Control of cardiac rate, contractility, and atrioventricular conduction by medullary raphé neurons in anesthetized rats

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Salo IM, Nalivaiko E, Anderson CR, McAllen RM. Control of cardiac rate, contractility, and atrioventricular conduction by medullary raphé neurons in anesthetized rats. Am J Physiol Heart Circ Physiol 296: H318–H324, 2009. First published December 12, 2008; doi:10.1152/ajpheart.00951.2008.—The sympathetic actions of medullary raphé neurons on heart rate (HR), atrioventricular conduction, ventricular contractility, and rate of relaxation were examined in nine adrenalectomized and given atropine methylnitrate (1 mg/kg iv) animals. Mean arterial pressure (MAP), ECG, and left ventricular pressure were recorded. The peak rates of rise and fall in the first derivative of LV pressure (dP/dt max and dP/dt min, respectively) and the stimulus-R (S-R) interval were measured during brief periods of atrial pacing at 8.5 Hz before and after ventral medullary raphé neurons were activated by DL-homocysteic acid (DLH, 0.1 M) or inhibited by GABA (0.3 M) in local microinjections (90 nl). LV dP/dt max values were corrected for the confounding effect of MAP, determined at the end of the experiments after giving propranolol (1 mg/kg iv) to block sympathetic actions on the heart. DLH microinjections into the ventral medullary raphé region increased HR by 44 ± 2 beats/min, LV dP/dt max by 1,055 ± 156 mmHg/s, and the negative value of LV dP/dt min by 729 ± 204 mmHg/s (all, P < 0.001) while shortening the S-R interval by 2.8 ± 0.8 ms (P < 0.01). GABA microinjections caused no significant change in HR, LV dP/dt max, or S-R interval but reduced LV dP/dt min from −5,974 ± 93 to −5,548 ± 171 mmHg/s and MAP from 115 ± 4 to 105 ± 5 mmHg (both, P < 0.01). Rises in tail skin temperature confirmed that GABA injections effectively inhibited raphé neurons. When activated, the neurons in the ventral medullary raphé region thus enhance atrioventricular conduction, ventricular contractility, and relaxation in parallel with HR, but they provide little or no tonic sympathetic drive to the heart.

CARDIAC SYMPATHETIC NERVE activity is heavily dependent on supraspinal sources (30). One established source of tonic and phasic sympathetic drive to the heart is the rostral ventrolateral medulla (RVLM; Refs. 4, 5, and 7), but the contributions of other sympathetic premotor cell groups (46) are less well defined. Of the latter, it is known that the stimulation of neurons in the hypothalamic paraventricular nucleus (25) and ventral medullary raphé (7, 18, 41, 53) causes sympathetically mediated tachycardia.

The medullary raphé neurons are of particular interest because they have been shown to mediate stress-induced tachycardia in conscious rats (54), and unlike the RVLM, chemical activation of these neurons causes tachycardia without much vasomotor response (7). It may be, therefore, that this group of sympathetic premotor neurons has a more specific role in controlling the heart. Under basal conditions, raphé neurons do not appear to contribute tonic activity to the sympathetic supply to the cardiac pacemaker, because the inhibition of raphé neurons by injections of muscimol in anesthetized or conscious rats causes no fall in resting heart rate (HR) (6, 18, 41, 53, 54).

Sympathetic nerves supplying different parts of the heart have different effects on cardiac function: those to the pacemaker region increase HR, those to the atrioventricular node reduce atrioventricular delay, and those to the ventricular myocardium increase contractile force (1, 14). Several lines of evidence indicate that the central pathways controlling these regional sympathetic responses are not identical and may be differentially regulated by central commands and reflexes (40). The actions of medullary raphé neurons on atrioventricular conduction and contractile force are unknown. It is also unknown whether such effects, if present, are mediated by the cardiac sympathetic nerves and whether or not they show tonic activity. In this study we therefore set out to measure the sympathetically mediated effects on HR, cardiac contractility, and atrioventricular conduction when medullary raphé neurons were activated. We then assessed their ongoing contribution to cardiac function by the effect of raphé neuron inhibition. For comparison, the actions of ongoing cardiac sympathetic tone were assessed in the same animals by the effect of β-adrenergic blockade with propranolol.

