Rostral ventral medulla 5-HT$_{1A}$ receptors selectively inhibit the somatosympathetic reflex

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Miyawaki, Takashi, Ann K. Goodchild, and Paul M. Pilowsky. Rostral ventral medulla 5-HT$_{1A}$ receptors selectively inhibit the somatosympathetic reflex. Am J Physiol Regulatory Integrative Comp Physiol 280: R1261–R1268, 2001.—The role of the 5-hydroxytryptamine (5-HT$_{1A}$) receptors in the rostral ventrolateral medulla (RVLM) on somatosympathetic, baroreceptor, and chemoreceptor reflexes was examined in anesthetized rats. Microinjection of the selective 5-HT$_{1A}$ agonist 8-hydroxy-di-n-propylamino tetralin (8-OH-DPAT) decreased arterial blood pressure and splanchnic sympathetic nerve activity (SNA). Electrical stimulation of the hindlimb evoked early and late excitatory sympathetic responses. Bilateral microinjection in the RVLM of 8-OH-DPAT markedly attenuated both the early and late responses. This potent inhibition of the somatosympathetic reflex persisted even after SNA and arterial blood pressure returned to preinjection levels. Preinjection of the selective 5-HT$_{1A}$ antagonist NAN-190 in the RVLM blocked the sympathoinhibitory effect of 8-OH-DPAT and attenuated the inhibitory effect on the somatosympathetic reflex. 8-OH-DPAT injected in the RVLM did not affect baroreceptor or chemoreceptor reflexes. Our findings suggest that activation of 5-HT$_{1A}$ receptors in the RVLM exerts a potent, selective inhibition on the somatosympathetic reflex.

5-hydroxytryptamine; baroreceptor; chemoreceptor; 8-hydroxy-di-n-propylamino tetralin; NAN-190

SYMPATHETIC NEURONS IN THE ROSTRAL VENTROLATERAL MEDULLA (RVLM) DIRECTLY INNervate SYmpathetic preganglionic neurons in the spinal cord and are critical for the maintenance of the resting level of sympathetic vasomotor tone (4, 29). Premotor sympathetic neurons also play a key role in many cardiovascular reflexes, including the baro-, chemo-, and somatosympathetic reflexes (4, 5). Changes in the activity of these peripheral receptors are thought to be integrated by neurons in the RVLM via excitatory or inhibitory amino acid receptors on these neurons, since the blockade of glutamatergic or GABAergic inputs in the RVLM abolishes the response to the activation of these receptors (14, 18, 25).

Compared with the vast literature on the role of amino acid neurotransmitters on the cardiovascular reflexes, much less is known about the involvement of amineogenic neurotransmitters (10).

Neurons in the RVLM receive a dense innervation from 5-hydroxytryptamine (5-HT) synthesizing medullary and dorsal raphe neurons (17, 34). Recently, the presence of 5-HT$_{1A}$ receptor immunoreactivity within spinoally projecting catecholaminergic and noncatecholaminergic neurons in the RVLM has been demonstrated (11).

The activation of the 5-HT$_{1A}$ receptor generally inhibits neuronal activity by inhibiting adenylate cyclase via $G_i$ proteins. Another important feature of this receptor is its modulatory effects on the release of other neurotransmitters, such as norepinephrine, ACh, and glutamate (3).

Local administration of 5-HT$_{1A}$ agonists to the RVLM elicits a sympathoinhibitory response (2, 16, 22). This response is presumed to occur via inhibition of the ongoing activity of the premotor sympathetic neurons (12, 15). However, the physiological significance of 5-HT$_{1A}$ receptor activation, or inhibition, in the RVLM remains unknown.

The aim of the present study was to investigate the role of 5-HT$_{1A}$ receptors in RVLM in modulating adaptive cardiovascular reflexes. The effects of local administration of 5-HT$_{1A}$ agonist or antagonist compounds in the RVLM on baroreceptor, chemoreceptor, and somatosympathetic reflexes were examined.

MATERIALS AND METHODS

General procedures. Male Sprague-Dawley rats weighing 380–500 g were anesthetized initially with halothane (2% in 100% O$_2$) followed by an intraperitoneal injection of pentobarbital sodium (60 mg/kg). The femoral artery and vein were catheterized for arterial pressure measurement and drug administration. The trachea was cannulated, and the right cervical vagus was cut. The left aortic, phrenic, and splanchnic sympathetic nerves were dissected and cut distally and then maintained in paraffin oil. Rats were then mounted in a stereotaxic frame, paralyzed with pancuronium dibromide (0.8 mg iv), and artificially ventilated with O$_2$-enriched air. The endtidal CO$_2$ was monitored and kept close to 4.5%. Subsequently, the left vagus was cut. A partial occipital crani-
otomy was performed to expose the dorsal surface of the medulla.

