Medullary inputs to nucleus accumbens neurons

GILBERT J. KIROUAC AND JOHN CIRIELLO
Department of Physiology, Health Sciences Centre, University of Western Ontario, London, Ontario, Canada N6A 5C1

Kirouac, Gilbert J., and John Cirillo. Medullary inputs to nucleus accumbens neurons. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R2080–R2088, 1997.—Extracellular single-unit recording experiments were done in \( \alpha \)-chloralose-anesthetized, paralyzed, and artificially ventilated rats to investigate the effect of stimulation of the nucleus of the solitary tract (NTS) and the ventrolateral medulla (VLM) in the region of the Ai noradrenergic cell group on the activity of neurons in the nucleus accumbens (NA). In addition, the response of NA neurons to activation of the arterial baroreceptors was investigated. Electrical or glutamate (Glu) stimulation of the ipsilateral NTS excited 47 of 99 (48%) and inhibited 10 of 99 (10%) of the units tested in the NA. Similarly, electrical or Glu stimulation of the ipsilateral VLM excited 24 of 97 (24.7%) or inhibited 7 of 97 (7.2%) of the units tested. Approximately 22% (17 of 77) of these units responded to stimulation of both the NTS and VLM. Simultaneous stimulation of both the NTS and VLM potentiated the response of the NA neuron tested. CoCl\(_2\) injection into the ipsilateral NTS did not alter the response of NA neurons to stimulation of the VLM. Similarly, CoCl\(_2\) injections into the ipsilateral VLM did not alter the response of NA neurons to NTS stimulation. The discharge rate of some of the units (6 of 49) that were activated by both NTS and VLM was also increased during the activation of arterial baroreceptors by the acute rise in systemic arterial pressure to phenylephrine injection. Units that responded to stimulation of the NTS and VLM and to baroreceptor activation were located in the shell region of the NA. These data indicate that afferent inputs from the NTS and VLM converge onto NA neurons and suggest that visceral and cardiovascular afferent inputs may influence the output of neurons in the shell region of the NA.

THE NUCLEUS ACCUMBENS (NA), which forms part of the ventral striatum, is distinguished from the dorsal striatum (caudate-putamen) on the basis of its connectivity and function (9, 11, 12). The caudate-putamen, along with other components of the basal ganglia (substantia nigra, globus pallidus, and sensorimotor cortex), plays a major role in the modulation of motor responses and cognitive processes (1, 21). The NA, in addition to its connections with the basal ganglia, is also connected with limbic structures (1). The NA receives afferent projections from the insular, prelimbic, infralimbic, cingulate, and piriform cortices; the basolateral and basomedial nucleus of the amygdala; the hippocampus; the ventral tegmental area (2, 3, 12, 13, 16, 17, 26); and the paraventricular nucleus of the thalamus (1, 3). In turn, the NA projects throughout the rostrocaudal extent of the lateral hypothalamic area, substantia innominata, bed nucleus of the stria terminalis, and periaqueductal gray matter (11, 16). The reciprocal connections between the NA and forebrain limbic structures suggests a possible role for the NA in the regulation of functions, such as species-specific behaviors, emotional reactions, motivational processes, and autonomic outflow (1, 20).

Recent neuroanatomical studies have demonstrated that the NA also receives direct afferent projections from the ventrolateral medulla (VLM) and dorsomedial medulla (3, 18, 27, 35). Injections of retrograde tracers into the NA resulted in labeled neurons in the lateral paragigantocellular nucleus and the lateral reticular nucleus of the ventrolateral medulla (15) and in the medial and commissural subnuclei of the caudal portion of the nucleus of the solitary tract (NTS) (3, 18, 27). These regions of the brain stem have been shown to function in the relay and integration of visceral information (for reviews, see Refs. 5, 8). In addition, the caudal region of the NTS receives afferent projections from carotid and aortic baroreceptors (4, 6) and carotid chemoreceptors and lung stretch receptors (15) and has been shown to be important in the integration of baroreceptor and chemoreceptor reflexes. The caudal NTS also receives afferent projections from the VLM (5). The VLM in turn receives inputs from a number of peripheral receptors (5), and central structures involved in visceral function, including projections from the NTS, the hypothalamus, and the limbic system (5, 8). The VLM has been shown to play an important role in mediating baroreceptor, chemoreceptor, and somatosympathetic reflexes (5).