MATERIALS AND METHODS

Animals. Nine adult male Sprague-Dawley rats (340–480 g) were used in this study. All procedures conformed to National Health and Medical Research Council guidelines and were approved by the Animal Experimentation Ethics Committee of the Howard Florey Institute.

Surgical procedures. Initial anesthesia was induced by pentobarbital sodium (45 mg/kg ip). Animals were then tracheotomized and artificially ventilated with isoflurane (2% in pure O2, Bomac) throughout the surgical preparation. Airway pressure was monitored by a transducer attached to the inspiratory line. The right femoral artery and vein were cannulated to measure arterial pressure and to administer drugs, respectively. The arterial cannula was filled with heparinized saline (20 IU/ml) and connected to a pressure transducer. Rectal temperature was recorded with a thermocouple and maintained at 36–37°C using a heating blanket. A second thermocouple was taped to the skin near the midpoint of the tail, which was laid over cotton wool.

The adrenal glands were accessed retroperitoneally via flank incisions and looped with silk sutures ready for subsequent adrenalectomy. The ECG was recorded between silver wire electrodes implanted subcutaneously on either side of the chest with a ground electrode inserted next to the femoral cannulae. A catheter tipped with...
a pair of pacing electrodes (~4 mm separation) was passed down the right jugular vein to lie at the right atrial-vena caval junction. Animals were mounted supine in a stereotaxic frame. The trachea and esophagus were ligated and cut rostrally to the tracheotomy and then retracted rostrally. Both diaphragm muscles were looped with sutures and pulled laterally to improve access to the base of the skull, which was exposed by removing the overlying muscles, and scraped clean. The skull was opened with a dental drill: the craniotomy extended ~2 mm on either side of the midline and 4 mm rostral from the atlanto-occipital membrane. The dura was incised and reflected to expose the ventral medullary surface. The tracheotomy and air lines were moved sufficiently far laterally to allow clear access to the medulla.

Left ventricular (LV) pressure (LVP) was measured using a microtip pressure transducer (SPR-249, Millar Instruments) advanced along the right carotid artery to the left ventricle of the heart, using the ventricular pressure profile to guide placement. The adrenal glands were removed bilaterally after tying them off with silk sutures. After the completion of surgical procedures, animals were given urethane (1–1.5 g/kg iv over ~30 min) and isoflurane was discontinued. All experimental protocols were carried out on rats under urethane anesthesia without any paralyzing agent. Atropine methylsulfate (1 mg/kg iv, Sigma) was administered to block parasympathetic actions on the heart.

Cardiac pacing. The ECG signal was amplified (×1,000), filtered (bandpass, 1–100 Hz; Neurolog, Digitimer, Harlow, UK), and led to an oscilloscope and audio speakers. The atrial pacing electrodes were connected to a Grass stimulator (model S44), and the heart was paced using rectangular 1-ms pulses. The position of the pacing electrodes, polarity, and voltage (1 to 2 V) of the pacing stimulus were adjusted to achieve full atrial capture, as confirmed by listening to and observing the ECG signal. During the experiment the heart was paced periodically at a frequency of 8.5 Hz, chosen to exceed the maximum spontaneous HR. The heart was paced for periods of ~10 s during the steady state before central microinjections (control pacing) and at the peak of the response following microinjections (experimental pacing) (see Fig. 1).

Data acquisition. The ECG signal, LVP, arterial and ventilatory pressures, and the pacing stimulus ($) event times were recorded using a computer interface (CED Power1401, Cambridge Electronic Design, Cambridge, UK) and displayed online. Signals were recorded for computer analysis using Spike2 software (Cambridge Electronic Design). HR (taken from the blood pressure trace) and the first derivative of LVP (LV dP/dt) were computed and displayed online. The peak and minimum values of LV dP/dt (LV dP/dtmax and LV dP/dtmin, respectively) and LV end-diastolic pressure (LVEDP) were computed from the arterial pressure trace. R waves and pacing stimulus artifacts ($) were detected in the ECG trace and used to calculate HR and S-R interval for subsequent analysis. Mean arterial pressure (MAP) was computed from the arterial pressure trace.