Adequacy of anesthesia was assessed by monitoring arterial blood pressure and phrenic nerve discharge. Additional doses of pentobarbital sodium (3–6 mg) and pancuronium bromide (0.2 mg) were given intravenously when required to maintain adequate anesthesia and neuromuscular blockade. Rectal temperature was monitored; it was maintained between 36 and 38°C with a heating pad and infrared lamp.

Nerve recording. Bipolar silver wire electrodes were used for recording splanchic nerve activity (SNA) and phrenic nerve discharge. The signals were amplified, filtered (100–3,000 Hz band pass), full-wave rectified, and integrated using a Paynter filter with a 50-ms time constant. The zero level of SNA was established by measuring activity during supramaximal stimulation of the aortic nerve at 50 Hz (see below).

Activation of cardiovascular reflexes. To activate baroreceptor afferent fibers selectively, the aortic nerve was stimulated electrically (15). Stimulation at 50 Hz (pulse width 0.2 ms, 5 V) was used to elicit maximum activation of baroreceptor afferent fibers. The stimulus voltage was adjusted so that it was just adequate to achieve maximal inhibition of SNA. This was normally in the range of 0.5–2.5 volts. To obtain averages of nerve activity in response to baroreceptor activation, the aortic nerve was also stimulated intermittently (0.2 ms duration, 2 pulses at a 2.5 ms interval, 0.5 Hz). The response of the SNA was averaged at least 50 times and was used to assess its barosensitivity.

Cutaneous afferent pathways were activated using bipolar stainless steel needle electrodes inserted subcutaneously in the right hindpaw (1 ms duration, 50 volts, 0.5 Hz). Again, the SNA response was averaged at least 50 times.

Carotid chemoreceptor activation was achieved by brief hypoxia (9). Rats were ventilated with 100% nitrogen for 8–10 s.

Microinjections. The selective 5-HT1A receptor agonist 8-hydroxy-di-n-propylamino tetralin (8-OH-DPAT, 10 mM; Sigma) and the selective 5-HT1A receptor antagonist NAN-190 (5 mM; Sigma) were prepared for microinjection. NAN-190 was first solubilized with DMSO. Both drugs were finally dissolved in 10 mM PBS (0.9%), pH 7.4. The pH was checked and found to be 7.3–7.5. In the first series of experiments, 8-OH-DPAT was mixed with albumin-10 nm colloidal gold (A5179 4:1; Sigma) for later histological analysis and was loaded in a single-barrel micropipette. In the second series, triple-barrel micropipettes were used to inject 8-OH-DPAT and NAN-190 in the same site. The third barrel was used to inject albumin-colloidal gold. Injection volumes were controlled by direct observation of the movement of the fluid meniscus in the micropipette. In all experiments, micropipettes were placed in the RVLM bilaterally.

Experimental procedures. The pressor region of the RVLM was identified by microinjection of L-glutamate (50 mM, 25 nl). After a site where a pressor response of >30 mmHg could be obtained was located, the glutamate micropipette was removed, and micropipettes containing 8-OH-DPAT and colloidal gold (single barrel) or 8-OH-DPAT, NAN-190, and colloidal gold (multibarrel) were placed in the same sites. Reflexes were then activated in the following order: 1) chemoreceptor activation by brief hypoxia; 2) after stabilization of arterial blood pressure and phrenic nerve discharge, normally 2–4 min, activation of cutaneous afferents by electrical stimulation of the hindpaw; and 3) baroreceptor activation by tetanic and intermittent stimulation of the aortic nerve. Next, drugs were microinjected in the RVLM bilaterally, and activation of reflexes (steps 1–3 above) was repeated.

Histological procedure. At the end of the each experiment, the rats were killed with an overdose of anesthetic. The medulla was removed and fixed with formaldehyde (10% formalin in 10 mM PBS). Transverse sections (100 µm) were cut with a vibrating microtome. Silver intensification of the gold particles (Sigma SE-100 Silver Enhancer kit) was performed to identify microinjection sites. Finally, the sections were stained with 1% neutral red for histological analysis.