The present study was done to provide electrophysiological evidence for afferent inputs from the VLM and NTS to the NA and to determine whether these inputs converge onto NA neurons. In addition, experiments were done to determine whether NTS inputs to the NA were mediated by the VLM or whether VLM inputs to NA were mediated through the NTS. Finally, the response of accumbal neurons to the activation of the arterial baroreceptors was investigated.

METHODS

Experiments were done in 24 male Wistar rats (300–450 g) anesthetized with \( \alpha \)-chloralose (60 mg/kg iv initially; supplemented by additional doses of 30 mg/kg iv every \( \sim \)1–2 h) after induction with equithesin (0.3 ml/100 g ip). All experimental procedures were done in accordance with the guidelines on the use and care of laboratory animals as set out by the Canadian Council on Animal Care and approved by the Animal Care Committee at the University of Western Ontario.

The trachea was cannulated, and PE-50 polyethylene catheters were inserted into the femoral artery and vein for the recording of arterial pressure (AP) and the administration of drugs, respectively. AP was recorded using a Statham P23 Db pressure transducer, and heart rate (HR) was monitored with a 7P3FG Grass tachograph triggered by the AP pulse, both of which were continuously recorded on a Grass...
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7D polygraph. The animals were paralyzed with pancuronium bromide (Pavulon, Organon Canada, Toronto, ON; 1 mg/kg iv initially and additional doses of 0.5 mg/kg iv when necessary) and artificially ventilated with 95% O2-5% room air. During the course of the experiment, the animals were allowed to recover periodically from the paralyzing agent to determine the depth of anesthesia by examination of withdrawal reflexes. Rectal temperature was monitored and maintained at 37 ± 0.2°C with a heating pad controlled by a Yellow Springs temperature controller (model 73).

The head of the animal was fixed in a Kopf stereotaxic frame, and access to the NA was obtained by partial parietal craniotomy. Access to the NTS and VLM was obtained by removing a portion of the caudal occipital bone and exposing the caudal portion of the floor of the fourth ventricle. All exposed nervous tissue was covered with Dow Corning 360 medical fluid to prevent drying.

Electrical stimulation of NTS and VLM. In 16 animals, concentric bipolar stainless steel electrodes (SNE-100, David Kopf, Tujunga, CA; 0.25 mm) were stereotaxically placed at a 10° angle to the rostrocaudal plane into the left NTS (0.8 mm rostral, 0.5–0.8 mm mediolateral, and 0.5–1.0 mm ventral to surface of brain stem) using the calamus scriptorius as the point of reference (22). A saline-based needle screw electrode was inserted at an angle of 20° to the rostrocaudal plane and aimed at the left caudal to intermediate VLM (1.5 mm rostral, 1.7 mm mediolateral, and 2.5–3.0 mm ventral to surface of brain stem) (5). The NTS was electrically stimulated using a 5-s train of pulses at current intensities of 10–30 µA (0.5-ms pulse duration, 20–40 Hz) to identify sites that elicited decreases of >15 mmHg in AP and 15 beats/min in HR. The VLM was stimulated using the same stimulus parameters that elicited either decreases or increases of >15 mmHg in AP and 15 beats/min in HR. The variable cardiovascular responses were the result of the exact placement within the caudal to intermediate VLM (5). The stimulus applied to the cardiovascular responsive sites in the NTS and VLM during recording of single units in the NA was a rectangular pulse at a current intensity of 10–150 µA and 0.5-ms pulse duration at 1 Hz.

