PVN boundaries were excluded from further analysis. Selective expression of ChR2 in the PVN using these methods are more fully described in our previous study.

The fluorescent retrograde labeling of parasympathetic CVNs was performed as described previously. Rat pups (postnatal days 4–5) were anesthetized with hypothermia and received a right thoracotomy. The heart was exposed, and 0.05 mL of 1% to 5% rhodamine (XRITC; Molecular Probes, Eugene, OR) was injected into the pericardial sac. Specificity of the cardiac vagal labeling has been confirmed in a previous study by the absence of any labeled neurons in the brain stem when rhodamine is injected either outside the pericardial sac or within the pericardial sac if the cardiac branch of the vagus nerve is sectioned. After surgery, buprenorphine was administered, and animals were monitored for 30 minutes and every 20 minutes thereafter until ambulatory.

**CIHH Exposures**

The animals that received both PVN lentiviral injections and CVN labeling were kept in animal research facility cages until they were 4 weeks old. At 4 weeks of age the animals, kept in their normal cages with unrestricted access to food and water, were placed in a commercial (Biospherix) chamber pod with computer-controlled atmospheric gas control. CIHH was performed by cycling between room air (20.9% oxygen, 79.1% nitrogen) and hypoxia/hypercapnia (6% oxygen, 5% CO₂, and 89% nitrogen). There were 4 phases to this CIHH cycle; in the first phase the room air was changed to hypoxia/hypercapnia in 90 seconds, and hypoxia/hypercapnia was maintained for an additional 90 seconds (second phase). In the third phase the hypoxic/hypercapnic gas mixture was returned to room air levels (over 90 seconds) and this room air mixture was maintained for 90 seconds (fourth phase). This CIHH protocol was maintained at a frequency of 10x each hour, 8 hours each day, 4 weeks long. Control animals were age-matched to CIHH animals and were subjected to the same handling and gas exchange conditions as CIHH rats except that the gas mixture was maintained with room air.

**Slice Preparation and Electrophysiology**

After 4 weeks of CIHH exposure, animals were euthanized and brain stem slices were obtained for electrophysiological experiments. To obtain viable brain slices from 8-week-old animals, glycerol-based artificial cerebrospinal fluid (aCSF) was used for cardiac perfusion and brain stem sectioning. Glycerol-based aCSF contained (in mmol/L): 110 NaCl, 1.2 NaHPO₄, 1.2 MgCl₂, 2.4 CaCl₂, 26 NaHCO₃, and 11 glucose. On the day of experiment, the animals were anesthetized with isoflurane, and glycerol-based aCSF (4°C) was perfused transcardially. Then brain was carefully removed and 300-µm-thick slices of the medulla that contained the CVNs in the DMV were obtained using a vibratome. Forebrain slices containing the PVN were also made for verification of the injection site. Animals that had injections outside the boundaries of the PVN were excluded from electrophysiological experiments. The obtained slices of the medulla were transferred to a solution of the following composition (in mmol/L): 110 NaCl, 2 KCl, 1.2 NaHPO₄, 25 NaHCO₃, 25 glucose, 110 HCl, 0.5 CaCl₂, and 10 MgSO₄ equilibrated with 95% O₂ and 5% CO₂ (pH 7.4) at 34°C for 15 minutes. This brief protective recovery step using N-methyl-d-glucamine–based aCSF reduces neuronal swelling during rewarming and is critically important for viable brain slice preparation in animals. The slices were then transferred from N-methyl-d-glucamine–based aCSF to a recording chamber, which allowed perfusion (5–10 mL/min) of aCSF at room temperature (25°C) containing (in mmol/L): 125 NaCl, 3 KCl, 2 CaCl₂, 26 NaHCO₃, 5 glucose, and 5 HEPES equilibrated with 95% O₂ and 5% CO₂ (pH 7.4) for ≥30 minutes before experiments were conducted. One to 3 slices from each animal were used in experiments.