Data analysis. Data were analyzed on-line and off-line using a CED 1401 data capture system and Spike 3 software (Cambridge, UK). The SNA responses to hindlimb stimulation and intermittent stimulation of the aortic nerve were analyzed with peristimulus averaging. The amplitude of SNA from −200 to 0 ms before the stimulus was taken as the baseline. The maximum response to stimulation was then expressed as a percentage of change from the baseline. To quantify the response to hypoxia, the average SNA within 10 s from the onset of the excitation of phrenic nerve discharge by nitrogen inhalation was expressed as a percentage of change from the baseline SNA obtained from the period of 10 s before phrenic excitation.

Data are expressed as means and SD. Statistical significance was assessed by paired and unpaired t-tests. The Wilcoxon matched-pairs signed-rank test was used to compare the changes of SNA from the baseline after conversion with a percentage of change. To evaluate the effect of treatment with NAN-190 and 8-OH-DPAT, a one-way ANOVA followed by multiple t-tests with Bonferroni’s correction was employed if the original F-value was significant. All statistical tests were carried out using Graphpad software.

RESULTS

A typical injection site in the RVLM is shown in Fig. 1. All injection sites were located in the RVLM, 0–0.3 mm caudal from the caudal tip of the facial nucleus, 1.8–2.1 mm lateral from the midline, and between the nucleus ambiguus and the ventral surface of the medulla.

![Fig. 1. Typical microinjection site in the rostral ventrolateral medulla (RVLM). Arrowhead, silver-intensified gold particles. The injection was made in the area just caudal to the caudal tip of the facial nucleus and ventral to compact formation of nucleus ambiguus (Amb). D, dorsal; M, medial.](https://via.placeholder.com/150)
After the injection of 8-OH-DPAT (10 mM, 50 nl) bilaterally in the RVLM, mean arterial pressure decreased gradually. The maximum decrease of $104 \pm 10$ mmHg from $117 \pm 11$ mmHg was reached within 2 min ($n = 6$, $P < 0.01$). Arterial blood pressure returned to preinjection levels after 8–15 min (Fig. 2A).

SNA was also significantly decreased ($14 \pm 6\%$) from its preinjection levels ($72 \pm 17$ to $62 \pm 13$ μV, $n = 6$, $P < 0.05$). Phrenic nerve discharge decreased in amplitude in three rats (Fig. 2A), increased in one rat, and was not significantly affected in the remaining two rats.

Bilateral microinjection of the 5-HT$_{1A}$ receptor antagonist NAN-190 (5 mM, 100 nl) did not significantly change mean arterial pressure or SNA ($117 \pm 11$ to $120 \pm 6$ mmHg and $40 \pm 18$ to $42 \pm 17$ μV, respectively, $n = 6$, Fig. 2B, left). The amplitude of phrenic nerve discharge was not significantly increased to $108 \pm 4\%$ of the control level, although this small increase occurred in every case ($n = 6$). Five to 10 min after injection of NAN-190, 50 nl of 8-OH-DPAT (i.e., one-half the volume of the NAN-190 injection) were injected in the same site from another barrel of the triple-barrel micropipette.

As shown in Fig. 2B, 8-OH-DPAT injection in the RVLM failed to decrease mean arterial pressure and SNA after pretreatment with NAN-190 ($115 \pm 8$ to $112 \pm 10$ mmHg and $43 \pm 15$ to $41 \pm 17$ μV, respectively).

Before drug injection, electrical stimulation of the hindlimb evoked two distinct excitatory responses on SNA with latencies to peak of $142 \pm 2$ and $221 \pm 3$ ms.

As shown in Fig. 3, A and C1, injection of 8-OH-DPAT in the RVLM eliminated both the early and late excitatory components of SNA even after arterial pressure and baseline SNA had returned to preinjection levels. The amplitude of the early and late peaks, expressed as a percentage of the amplitude in the prestimulus period, decreased from $288 \pm 42$ to $115 \pm 7\%$ and from $243 \pm 75$ to $109 \pm 5\%$, respectively ($P < 0.01$, $n = 6$), i.e., virtually complete inhibition. This potent inhibition of the somatosympathetic reflex lasted >60 min after injection of 8-OH-DPAT in the RVLM.
8-OH-DPAT and never returned completely to the preinjection levels over the 80- to 90-min postinjection observation period.