Chemical stimulation of NTS and VLM. In eight additional animals, injections of glutamine (Glu; 0.25 M in 0.9% saline, pH 7.2; Sigma Chemical, St. Louis, MO) were made using glass micropipettes pulled from 5 µl Socorex capillary tubing, with internal tip diameters ranging between 30 and 50 µm, were stereotaxically placed at a 50° angle to the rostrocaudal plane into either the left NTS (0.3 mm caudal, 0.8 mm medial, and 1.5 mm ventral) or the left VLM (1.0 mm rostral, 1.8 mm medial, and 4.5 mm ventral). Stimulating electrode were placed in both the NTS and VLM ipsilateral to the placement of the double-barreled micropipette. Units in the NA that responded with excitation to both NTS and VLM stimulation were identified, and CoCl2 or artificial cerebrospinal fluid (CSF) was then microinjected into either the NTS or VLM. Five minutes after the microinjection into one of the sites, the other site was electrically stimulated using the same stimulation parameters that evoked the original single-unit response in the NA. Solutions of CoCl2 (10 mM; Fisher Scientific, Fair Lawn, NJ) dissolved in artificial CSF (in mM: 126 mM NaCl, 2.5 KCl, 1.24 NaH2PO4, 1.3 MgCl2, 2.4 CaCl2, 26.0 NaHCO3, and 10.0 glucose; pH 7.4) or artificial CSF only were microinjected (50 nl) by the application of pressurized nitrogen pulses controlled by a pneumatic pump (Medical Systems, NY). The injected volumes were measured by direct observation of the fluid meniscus in the micropipette by use of a microscope fitted with an ocular micrometer.

Recording of single units in NA. In the studies during which the NTS or VLM were stimulated with Glu, the region of the ipsilateral NA (9.5–11.5 mm rostral to intra-aural line) was explored systematically for spontaneously discharging units using glass microelectrodes filled with 2% Pontamine sky blue dissolved in 0.5 M sodium acetate (5–10 MΩ impedance, 1–3 µm tip diam). In the electrical stimulation studies, in addition to testing spontaneously active units encountered during the electrode penetrations, the NTS and/or VLM were electrically stimulated (150 µA, 0.5-ms pulse, 1 Hz) as the electrode was advanced through the region of NA. This was done because most of the units in the NA have previously been reported to be silent or have discharge rates <0.2 spikes/s (30, 32). Electrode penetrations were made on a grid pattern with points ~300 µm apart. Extracellular, single-unit activity was amplified through a multipurpose microelectrode amplifier (Axoprobe-1A, Axon Instruments, Foster City, CA) and displayed on a Tektronics R5113 oscilloscope for observation and photography. The action potentials were also discriminated by a slope-height window discriminator (Friederich Haer, Brunswick, ME) and peristimulus time histograms (PSTH) were generated using a AST 286 computer (analog-to-digital conversion board from Datal Translation, Marlboro, MA). The activity of units that responded to NTS and/or VLM stimulation were also tested during the acute rise in AP (mean ± SE, 75 ± 6 mmHg) elicited by the intravenous administration (0.1–0.2 ml) of a phenylephrine solution (10 µg/kg, Sigma). The reflex decrease in HR (103 ± 17 beats/min) to the rise in systemic AP was taken to indicate the activation of arterial baroreceptors.

Administration of CoCl2 in NTS or VLM. Double-barreled micropipettes pulled from 5 µl Socorex capillary tubing, with internal tip diameters ranging between 30 and 50 µm, were stereotaxically placed at a 50° angle to the rostrocaudal plane into either the left NTS (0.3 mm caudal, 0.8 mm medial, and 1.5 mm ventral) or the left VLM (1.0 mm rostral, 1.8 mm medial, and 4.5 mm ventral). In brief, changes in the discharge rate of neurons to stimulation of the NTS were identified and quantified by comparing the height of each poststimulus bin of the PSTH with the average bin height for the period of 100 ms before the stimulus (baseline activity). The onset latency of an orthodromic response was determined from the PSTH as the time interval from the stimulus artifact to the first five consecutive bins with heights that were >1 SD from the mean baseline discharge rate. The boundaries of possible periods of significant responses (duration) were defined as the occurrence of a period of time after stimulation during which the mean height of the PSTH was at least 30% above or below the mean baseline discharge rate.