Central microinjection protocol. A narrow bore glass micropipette (tip diameter, 30–40 μm) containing either DL-homocysteic acid (DLH, 0.1 M, Sigma) with a small admixture of red fluorescent polystyrene microspheres (Fluospheres) in artificial cerebrospinal fluid (aCSF) (47) or γ-aminobutyric acid (GABA, 0.3 M, Sigma) with admixed green fluorescent microspheres in aCSF was inserted into the ventral medulla next to the basilar artery and just caudal to the anterior inferior cerebellar artery. Insertions were made ~0.5 mm deep into the medulla at an angle of 5–10° lateral to the vertical, so as to reach the ventral medullary midline while avoiding the basilar artery. Brain microinjections were made over 5–10 s, using air pressure. The injected volume was measured by the movement of the meniscus, observed through a microscope. DLH (90 nl) was injected first, and the site was considered correct if there was an increase in HR of >35 beats/min. In one animal, the pipette was repositioned caudally to the first injection site to achieve this. The pipette was then withdrawn, flushed 2 to 3 times with aCSF, and filled with GABA. After stable baseline conditions had been reestablished for at least 30 min, the pipette was reinserted into the same site, where GABA (90 nl) was injected. Because the neurons in this same raphe region tonically drive the vasomotor supply to the tail (34), a rise in tail skin temperature, indicating vasodilatation (48), was used to confirm that GABA effectively inhibited the raphe neurons.

Measurement of intrinsic cardiac parameters and the effects of afterload. After the completion of the central microinjections, all nine animals were given a further dose of atropine methylsulfate (0.25 mg/kg iv), followed by propranolol (1 mg/kg iv, Sigma) to block autonomic actions on the heart. Measurements were then made of intrinsic HR and, during atrial pacing, of basal S-R interval, LV dP/dtmax, and LV dP/dtmin.

The direct effect of arterial pressure on LV dP/dtmax was then quantified in four rats. The atria were paced continually while bolus doses of phenylephrine (3–15 μg iv, Sigma) were used to raise arterial pressure. LV dP/dtmax was plotted against MAP for each heartbeat over the rising phase of the pressor response (lasting 4–14 s) and the regression lines were constructed to quantify the relationship. The direct effect of MAP on LV dP/dtmax calculated in each of the four rats was directly subtracted from experimental measurements. In the remaining five rats, the mean of the four slopes was used to adjust LV dP/dtmax measurements for changes in MAP. Unless otherwise stated, LV dP/dtmax measurements quoted have been corrected for MAP.

Data analysis. All analysis was done off-line using Spike2 software. Five-second means of HR, MAP, LV dP/dtmax, LV dP/dtmin, LVEDP, tail skin temperature, and S-R interval were used for statistical analyses. These were taken from near the end of each pacing period, once a steady state had been reached. Five-second means of HR (unpaced) were taken just before periods of pacing. Control data, both unpaced and paced, were taken 30–120 s before injections of DLH, GABA, or intravenous propranolol. Response data, unpaced and paced, were taken during the maximal HR response after DLH injection, when the tail skin temperature rose following the GABA injection and when HR reached a stable level after intravenous propranolol. For illustration, Δ values (response – control) were calculated for each animal’s response to each injection (corrected for MAP in the case of LV dP/dtmax measurements). Group mean and group mean Δ values were calculated for HR, MAP, S-R interval, LV dP/dtmax, LV dP/dtmin, tail skin temperature, and LVEDP. Results are reported as means ± SE.

To test the significance of changes in these parameters following the microinjection of DLH and GABA and intravenous propranolol, paired t-tests were performed between control and experimental data. For all cited measurements except HR and MAP, comparisons were made using paced data, and all LV dP/dtmax values were adjusted for the direct effect of MAP (measured during pacing). P < 0.05 was considered significant.

Histology. At the end of the experiment, rats were deeply anesthetized with pentobarbital sodium (100 mg/kg iv) and perfusion-fixed by perfusing first normal saline and then 4% paraformaldehyde through the heart. The brain stem was then removed, postfixed at least overnight in paraformaldehyde, and then cryoprotected by immersion in 20% sucrose in phosphate buffer. Transverse frozen sections (60 μm) were cut through the appropriate region of rostral medulla. These were mounted on gelatin-subbed glass slides and coversonized with crystalmount (Biomeda). The sections were viewed by fluorescence microscopy with appropriate filters to reveal red and green polystyrene microsphere deposits, and the centers of the injection sites were mapped onto standard brain atlas sections (36).