Injection of NAN-190 bilaterally to the RVLM also tended to decrease the amplitude of the hindlimb stimulation-evoked excitatory response of SNA (226 ± 45 to 198 ± 42% for the early peak and 206 ± 48 to 198 ± 35% for the late peak, n = 6, Fig. 3B, middle). In the NAN-190-pretreated animals, hindlimb stimulation-evoked excitatory responses of the SNA were largely preserved after the injection of 8-OH-DPAT (198 ± 42 to 190 ± 51% for the early peak and 198 ± 35 to 164 ± 23% for the late peak, n = 6, Fig. 3B, right). However, as summarized in Fig. 3C2, ANOVA did not detect any significant changes in the magnitude of the hindlimb stimulation-evoked response in animals pretreated with NAN-190. The magnitude of the excitatory responses was significantly greater than in the animals without NAN-190 pretreatment (P < 0.01, n = 6, unpaired t-test). Group data are shown in Fig. 3, C1 and C2.

Finally, in three rats, we compared the SNA response to electrical stimulation of the RVLM and hindlimb. In these animals, a bipolar stimulation electrode (SNE-100; Rhodes) was placed in the left RVLM, and square-wave pulses (0.5 mA, 0.2 ms) were delivered at 0.5 Hz. Next, electrical stimulation of the RVLM was performed using the parameters outlined in MATERIALS AND METHODS (Fig. 3D). Stimulation of the RVLM evoked two excitatory components on SNA with latencies to peak of 110 ± 7 and 213 ± 11 ms. The interval between these peaks was essentially the same as the interval between the peaks evoked by hindlimb stimulation (102 ± 5 vs. 98 ± 9 ms, respectively).

Stimulation of the chemoreceptors with hypoxia (nitrogen, 8–10 s) evoked a burst discharge in the activity of the phrenic nerve, followed by an increase in SNA and arterial blood pressure. The example in Fig. 4A was obtained in the period just before the period of hindlimb stimulation seen in Fig. 3A. The sympathoexcitatory response to hypoxia was not affected by injection of 8-OH-DPAT when examined in the period when the arterial blood pressure and SNA had returned to preinjection levels. Chemoreceptor stimulation with nitrogen inhalation increased SNA to 155 ± 30% of control before 8-OH-

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Fig. 3. A: electrical stimulation of the hindlimb (arrowheads) evoked 2 distinct excitatory responses in SNA. These excitatory components were abolished after injection of 8-OH-DPAT in the RVLM. B: after preinjection of NAN-190 in the RVLM, 8-OH-DPAT in the RVLM did not abolish the somatosympathetic reflex. C: summary of data in A and B. Injection of 8-OH-DPAT almost abolished the somatosympathetic reflex (n = 6, C1). Pretreatment with NAN-190 antagonized the inhibitory effect of 8-OH-DPAT (n = 6, C2). *P < 0.01. D: electrical stimulation of the RVLM evoked early and late excitatory potentials in SNA that were similar to the hindlimb-evoked potential. Note that the interval between the early and late excitatory potentials evoked by RVLM and hindlimb stimulation is the same.
DPAT vs. 164 ± 41% after 8-OH-DPAT (n = 6, not significant (NS)). The increase in mean arterial pressure was also not affected by 8-OH-DPAT injection (14 ± 5 vs. 17 ± 8 mmHg from the level before nitrogen inhalation, n = 6, NS). In addition, a respiratory-related discharge pattern of the SNA, phase-locked to the phrenic discharge, was clearly preserved after injection of 8-OH-DPAT (Fig. 4A).

The effect of 8-OH-DPAT on baroreceptor stimulation is shown in Fig. 4, B and C. The response of SNA and arterial pressure to the tetanic and intermittent stimulation of aortic nerve was examined during the control period and just after the hindlimb stimulation. Tetanic stimulation of the aortic nerve after injection of 8-OH-DPAT decreased arterial pressure to the same extent as in the control period (−25 ± 4 vs. −26 ± 3 mmHg, Fig. 4B). These inhibitory effects were clearly preserved even when the stimuli were repeated during the maximum depressor and sympathoinhibitory period shortly after the administration of 8-OH-DPAT (data not shown). Quantitative analysis of the averaged response of the SNA after intermittent stimulation of the aortic nerve revealed that the inhibitory potential was not changed by injection of 8-OH-DPAT (−95 ± 2% vs. −93 ± 3% change from prestimulus period (n = 6, NS)). The duration of the inhibitory response was also not affected by 8-OH-DPAT injection (501 ± 22 vs. 496 ± 9 ms, n = 6, NS, Fig. 4C).