The discharge rates of units were also monitored during the acute rise in AP after intravenous administration of phenylephrine and during microinjection of Glu into either the NTS or VLM. In these cases, a running rate-meter record of the discharge rate of the unit during the administration of the drugs was compared with the baseline discharge rate before the drug injections. A mean bin height of at least 30% above or below the mean baseline discharge rate for at least three consecutive bins was accepted as a significant response.

Response latencies and durations, spontaneous discharge rates, and magnitude of the responses were compared statistically using the Student’s t-test. P < 0.05 was considered to indicate statistical significance.
Histological localization of recording and stimulating sites. Most recording sites and all stimulation and injection sites were marked at the end of each experiment. Recording sites were also determined by interpolation from Pontamine sky blue deposits (4–5 µA cathodal DC current for 15–30 min) in an electrode penetration. Stimulation sites were marked by depositing iron from the electrode tip (20–30 µA anodal DC current for 20–30 s) or by the injection (10–20 nl) of Pontamine sky blue from the microinjection pipette. The center of the CoCl₂ injections into the NTS or VLM were marked by injecting a similar volume (50 nl) of Pontamine sky blue. The animals were perfused with 50 ml of 0.9% saline solution followed by 50 ml of 1% potassium ferrocyanide in 10% buffered formaldehyde solution to reveal the marked stimulation sites by the Prussian blue reaction. The brains were postfixed in the buffered formaldehyde solution for 2–4 days. Frozen transverse sections were cut in a cryostat at 50 µm, mounted on glass slides, and stained with neutral red. Recording and stimulation sites were mapped on projection drawings of the rat brain and later mapped onto a set of drawings of the rat brain modified from the stereotaxic atlas of Paxinos and Watson (22).

RESULTS

A total of 119 neurons with a mean discharge rate of 2.2 ± 0.3 spikes/s (range, 0–14.7 spikes/s) were recorded from the NA. Of the 119 neurons, 66 (56%) had discharge rates of <0.2 spikes/s. These slowly discharging neurons often had periods of inactivity interspersed with periods of higher activity.

Effect of electrical stimulation of NTS and VLM on accumbal neurons. Focal electrical stimulation (mean threshold current, 92 ± 7 µA) of histologically verified sites located in the ipsilateral medial, commissural, and dorsolateral subnuclei of the caudal portion of the NTS (Fig. 1) evoked responses in 48 (62%) of 77 NA units tested. The remaining 29 units (38%) did not respond to stimulation of the NTS. Of these 48 responsive units, 41 (85%) responded with an increase in discharge rate (mean onset latency, 44.4 ± 4.5 ms; Figs. 2A and 3A), and 7 (15%) responded with a decrease in discharge rate (mean onset latency, 34.8 ± 7.9 ms; Fig. 2C) to stimulation of the NTS. Most of the units responsive to NTS stimulation (21 of 48, 44%) had discharge rates of <0.2 spikes/s and were located in the shell region of the NA. On the other hand, nonresponsive units were found in both the core and shell regions (Fig. 4A).

Focal electrical stimulation (mean threshold current, 102 ± 9 µA) of histologically verified sites in the caudal and intermediate VLM (Fig. 1), where the A₁-C₁ catecholaminergic cell group are intermixed (5), altered the discharge rate of 24 of 77 (31%) of the units in the ipsilateral NA. Of the 24 units responding to the stimulation of the VLM, 20 (83%) responded with an increase in discharge rate (mean onset latency, 37.4 ± 7.8 ms; Figs. 2B and 3B), and 4 (17%) responded with a decrease in discharge rate (mean onset latency, 31.5 ± 4.2 ms; Fig. 2D). The remaining units (53 of 77; 69%) did not respond to stimulation of the VLM. Similar to units responding to NTS stimulation, units responsive to VLM stimulation were found scattered throughout the shell region of the NA, whereas nonresponsive units were found in the core and shell region (Fig. 4B).