Individual CVNs were identified by the presence of the fluorescent tracer. These identified CVNs were then imaged with differential interference contrast optics, infrared illumination, and infrared-sensitive video detection cameras to gain better spatial resolution. Patch pipettes (2.5–3.5 MΩ) were filled with a solution consisting of 135 mmol/L K-gluconic acid, 10 mmol/L HEPES, 10 mmol/L ethylene glucol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid, 1 mmol/L CaCl₂, and 1 mmol/L MgCl₂, pH 7.35, and guided to the surface of individual CVNs. Voltage clamp whole-cell recordings were made at a holding potential of ~80 mV with an Axopatch 200 B and pClamp 8 software (Axon Instruments, Union City, CA). At the end of the experiments, d-α-amino-5-phosphonovalerate (AP-5, 50 mmol/L) and 6-cyano-7-nitroquinazoline-2,3-dione (50 mmol/L) were bath-applied to block glutamatergic N-methyl-d-glucamine and alpha-amino-3-hydroxy–5-methyl-4-isoxazolepropionic acid/kainate receptors, respectively. All drugs used in this study were purchased from Sigma-Aldrich Chemical Co (St. Louis, MO). Selective photostimulation of ChR2 expressing PVN fibers surrounding the CVN was performed using a 473-nm blue laser light (CrystaLaser, Reno, NV). The laser was attached to the microscope using a dual housing adapter (Nikon). The numeric aperture of the x40 water immersion objective was 0.8 and the working distance 2.0 mm. Three types of stimulation were performed including: single stimulation (3-ms light pulses at 1 Hz), paired-pulse stimulation (paired 3-ms pulses at frequency 10 Hz), and multiple stimulations (4 pulses, 3-ms duration, at frequency 10 Hz). Laser light intensity was kept constant across all experiments at an output of 10 mW. All CVNs selected for the analysis had a latency of the response ranging from 3.1 to 8.9 ms, in accordance with the criteria for a monosynaptic connection.

In experiments that examined the role of acute H/H in modulation of the evoked responses in CVNs, slices were exposed to H/H by changing control aCSF equilibrated with 95% O₂ and 5% CO₂, pH 7.4, to an identical solution equilibrated with 85% N₂, 6% O₂, and 9% CO₂, pH 7.1. Slices were exposed to acute H/H for 10 minutes and then slices were reoxygenated during 20 minutes by returning the perfusate to the control aCSF.
Data Analysis and Statistics
Synaptic latency of the evoked responses was measured as the time between the onset of the stimulation and the onset of synaptic current. Short-latency (<10 ms) excitatory postsynaptic currents (EPSCs) were measured using the pClamp 8 software (Molecular Devices, Sunnyvale, CA). The responses to a series of consecutive photostimulations (60 single stimulations, 9 paired-pulse stimulations, and 9 bursting stimulations) in each neuron were averaged in all series of experiments. The mean value from each neuron in the population was averaged for the population of neurons to create a summary of results for each condition. During acute H/H, a series of 60 consecutive single stimulations (at frequency of 1 Hz) were applied at 1, 4, and 9 minutes after onset of acute H/H and at 14 minutes after acute H/H.

The analysis of prolonged responses (>0.5 seconds) was performed using MiniAnalysis (version 4.3.1; Synaptosoft, Decatur, GA). The frequency and amplitude of EPSCs were analyzed from 2-second periods before multiple stimulations (control) and from 2-second periods during 8 minutes after multiple stimulations. Threshold was set at root-mean-square noise multiplied by 5. Results are presented as mean±SE and statistically compared using the GraphPad Prism 5 software and using Student paired t test, ANOVA with repeated measures and Dunnett post-test, or the Mann–Whitney U test, as appropriate. Significant difference was set at P<0.05.