Fig. 4. A: brief hypoxia with N2 inhalation evoked hypertension and sympathoexcitation. These responses were not significantly changed after the 8-OH-DPAT injections in the RVLM. B: sympathoinhibitory and depressor responses evoked by tetanic stimulation of aortic nerve (AN) were also not changed after the 8-OH-DPAT injections in the RVLM. C: averaged inhibitory potential of SNA, elicited by intermittent stimulation of the AN (arrowheads), was also not affected by injection of 8-OH-DPAT.
DISCUSSION

The most important finding of the present study is that activation of 5-HT_{1A} receptors in the RVLM selectively inhibits the somatosympathetic reflex without affecting any of the other adaptive reflexes tested.

Role of 5-HT_{1A} receptors in the RVLM on arterial pressure and SNA. The depressor and sympathoinhibitory effects of 5-HT_{1A} receptor activation in the RVLM have already been reported by other investigators (2, 22). Blockade of these responses by preadministration of the 5-HT_{1A} antagonist NAN-190 supports the contention that 8-OH-DPAT inhibits SNA via this specific subtype of 5-HT receptors.

The 5-HT_{1A} receptor is negatively coupled to adenyl cyclase via Gi proteins. This receptor subtype also elicits neuronal hyperpolarization by opening K^+ channels when activated (3). Thus it is likely that 8-OH-DPAT injected in the RVLM may inhibit the ongoing activity of bulbospinal presympathetic neurons in the RVLM neurons, thereby decreasing SNA and arterial blood pressure.

Effects of hindlimb stimulation on SNA. Morrison and Reis (20) reported that stimulation of the sciatic nerve of rats evokes an early and a late excitatory response on SNA, as was also seen in the present study. The latencies of the peak responses of SNA evoked by stimulation of the hindlimb were similar to those observed after direct activation of the sciatic nerve (20). Furthermore, in a previous study from our laboratory, we found that both of the excitatory components of the SNA evoked by the electrical stimulation of the hindlimb were dramatically attenuated after microinjection of the excitatory amino acid antagonist 6-cyano-7-nitroquinoxaline-2,3-dione in the RVLM (18). Therefore, it is reasonable to suggest that the excitatory components evoked by hindlimb stimulation originate in the RVLM and are identical to the somatosympathetic reflex demonstrated in the previous studies (20, 21, 30, 35). The first excitatory component is most likely mediated via A-δ fibers given the short latency. The late component is probably due to a reflex mediated via slowly conducting efferent fibers from bulbospinal RVLM neurons, rather than slowly conducting C fiber afferent axons to the RVLM since the interval between the two excitatory components on SNA after hindlimb stimulation was essentially the same as that evoked after stimulation of the RVLM.

Role of the 5-HT_{1A} receptor in the RVLM on the somatosympathetic reflex. Previous studies from our, and other, laboratories have demonstrated convincingly that many adaptive cardiovascular reflex pathways to RVLM neurons, including the somatosympathetic, chemoreceptor, and baroreceptor reflex, are mediated via amino acid neurotransmitters (14, 19, 25, 35). In the present study, activation of 5-HT_{1A} receptors in the RVLM with 8-OH-DPAT attenuated the magnitude of the somatosympathetic reflex to the same extent as blockade of excitatory amino acid receptors in this area but without any significant effect on sympathetic baroreceptor and chemoreceptor reflexes. It is unlikely that 8-OH-DPAT acts as an excitatory amino acid antagonist in the RVLM, since the remarkable attenuation of the somatosympathetic reflex by 8-OH-DPAT was antagonized by the preinjection of the selective 5-HT_{1A} antagonist NAN-190. It is therefore also unlikely that this effect is mediated via 5-HT_{1A} receptor for which 8-OH-DPAT is also an agonist (3).

It is possible that activation of 5-HT_{1A} receptors exerts an inhibitory effect on the neuronal activity of RVLM neurons through a direct pathway, as suggested above. However, we believe that it is difficult to attribute the suppression of the somatosympathetic reflex after 8-OH-DPAT injection to a direct inhibitory effect via 5-HT_{1A} receptors on RVLM neurons for several reasons. First, the suppression of the somatosympathetic reflex was sustained significantly longer than the sympathoinhibitory and hypotensive response. Second, another excitatory reflex, the sympathetic chemoreceptor reflex that is mediated by the RVLM, was not affected by 8-OH-DPAT. Third, the respiratory modulation of SNA, which is probably generated within the RVLM, at least in part, by an excitatory amino acidergic input from respiratory neurons to the sympathetic premotor neurons in this area (8, 18), was also preserved after 8-OH-DPAT injection.