Single units in the NA responsive to NTS or VLM stimulation had a wide range of onset latencies (8–153 ms; Fig. 5) and response durations. No significant differences were found between the onset latency (mean onset latency to NTS stimulation, 42.3 ± 4.1 ms, n = 48; mean onset latency to VLM stimulation, 36.3 ± 6.5 ms, n = 24), response duration, and stimulus threshold for single-unit responses elicited by NTS and VLM stimulation.

Of the 77 units tested, 17 (22%) responded to both stimulation of the NTS and VLM. Of these units, 15 (88%) responded with excitation to stimulation of the NTS (mean onset latency, 39.7 ± 6.2 ms; mean duration, 64.5 ± 24.6 ms) and VLM (mean onset latency, 42.8 ± 9.4 ms; mean duration, 70.2 ± 13.5 ms). The two remaining units responded with inhibition to stimulation of the NTS and VLM.

When the NTS and VLM were simultaneous stimulated (Fig. 7), the evoked response of the unit was approximately double (198%, P < 0.05) that calculated...
from the sum of the responses to stimulation of either the NTS or VLM alone. The baseline discharge rate of these units was also found to be increased during simultaneous stimulation of the NTS and VLM (Fig. 7). Furthermore, a shortening of the latency of the response by ~3–5 ms occurred during simultaneous stimulation of the NTS and VLM (Fig. 7).

**Effect of Glu stimulation of NTS or VLM on accumbal neurons.** To determine whether the response of neurons in the NA during electrical stimulation of the NTS or VLM was due to activation of neurons and not fibers of passage within these medullary regions, the effect of activation of NTS or VLM neurons with Glu on the discharge rate of accumbal neurons was investigated. Discrete local injections (10 nl) of Glu into the ipsilateral caudal NTS (Fig. 1) altered the discharge rate of 9 of 22 (40%) of the NA tested: 6 were excited and 3 were inhibited (Fig. 8A). Similarly, Glu injections into the ipsilateral caudal VLM (Fig. 1) altered the discharge rate of 7 of 20 (35%) neurons in the NA: 4 were excited and 3 were inhibited (Fig. 8B). The excitatory response to stimulation of the VLM was either a short burst of activity similar to that observed during stimulation of the NTS (Fig. 8A) or a long-lasting excitation (n = 2; Fig. 8B). The location of these responsive neurons within the shell region of the NA is shown in Fig. 8C. The distribution of these neurons did not differ from that of NA neurons that responded to electrical stimulation of either the NTS or VLM.

**Effect of baroreceptor inputs on accumbal neurons.** Units that responded to electrical stimulation of the NTS and VLM were also tested during the activation of the baroreceptors. Of 49 units tested, 6 (12%) units activated by NTS stimulation responded with excitation during the acute rise in systemic AP (Fig. 3C). In addition, 4 (8%) units activated by both NTS and VLM stimulation were also excited by the activation of the baroreceptors (Fig. 3); the remaining 39 units tested (80%) did not respond to the activation of baroreceptors. The location of units that responded to baroreceptor activation were found predominately in the shell region of the caudal aspect of the NA (Fig. 4C).

**Effect of synaptic blockade in NTS or VLM on responses of accumbal neurons to NTS and VLM stimulation.**
tion. Microinjection of CoCl₂ into the ipsilateral VLM did not attenuate the excitatory response of units in the ipsilateral NA to stimulation of the ipsilateral NTS (n = 5). Similarly, injections of CoCl₂ into the ipsilateral NTS did not attenuate the excitatory response in accumbal units produced by stimulation of the ipsilateral VLM (n = 5).

DISCUSSION

This study has provided the first electrophysiological evidence to indicate that neurons within medullary regions of the VLM and NTS provide afferent inputs to the NA and that these inputs converge on NA neurons. In addition, a few units activated by stimulation of the NTS were found to respond with excitation to baroreceptor activation. The response of accumbal neurons to stimulation of the NTS (83%) and VLM (77%) and arterial baroreceptors (100%) was predominately excitatory. Only a few neurons responded with inhibition to NTS and VLM stimulation. Many of the units activated by stimulation of the brain stem were found to have low discharge rates (~56% of responsive units had discharge rates of <0.2 spikes/s) and located within the shell region of the NA.