RESULTS

Confounding effect of MAP on LV dP/dtmax in rats. The confounding influence of MAP on LV dP/dtmax was established following β-blockade at the end of the experiment in
four animals (Fig. 2F) as described in MATERIALS AND METHODS. The slopes of this relationship in the four animals were 22.2, 32.3, 32.4, and 35.6 mmHg/s/mmHg, yielding a mean slope of 30.6 mmHg/s/mmHg, the value of which was used in the remaining five rats to correct LV dP/dt_max measurements for changes in MAP.

Responses to DLH microinjection into the ventral medullary raphe. Figure 1A shows a representative example, and Fig. 2, A–E, shows group responses to microinjection of DLH into the ventral medullary raphe region. Raphe DLH injections evoked significant increases in HR and LV dP/dt_max, with significant decreases in LV dP/dt_min, $-R$ interval, and LVEDP. HR increased from a basal rate of 408 ± 11 to 452 ± 10 beats/min ($P < 0.001$, Fig. 2A), and corrected LV dP/dt_max increased from 1,339 ± 228 to 2,388 ± 403 mmHg/s ($P < 0.001$, Fig. 2B). $-R$ interval decreased from 59.4 ± 3 to 56.5 ± 3 ms ($P = 0.007$, Fig. 2C), LV dP/dt_min changed from $-5,683 ± 206$ to $-6,412 ± 201$ mmHg/s ($P < 0.001$, Fig. 2D), and LVEDP from 4.3 ± 0.5 to 3.7 ± 0.4 mmHg ($P = 0.009$).

MAP increased significantly following the microinjection of DLH into the medullary raphe region, from 109.2 ± 4 to 128.4 ± 3 mmHg ($P < 0.001$, not shown). Tail skin temperature did not change significantly, being 26.8 ± 0.3°C before and 27.0 ± 0.2°C after DLH microinjection ($P = 0.120$, Fig. 2E).

Responses to GABA microinjection into the ventral medullary raphe. Figure 1B shows a representative response to GABA microinjection into the ventral medullary raphe region. Grouped data showed that GABA evoked no significant change.
in HR, LV dP/dt max, S-R interval, or LVEDP, although LV dP/dt min became less negative. Mean HR was 434 ± 9 at baseline and 428 ± 9 beats/min after GABA (P = 0.09, Fig. 2A), LV dP/dt max was 1,850 ± 432 before and 1,745 ± 479 mmHg/s after GABA (P = 0.436, Fig. 2B), and S-R interval was 55.7 ± 2.6 before and 56.0 ± 2.6 ms after GABA (P = 0.344, Fig. 2C), whereas LVEDP was 3.6 ± 0.6 before and 3.7 ± 0.6 mmHg after GABA (P = 0.818, not shown). LV dP/dt min changed from −5,974 ± 93 to −5,548 ± 171 mmHg/s following GABA microinjection (P = 0.003, Fig. 2D).

MAP decreased significantly following raphe GABA microinjections, from 114.6 ± 4 to 105.3 ± 5 mmHg (P < 0.008, not shown). Tail skin temperature increased from 26.8 ± 0.3°C before to 30.3 ± 0.3°C after GABA (P < 0.001, Fig. 2E).

Responses to propranolol. Figures 1C and 2, A–E, show a representative example and group responses to intravenous propranolol, respectively. Propranolol significantly decreased HR and LV dP/dt max while increasing S-R interval, LV dP/dt min, and LVEDP. Mean HR fell from 428 ± 9 to 350 ± 8 beats/min (P < 0.001, Fig. 2A), and LV dP/dt max fell by 1,653 ± 348 (corrected) to a raw baseline value of 3,486 ± 375 mmHg/s (Fig. 2B). S-R interval was 54.6 ± 3.1 before and 71.7 ± 3.4 ms after propranolol treatment (P < 0.001, Fig. 2C), whereas LVEDP was 3.5 ± 0.6 before and 6.1 ± 0.5 mmHg after propranolol treatment (P < 0.001, not shown). LV dP/dt min changed from −5,322 ± 202 to −3,524 ± 387 mmHg/s after propranolol treatment (P < 0.001, Fig. 2D).