The robust suppression of the somatosympathetic reflex, while having little or limited effect on other excitatory and inhibitory afferents or on basal sympathetic activity, suggests that the 5-HT_{1A} receptor selectively blocks, or gates, the somatic excitatory inputs to the RVLM neurons. Selective suppression of the somatosympathetic reflex may indicate that activation of the 5-HT_{1A} receptor presynaptically inhibits release of an excitatory amino acid from the axon terminals of somatic afferents that synapse with RVLM neurons.

Because the somatosympathetic reflex was not enhanced after blockade of 5-HT_{1A} receptors by NAN-190, it appears that 5-HT may not be tonically inhibiting this reflex in the RVLM. The small suppression of this reflex after NAN-190 injection is most likely due to a partial agonist effect of this drug at the 5-HT_{1A} receptor (7).

A recent study by Schreihofer and Guyenet (27) characterized RVLM neurons with fast- and slow-conducting axons as noncatecholaminergic and catecholaminergic, respectively, by juxtaglomerular dye filling combined with tyrosine hydroxylase immunocytochemistry. Because injection of 8-OH-DPAT in the RVLM attenuated both excitatory components of the somatosympathetic reflex equally, it seems that 5-HT_{1A} receptors exert an identical effect on the responsiveness of both types of RVLM neuron to somatic stimulation.

Effect of 5-HT_{1A} receptor activation in the RVLM on central respiration. There is considerable disagreement among investigators about the effects of systemic administration of 5-HT_{1A} agonists on respiratory function. A stimulatory effect on phrenic nerve activity with an increase in frequency and amplitude after intravenous administration of the 5-HT_{1A} agonist buspirone was reported by Garner et al. (6), whereas a
depressant effect on phrenic discharge by buspirone or 8-OH-DPAT was reported by Richter et al. (26).

The present study sheds little additional light on this issue since 8-OH-DPAT injected in the RVLM either increased or decreased the amplitude of the phrenic nerve discharge, although NAN-190 increased it without exception. These variable results could be attributed to a range of factors, including the diversity of respiratory neurons located in this area (31). Because the RVLM contains neurons in the Botzinger complex that may exert inhibitory effects on central respiratory drive (32), the inhibition of these neurons by 8-OH-DPAT may cause disinhibition of the respiratory output. Alternatively, the effect could depend on other factors such as temperature, PCO2, or the level of anesthesia.

Recently, Richter’s group (26) demonstrated that microinjection of 8-OH-DPAT in the pre-Botzinger complex, which is considered to be essential for central respiratory rhythm generation, elicits a robust inhibition of phrenic nerve activity. However, these neurons are located quite caudal to the sites of injection in this study, so it is unlikely that the inhibition of phrenic nerve discharge could be attributed to the spread of 8-OH-DPAT into the pre-Botzinger complex.

Physiological significance and clinical implications of 5-HT1A receptors in the RVLM. 5-HT is one of the major neurotransmitters/modulators involved in central neural processing of somatic sensation and nociception. The present findings indicate that the 5-HT1A receptor selectively modulates the somatosympathetic reflex at the level of the RVLM, a site that is known to be a key interface between the sensory and sympathetic nervous systems. The lack of effect of 5-HT1A receptor activation on any reflex pathway, other than the somatosympathetic reflex, is especially noteworthy.

Interestingly, modulatory effects of 5-HT on the amino acid transmission are seen in the other brain areas, such as the lateral amygdala and locus coeruleus (1, 28). These sites are also implicated in sensation, stress, and nociception. Serotonergic neurons, therefore, may widely modulate sensory-related transmission by interacting with amino acid neurotransmitters.

5-HT has also been implicated in mental illnesses, including stress and anxiety disorders. Patients with these disorders often complain of cardiovascular-related symptoms (24). The findings here raise the possibility that a disturbance of 5-HT1A receptor function in the RVLM may play a role in the genesis of these side effects. Indeed, many therapeutic drugs that modulate serotonergic tone improve symptoms related to “panic”-like syndromes such as chest pain, hyperventilation, and tachycardia, as well as the mood of these patients (23, 33).

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