Results
In unexposed animals single photostimulation of PVN fibers elicited an EPSC in DMV CVNs in the brain stem slices (peak amplitude, 55±12 pA; latency, 5.3±0.3 ms; n=23 neurons from 14 animals; Figure 1A, left). The response was significantly diminished by application of AP-5 (from 74±27 to 18±6 pA; P<0.04; n=9 neurons from 6 animals; Student paired t test) and nearly completely blocked by coapplication of AP-5 and 6-cyano-7-nitroquinoxaline-2,3-dione (from 38±10 to 2±0.4 pA; P<0.002; n=16 neurons from 8 animals; Student paired t test). A comparison between unexposed and CIHH animals indicated that the peak amplitude of EPSCs evoked by PVN fiber photostimulation was significantly greater in unexposed animals compared with CIHH animals (55±12 [n=23 neurons from 14 animals] versus 35±7 pA [n=24 neurons from 10 animals], respectively; P=0.02; Mann–Whitney U test; Figure 1A and 1B).

In unexposed animals paired-pulse photostimulation of ChR2 PVN fibers elicited paired-pulse facilitation in CVNs in the DMV, as the second EPSC amplitude was greater than the magnitude of the first response (first response amplitude, 34±6 pA, versus second response amplitude, 47±11 pA; n=19 neurons from 12 animals; P=0.02; Student paired t test; Figure 2A). However, in CIHH animals the paired-pulse facilitation was absent (first response amplitude, 25±4 pA, versus second response amplitude, 30±5 pA; n=22 neurons from 9 animals; P>0.05, Student paired t test; Figure 2B).

Bursting stimulations with 4 light pulses each evoked short-latency EPSCs in CVNs in the DMV. The third and fourth responses were significantly enhanced when compared with the first response in both unexposed and CIHH animals (unexposed animals: first response, 45±9 pA, versus third response,
74±15 pA, and fourth response, 76±13 pA; *P<0.001; n=17 neurons from 12 animals; CIHH animals: first response, 34±7 pA, versus third response, 47±12 pA, and fourth response, 53±13 pA; *P<0.05; n=16 neurons from 8 animals; ANOVA with repeated measures and Dunnett post-test, Figure 3).

In addition to the short-latency responses, the bursting stimulations also elicited prolonged (>0.5 seconds) increases in spontaneous EPSC frequency and amplitudes in CVNs in the DMV from unexposed animals. The frequency of EPSCs in CVNs was significantly increased 2 seconds after bursting PVN photostimulation (from 4±1 to 7±1 Hz; *P<0.001; n=17 neurons from 12 animals; ANOVA with repeated measures and Dunnett post-test). Similarly, the amplitude of EPSCs was significantly increased 4 seconds after stimulations (from 22±2 to 24±2 pA; *P<0.05; n=17 neurons from 12 animals; ANOVA with repeated measures and Dunnett post-test; Figure 4, right).

In CIHH animals, however, no significant changes either in frequency or in amplitude of EPSCs in CVNs occurred after bursting PVN photostimulation, ANOVA with repeated measures and Dunnett post-test (Figure 4, right).

Because acute H/H strongly affects central parasympathetic cardiac activity and the neurotransmission to CVNs, the responses in CVNs on photoactivation of PVN fibers were studied before, during, and after acute H/H (Figure 5). In unexposed animals, the peak amplitude of EPSCs evoked by photoactivation of PVN fibers was not altered during acute H/H. However, 15 minutes after H/H, the amplitude of EPSC was significantly increased (from 54±8 to 118±29 pA; *P<0.001; n=13 neurons from 11 animals; ANOVA with repeated measures and Dunnett post-test; Figure 5, left). In CIHH animals, in contrast, the peak amplitude was significantly decreased during acute H/H (from 50±15 to 23±6 pA; 5 minutes acute H/H; *P<0.05; n=10 neurons from 9 animals; ANOVA with repeated measures and Dunnett post-test), and no significant changes occurred in the recovery period (Figure 5, right).