Propranolol decreased MAP from 104 ± 6 to 63 ± 7 mmHg (P < 0.008) and tail skin temperature from 28.1 ± 0.5°C to 27.8 ± 0.4°C (P < 0.001, Fig. 2E).

Calibration of ventral medullary raphe actions by comparison with basal sympathetic tone. Measuring the intrinsic HR and other cardiac parameters after full autonomic blockade allows us to infer the contributions made by sympathetic tone to their basal levels before propranolol. Cardiac responses to raphe injections can then be compared quantitatively with the levels sustained by basal sympathetic tone. Thus we may calculate that DLH injections into the raphe increased HR by a further 94 ± 18% and LV dP/dt max by 78 ± 11% from their basal levels, whereas the corresponding (negative) magnitudes of LV dP/dt min and S-R interval responses were enhanced by 35 ± 4% and 24.9 ± 0.5%, respectively.

In comparison with preinjection basal tone, the nonsignificant trends after GABA microinjections amounted to −8 ± 4% for HR, −7 ± 8% for LV dP/dt max, and +2.1 ± 2% for S-R interval. The significant change in LV dP/dt min amounted to a 16 ± 4% reduction of its negative magnitude.

Ventral medullary raphe injection sites. Figure 3 shows the centers of injection sites in nine rats. In line with previous findings with respect to HR (7, 53) and tail temperature (48),
Do ventral medullary raphe neurons contribute to basal cardiac sympathetic tone? The profound decreases in HR, LV contractility, and atrioventricular conduction velocity following propranolol indicate that there was a substantial degree of cardiac sympathetic tone under the conditions of this study, no doubt partly due to general anesthesia and surgical trauma (28).

Previous work on conscious rats found that inhibiting the raphe neurons with muscimol caused no fall in HR (6, 18, 41, 53, 54), a result confirmed here in anesthetized rats. GABA injections caused a small fall in arterial pressure, however, the effective injection sites were centered around the raphe pallidus nucleus at the level of the caudal part of the facial nucleus.

**DISCUSSION**

The results of this study show for the first time that in addition to increasing HR, the activation of neurons within the medullary raphe region causes sympathetically mediated increases in the contractility and rate of relaxation of the left ventricle, as well as a decrease in atrioventricular conduction delay. In line with previous observations on HR (6, 18, 41, 53, 54), we found little effect on contractility or atrioventricular conduction after the raphe neurons were inhibited, although tail vasodilatation proved that the inhibitory injections were effective (cutaneous vasomotor and cardiac premotor neurons occupy the same raphe location) (53). These findings indicate that most basal cardiac sympathetic tone to the atrioventricular node and to the ventricles, like that to the pacemaker, is driven by premotor cell groups other than the raphe.

**Methodological issues.** LV dP/d_{max} is a well-accepted measure of cardiac contractility, and we used it here to measure sympathetic inotropic actions in anesthetized rats. Unlike in other species (e.g., Refs. 12, 13, 33, 38, and 39), however, LV dP/d_{max} in the rat is strongly affected by afterload (22). We confirmed this observation in rats whose cardiac autonomic inputs had been blocked and found a tight, reproducible relationship between MAP and LV dP/d_{max}. This relationship allowed us to calculate and subtract the effects of afterload on our measurements, removing that confound. In these experiments we used LVEDP to monitor ventricular preload. Although changes in ventricular filling may affect cardiac contractility through the Frank-Starling mechanism (37), we found in the present experiments that rises in LV dP/d_{max} were accompanied by falls in LVEDP, presumably reflecting more complete ventricular emptying in the inotropic state. Those changes were in the wrong direction for ventricular preload to have made any contribution to the raised inotropic state following raphe stimulation. Finally, changes in HR are another potential confound for measurements of contractility (20, 44) and also of atrioventricular conduction (15). This problem was avoided by pacing the heart at a fixed rate during these measurements. We are therefore confident that our measures of contractility and atrioventricular conduction are reliable.

We are less certain about our measurements of ventricular relaxation rate (luskrotopy) because the potential confounds affecting LV dP/d_{min} in rats are not adequately known. Myocardial contractility and relaxation are both under β-adrenergic control, although they are affected by different aspects of intracellular calcium handling (21). Generally, LV dP/d_{min} and LV dP/d_{max} responses to sympathetic activation occur in parallel (43), although one or the other may quantitatively predominate, depending on species and circumstances (3, 17). In the present study, we found that sympathetically mediated increases in LV dP/d_{max} were proportionately greater than those in LV dP/d_{min}. We are not aware of any comparable data in the literature on rats.