The finding that activation of NTS or VLM neurons alters the discharge rate of NA neurons is consistent with previous anatomic data showing direct projections from the NTS or VLM to the NA. Injections of retrograde tracers into the posteromedial region of the NA has been shown to result in retrogradely labeled neu-

Fig. 4. Projection drawings of transverse sections of ventral striatum taken at 9.7–10.7 mm rostral to intra-aural line showing location of histologically verified recording sites in NA. A: sites tested during stimulation of NTS. B: sites tested during stimulation of VLM. • Units excited; º units inhibited; □, nonresponsive units. C: sites responding to NTS, VLM, and baroreceptor activation. • Units excited by both NTS and VLM; º, units inhibited by both NTS and VLM; star, units responding to NTS, VLM, and baroreceptor activation. AC, anterior commissure; CPu, caudate-putamen; DBB, diagonal band of Broca; NAC, core of NA; NAS, shell of NA; Pir, piriform cortex; OT, olfactory tubercle; VP, ventral pallidum. Calibration mark, 1 mm.

Fig. 5. Histogram of latencies of units in NA orthodromically activated by stimulation of NTS (n = 48) or VLM (n = 24).

Fig. 6. Plots of regression analysis of latencies (ms; A) and response durations (ms; B) of excitatory responses evoked in units by stimulation of both NTS and VLM.
rons in the medial and commissural subnuclei of the NTS (3, 18, 27). These regions of the NTS have previously been shown to receive primary afferent projections from baroreceptors and to function in the integration of baroreceptor reflexes (4, 6). The location of the stimulation sites in the NTS that evoked responses in accumbal neurons were found in these regions of the NTS that received primary baroreceptor afferent inputs. Electrical and Glu stimulation of these same sites in the NTS were also found in this study to elicit depressor and bradycardic responses. Anterograde and retrograde studies have also demonstrated direct projections from the NTS and VLM (7, 23), such as the paraventricular nucleus of the thalamus, the bed nucleus of the stria terminalis, prefrontal cortex, amygdala, lateral hypothalamus, and substantia innominata, which are known to project to the NA (3).

However, it should be noted that a considerable number of NA neurons responded to stimulation of the NTS and VLM with relatively long and variable latencies (refer to Fig. 5). These data suggest that the NTS and VLM probably modulate the discharge rate of NA neurons predominantly through polysynaptic pathways. The polysynaptic pathways may involve several forebrain structures that receive relatively dense direct afferent projections from the NTS and VLM (7, 23), such as the paraventricular nucleus of the thalamus, the bed nucleus of the stria terminalis, prefrontal cortex, amygdala, lateral hypothalamus, and substantia innominata, which are known to project to the NA (3).

It was interesting to note the significant correlation between the onset latency of a unit that responded to stimulation of the NTS and the onset latency of the same unit that responded to stimulation of the VLM. A similar correlation in the response duration was found in units that responded to both NTS and VLM stimulation. In addition, the onset latencies and response duration to stimulation of the NTS were found not to be different from those to stimulation of the VLM. These data argue against the possibility that the effect of stimulating either the NTS or VLM on NA neurons was due to activation of neurons that relay between either site, even though these two medullary sites have been shown to be strongly interconnected (5, 8). Furthermore, injections of CoCl$_2$, which is known to block synaptic transmission (19) in the VLM, had no effect on the response of units in the NA to stimulation of the NTS. Similarly, administrations of CoCl$_2$ in the NTS had no effect on the response of accumbal units to stimulation of the VLM. It is therefore likely that information from the NTS or VLM is mediated to the NA through at least two independent pathways which do not involve either the VLM or NTS, respectively, as a relay.