Discussion

In accordance with the previous work, a lentiviral vector injection that drives robust ChR2 expression in PVN neurons enables selective photostimulation of brain stem PVN fibers that evoke EPSCs in CVNs in both unexposed and CIHH animals. The short-latency of the evoked EPSC indicates that the response is monosynaptic. Because the response is diminished by the N-methyl-d-glutamate receptor antagonist AP-5 and nearly completely blocked by adding the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione, both types of glutamatergic receptors are involved in the excitation of CVNs evoked on photostimulation of PVN fibers.

CIHH significantly alters 4 properties of the neurotransmission from PVN fibers to CVNs. (1) The peak amplitude of glutamatergic EPSC evoked by single photostimulation of the PVN fibers is diminished in CIHH animals when compared with control unexposed rats. (2) The paired-pulse facilitation of the EPSC that occurs in unexposed rats is significantly blunted in CIHH animals. (3) The increased EPSC frequency and amplitude after bursting PVN photostimulations are present in unexposed animals but absent in CIHH rats. (4) The amplitude of EPSCs evoked by single photostimulation is unchanged during acute H/H but increased after acute H/H in unexposed animals. In contrast, EPSC amplitude is inhibited during acute H/H and was not different from control EPSC amplitudes after acute H/H in rats exposed to CIHH.

PVN Pathway to Parasympathetic CVNs

Although the PVN is well known as an important site for sympathetic cardiovascular regulation that include projections to presympathetic neurons in the rostral ventrolateral medulla and preganglionic neurons in the upper spinal cord, previous studies have also shown that PVN plays a role in parasympathetic control of heart rate. Indeed, acute bilateral PVN inhibition results in decreasing baroreflex bradycardia without affecting tachycardic responses. These results suggest that a population of PVN neurons provides a facilitatory influence on cardiac parasympathetic activity. The results from other work indicate that electrical stimulation of the PVN evokes bradycardia which is inhibited by injections of an oxytocin receptor antagonist into the DMV, suggesting a possible parasympathetic cardiac pathway from the PVN to the DMV. The result from this project extends the findings of previous studies and provides direct evidence for the existence of a monosynaptic glutamatergic pathway from the PVN to identified CVNs that project to the heart and provide tonic and reflex control of cardiac parasympathetic activity. Different types of photostimulation of PVN fibers, including single, paired-pulse, and bursting stimulations, evoke glutamatergic EPSCs in CVNs.

CIHH Impairs Excitatory Pathway From the PVN to CVNs

Although reduced parasympathetic activity to the heart and decreased baroreflex control of heart rate have been found in
individuals with OSA and animals exposed to CIH, the neurophysiological mechanisms underlying these adverse effects on parasympathetic activity are not well understood. This study discovered a central neurophysiological mechanism including CIHH-induced alteration in the specific pathway from the PVN to CVNs that likely contributes to such parasympathetic impairment, particularly if this hypothalamic pathway is tonically active. The amplitude of
glutamatergic EPSC evoked by a single photostimulation of PVN fibers is diminished in CIHH-exposed animals. The diminishing excitatory neurotransmission to CVNs would predict CVN inhibition, reduced parasympathetic activity to the heart, tachycardia with increased risk of arrhythmias, and sudden cardiac death.

Paired-pulse facilitation, as well as postbursting photostimulation augmentation of EPSC frequency and amplitude in CVNs, occurred in control animals but were blunted in CIHH rats. The mechanisms underlying paired-pulse facilitation are attributed to enhanced transmitter release by the second stimulus after an increase in intracellular calcium elicited by the first stimulus. A change in paired-pulse responses, therefore, indicates a presynaptic site of action. The absence of paired-pulse facilitation in CIHH animals suggests impaired presynaptic mechanisms of transmitter release from PVN synaptic terminals, which may include alteration in neurotransmitter synthesis, neuromodulation by coreleased peptides, vesicular accumulation or release properties, including impaired expression of ChR2 or diminished photoactivation of ChR2 in CIHH animals. Similar to the results in this study, the findings from other groups have found that CIH diminishes evoked excitatory synaptic transmission between sensory afferents and second-order cells in the nucleus tractus solitarius, which occurs via presynaptic mechanisms.