**Cardiac effects of activating neurons in the ventral medullary raphe region.** This study confirms previous findings that the activation (or disinhibition) of neurons within the ventral medullary raphe region evokes a tachycardia (7, 18, 53, 54), which is mediated by cardiac sympathetic nerves (7). This raphe-cardiac sympathetic pathway relays the tachycardia caused by disinhibition of the dorsomedial hypothalamus (6, 41) and the tachycardia caused by acute air-jet stress or by restraint in the conscious rat (32, 54). The present study extends these findings to demonstrate that the medullary raphe region neurons drive the sympathetic supplies to the atrioventricular node and the ventricular myocardium as well as to the pacemaker region. The cardiac sympathetic nerves must have been the pathway, because vagal and adrenal mechanisms had been disabled.

The present experiments did not attempt to map the distribution of neurons in the ventral medullary raphe region with cardiac actions. Although centered in the raphe pallidus nucleus, injections of DLH and GABA would doubtless have spread to affect some neurons in adjacent areas such as the raphe magnus nucleus and parapyramidal cell group. However, previous work has established the location of cell groups regulating cardiac sympathetic nerve activity and HR as being in or around the raphe pallidus nucleus, level with the caudal pole of the facial nucleus (7, 18, 53). This region also contains premotor cell groups regulating cutaneous vascular tone (34, 48, 49), thermogenesis by brown adipose tissue (8), and fusimotor activity (50). As argued elsewhere (49, 50), these would be different populations of raphe premotor neurons. This same raphe region has been shown by viral tracing experiments to contain sympathetic premotor neurons with disynaptic connections to the stellate ganglion (19, 46) and trisynaptic to the heart (45, 51). It is therefore likely that the effects of raphe microinjections on the heart are attributable to cells with monosynaptic excitatory connections to preganglionic cardiac sympathetic neurons.

**Fig. 3.** Coronal sections of rostral medulla, redrawn from levels bregma −11.3 mm and bregma −11.6 mm in the atlas of Paxinos and Watson (36). The centers of the DLH and GABA injection sites in 9 rats are shown by the gray-filled circles. P, pyramidal tract; RP, raphé pallidus nucleus; VII, facial nucleus.

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presumably due to cutaneous vasodilatation (34, 49). Interestingly, no cardiac parameter increased after this baroreceptor unloading. We therefore cannot exclude the possibility that a minor degree of cardiac sympathetic tone was removed by the inhibition of neurons in the ventral medullary raphé region.

Differential control of cardiac functions by ventral medullary raphé neurons? The vagal and sympathetic nerves innervating the pacemaker region, atrioventricular node, and ventricles are distinct, and there is evidence that their functions may be regulated independently, or at least differentially, by basal tone (42) and by the activity of particular brain cell groups (40). Rostrocaudal differences in the nucleus ambiguus have been documented for the vagal control of cardiac functions (11, 16, 26, 27), for example, and the left-right differences in the RVLM for the sympathetic control of the heart (4). Despite the findings that activating neurons in the ventral raphé region caused comparatively large changes in LV $dP/dt$max and HR but smaller proportional changes in $-dR$ interval and LV functions by the raphe´ region neurons.

Whether or not there exists any selective control of cardiac different premotor cell groups (e.g., RVLM vs. raphe´) or by the differential control is mediated by the relative activity of Refs. 31 and 40). Future studies may resolve whether such evidence that it does, regulate HR, contractile force, and supply not only to the pacemaker but to all heart regions.

There is ample evidence that the brain can, and some evidence that it does, regulate HR, contractile force, and atrioventricular conduction differentially (29, 40, 42). The mix of chronotropic, inotropic, and dromotropic drives to regulate cardiac function optimally can be expected to vary during the different challenges to which the cardiovascular system is subjected (e.g., exercise in warm vs. cold conditions, hemorrhage, fever, or acute or chronic mental or physical stresses; Refs. 31 and 40). Future studies may resolve whether such differential control is mediated by the relative activity of different premotor cell groups (e.g., RVLM vs. raphé) or by the relative activity of neuronal subgroups within these nuclei (e.g., Ref. 4).

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