The observation that fewer neurons were found to be excited during baroreceptor activation compared with the relatively large number of units excited by NTS or VLM stimulation would argue against the NA receiving a significant baroreceptor input. However, the possibility exists that any one afferent source of visceral input may not be of sufficient intensity to activate NA neurons. This may be due to the unique electrophysiologic properties of the spiny projection neurons, which have been estimated to account for 95% of the neurons in the NA (10). As previously discussed by Wilson (28), the membrane of the NA spiny neuron is characterized by a strong inward rectifying potassium current that keeps the neuron hyperpolarized. Because of this hyper-
polarization, these spiny neurons must receive and utilize a wide range of subthreshold membrane potentials from a variety of inputs to produce action potentials (28). In fact, the temporal pattern of action potentials in the spiny neuron probably reflects a combination of afferent activity from a variety of inputs integrated over periods of hundreds of milliseconds, with the neuron undergoing alternating periods of hyperpolarization and depolarization (28, 29). The extracellular recordings made from accumbal units in this study and in that of others (29) show that these neurons often generate action potentials episodically, with long periods of inactivity interspersed with periods of activity. It has been hypothesized that neurons in the NA need a degree of cooperativity and synchrony in the inputs it receives to generate action potentials (28). This hypothesis is supported by our observation that electrical stimulation of the NTS and VLM together activated accumbal units more strongly than stimulation of either the NTS or VLM alone. In addition, it was found that the spontaneous discharge of the neuron increased over time as stimuli were delivered to either the NTS, VLM, or both medullary sites. Therefore stimulation of these medullary regions may result in the activation of neurons that subserve functions not related to baroreflexes. The VLM is well known to play an important role in chemoreceptor and somatosympathetic reflexes as well as in the baroreceptor reflex (5). Similarly, the caudal NTS receives visceral afferent projections from chemoreceptors in the carotid bodies and stretch receptors in the lungs (15), along with non-cardiovascular-related inputs from other visceral receptors. Therefore stimulation of the NTS and VLM could have activated neurons that subserve other visceral information and activated neurons in the NA that respond to a variety of visceral inputs.

Perspectives

This study has provided evidence for the convergence of inputs from medullary sites that are involved in a variety of visceromotor functions and from afferent baroreceptor inputs onto neurons in the shell region of the NA. The caudal two-thirds of the NA has been shown to contain two subterritories with distinct afferent and efferent projections (33, 34). The core and shell region of the NA receive afferent projections from the midline and intralaminar thalamic nuclei, basolateral amygdala, hippocampus, ventral pallidum, dopaminergic cell groups of the ventral mesencephalon (A8, A9, and A10), and limbic cortex (3). However, the core region also receives afferent projections from other basal ganglia structures, such as the subthalamic nucleus and globus pallidus (3, 12). On the other hand, the shell...
region receives projections from the lateral hypothalamus, bed nucleus of the stria terminalis, preoptic area, substantia innominata, medial amygdala, NTS, VLM, and the spinal cord (3, 18, 27, 35). The shell region of the NA is also distinguishable from the core region by its numerous efferent projections to the lateral hypothalamic area, bed nucleus of the stria terminalis, periaqueductal gray matter, substantia innominata, and amygdala (11, 16). It has been proposed that the NA may serve as a central node that integrates a variety of peripheral and central signals, which, in turn, serve to provide the incentive for motivated behaviors, such as drinking and feeding (20). It has been hypothesized that afferent information associated with the physiological states occurring during thirst and hunger is relayed to regions of the forebrain including the NA, which, along with cognitive processes, induces the organism to produce the behaviors that correct the physiological needs (20). It is also interesting to note that most of the structures that project to or receive projections from the shell region of the NA have been shown to play a role in the regulation of the autonomic nervous system (8).

On the basis of its anatomic connections, the shell region of the NA is in a position to integrate information from a variety of brain structures involved in autonomic regulation. The output of the system could be directed at the lateral hypothalamus, which can influence the autonomic nervous system by way of its connections with centers in the brain stem and limbic system (8). It is also possible that the output of the NA could be redirected back to its source of input by reciprocal connections or by way of a ventral pallidum-thalamus pathway. In this way, the NA could play a major influence on the output of many structures involved in the regulation of the autonomic nervous system. In addition, the transthalamic feedback loops may also be important in integrating the autonomic nervous system with the somatic motor system.

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REFERENCES