**CIHH Alters Responses to Acute H/H**

Acute H/H induces stress in the central nervous system and triggers important adaptive responses promoting neuronal survival and enabling the organism to cope with such changes. However, these adaptive responses could be altered by chronic exposures to repetitive episodes of H/H. Previous work has shown dramatic changes in both excitatory and inhibitory neurotransmission to CVNs elicited by acute hypoxia or acute H/H. For example, respiratory-related glutamatergic neurotransmission to CVNs is recruited after hypoxia increasing EPSC frequency during reoxygenation. Extending from the results in this previous study, the results in this project show that the amplitude of glutamatergic EPSC elicited in CVNs on PVN fiber photostimulation is significantly enhanced after acute H/H. Activation of CVNs via increasing excitatory neurotransmission would increase parasympathetic activity to the heart and play a cardioprotective role during recovery from acute H/H. However, in animals exposed to CIHH there is no enhancement in EPSC amplitude after acute H/H. Moreover, in contrast to unexposed animals, a significant inhibition of glutamatergic EPSC amplitude occurs during acute H/H in CIHH rats.

Thus, particularly when the pathway from the PVN to CVNs is tonically active, cardioprotective parasympathetic activity to the heart would be diminished in CIHH animals during exposure to acute H/H increasing the risk of adverse cardiovascular events. Similar to the responses in animal models, in humans an apnea elicits a bradycardia, because of parasympathetic activation. The results of this study would predict a parasympathetic impairment or sympathovagal imbalance or both during apnea events in individuals with OSA. The reduced parasympathetic activity to the heart and diminished baroreflex control of cardiovascular function, along with sympathetic hyperactivity, may contribute not only to blunted baroreflex and hypertension often found in OSA individuals, but also to the increased risk of tachycardia and sudden cardiac death that may occur during each apnea episode in patients with OSA.

**Perspectives**

The glutamatergic PVN pathway to CVNs in the brain stem is diminished in response to both acute and chronic exposures to H/H. This work provides a foundation for the diminished cardiac parasympathetic activity and decreased baroreflex control of heart rate in individuals with OSA by providing direct evidence that many critical properties of the important central excitatory pathway from the PVN to CVNs are impaired in animals exposed to CIHH. Additional studies will be necessary to determine the effect of CIHH on different pathways to specific cardiorespiratory parasympathetic CVNs in the brain stem and identify targets to increase and restore cardiac vagal function in animals exposed to CIHH and individuals with OSA.

**Sources of Funding**

This work was supported by National Institutes of Health grants HL49965, HL59895, and HL72006 to D. Mendelowitz.

**Disclosures**

None.

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Hypoxia Alters Hypothalamic–Brain Stem Pathway


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Novelty and Significance

**What is New?**

- Critical properties of the central excitatory pathway from the paraventricular nucleus to CVNs are impaired in animals exposed to chronic intermittent hypoxia/hypercapnia (CIHH).
- Acute hypoxia and hypercapnia diminishes the central excitatory pathway from the paraventricular nucleus to CVNs in animals exposed to CIHH but not in control animals.

**What is Relevant?**

- Impairment of excitatory pathway from the paraventricular nucleus to CVNs would result in diminished protective parasympathetic activity to the heart and increased risk of arrhythmias, sudden cardiac death, and hypertension.

- This study provides a neurophysiological mechanism for the impaired cardiovascular regulation in animals exposed to CIHH and individuals with obstructive sleep apnea.

**Summary**

CIHH diminishes excitatory glutamatergic pathway from the paraventricular nucleus to parasympathetic CVNs which would predict an impaired parasympathetic control of heart rate in CIHH animals and individuals with obstructive sleep apnea.
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_Hypertension_. 2014;64:597-603; originally published online June 23, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.03603
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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