Differential chemoreceptor reflex responses of adrenal preganglionic neurons

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Cao, Wei-Hua, and Shaun F. Morrison. Differential chemoreceptor reflex responses of adrenal preganglionic neurons. Am J Physiol Regulatory Integrative Comp Physiol 281: R1825–R1832, 2001.—Adrenal sympathetic preganglionic neurons (ADR SPNs) regulating the chromaffin cell release of epinephrine (Epi ADR SPNs) and those controlling norepinephrine (NE ADR SPNs) secretion have been distinguished on the basis of their responses to stimulation in the rostral ventrolateral medulla, to glucopenia produced by 2-deoxyglucose, and to activation of the baroreceptor reflex. In this study, we examined the effects of arterial chemoreceptor reflex activation, produced by inhalation of 100% N2 or intravenous injection of sodium cyanide, on these two groups of ADR SPNs, identified antidromically in urethane-anesthetized, artificially ventilated rats. The mean spontaneous discharge rates of 38 NE ADR SPNs and 51 Epi ADR SPNs were 4.4 ± 0.4 and 5.6 ± 0.4 spikes/s at mean arterial pressures of 98 ± 3 and 97 ± 3 mmHg, respectively. Ventilation with 100% N2 for 10 s markedly excited all NE ADR SPNs (+222 ± 23% control, n = 36). In contrast, the majority (40/48; 83%) of Epi ADR SPNs were unaffected or slightly inhibited by ventilation with 100% N2 (population response: +6 ± 10% control, n = 48). Similar results were obtained after injection of sodium cyanide. These observations suggest that the network controlling the spontaneous discharge of NE ADR SPNs is more sensitive to brief arterial chemoreceptor reflex activation than is that regulating the activity of Epi ADR SPNs. The differential responsiveness to activation of the arterial chemoreceptor reflex of the populations of ADR SPNs regulating epinephrine and norepinephrine secretion suggests that their primary excitatory inputs arise from separate populations of sympathetic premotor neurons and that a fall in arterial oxygen tension is not a major stimulus for reflex-mediated adrenal epinephrine secretion.

THE SECRETION OF EPINEPHRINE and norepinephrine from adrenal medullary chromaffin cells contributes importantly to the homeostatic responses to a variety of challenges including cold exposure, hemorrhage, myocardial ischemia, shock, and hypoglycemia (2, 3, 27, 47, 48, 51, 52). Based on differential adrenal catecholamine secretions after hypothalamic stimulation at different sites, Folkow and von Euler proposed (10) that the two hormones are secreted from different chromaffin cells innervated by distinct, separately regulated preganglionic pathways. Anatomical data have provided extensive support for the former hypothesis (6, 7, 9, 12, 13, 20, 45, 46), and measurements of adrenal and plasma catecholamines and adrenal nerve activity have indicated that differential adrenal epinephrine and norepinephrine responses can be evoked with physiological stimuli including hypoglycemia, cold exposure, and hemorrhage (5, 11, 38, 39, 43, 48, 49).

Based on their differential excitatory responses to stimulation of the rostral ventrolateral medulla (RVLM) and to the glucopenia produced by 2-deoxyglucose (2-DG), adrenal sympathetic preganglionic neurons (ADR SPNs) have been separated into those (Epi ADR SPNs) that regulate the release of epinephrine and those (NE ADR SPNs) that control secretion of norepinephrine from adrenal medullary chromaffin cells (31). In contrast to the NE ADR SPNs, the population of Epi ADR SPNs exhibited little or no sensitivity to the activation of baroreceptor reflex: their discharge was relatively unaffected by increases in arterial pressure (AP) or stimulation of baroreceptor afferents in the aortic depressor nerve and exhibited no synchronization to the cardiac cycle (31). The two groups of ADR SPNs did not differ, however, in their inhibitory response to stimulation of cardiopulmonary receptors with right atrial administration of phenylbiguanide (4). To increase our understanding of the reflex regulation of the central networks controlling adrenal catecholamine secretion, the present study was undertaken to determine the responses of Epi ADR SPNs and NE ADR SPNs to arterial chemoreceptor reflex inputs and to characterize the relationship of their spontaneous discharge to the central respiratory cycle as monitored by the phrenic nerve activity.

METHODS

General procedures. Experiments were performed on 45 male Sprague-Dawley rats (300–500 g), anesthetized with urethane (1.2 g/kg iv) after the trachea, femoral vein, and femoral artery were cannulated for artificial ventilation, drug administration, and measurement of AP with a poly-
ethylene catheter in the abdominal aorta, respectively. Additional doses (0.3 g·kg⁻¹·h⁻¹) of urethane were administered after 6 h to maintain a stable level of anesthesia. The animals were paralyzed with d-tubocurarine (initially 0.6 mg/rat, thereafter 0.2 mg/h) and artificially ventilated with 100% O₂ at a minute volume of 140–180 ml. Respiratory rate was adjusted to maintain end-tidal CO₂ between 3.5 and 4.5%. Bilateral pneumothoraces reduced respiratory pump-related movements of tissue near the recording and stimulating electrodes. Rectal temperature was maintained at 37°C with a thermostatically controlled heating pad and lamp. Rats were placed prone in a stereotaxic apparatus and the interaural line and a spinal clamp on the T₁₀ and T₁₁ vertebral processes. An occipital craniotomy and T₁₂-T₁₃ laminectomy were performed. To record phrenic nerve activity, the left phrenic nerve was dissected medial to the scapula using a dorsal approach, the central cut end was placed on a bipolar hook electrode, and the activity was filtered between 300–3,000 Hz and then rectified and integrated (50 ms, CWE model MA-821).

Stimulation of chemoreceptor reflex. The arterial chemoreceptor reflex was activated either by ventilating the animal with 100% N₂ for 10 s or by intravenous injection of a bolus of sodium cyanide (NaCN, 50 µg). These were applied at intervals of at least 5 min. Experiments by others (16, 28) have consistently shown that the sympathoexcitation and pressor responses to both of these stimuli are eliminated by section of the carotid sinus nerve, indicating that they arose from activation of the arterial chemoreceptor reflex. This was not independently verified in the current study.

Recording and identification of adrenal sympathetic preganglionic neurons. The extracellular action potentials of ADR SPNs were recorded with glass pipettes containing a 7-µm-diameter carbon filament etched to a fine tip, and the reference electrode was inserted into nearby muscle. Spinal cord penetrations were made along the dorsal root entry zone, and ADR SPNs were located 0.7–1.1 mm below the dorsal surface. Neuronal signals were amplified and filtered (bandpass frequencies: 300–3,000 Hz) and monitored on an oscilloscope. ADR SPNs were antidromically identified with stimuli (50–400 µA, 1 ms) applied to the left adrenal nerve, which was dissected close to the adrenal capsule and placed on a monopolar hook electrode at its entry to the adrenal gland. The anode was clipped to nearby muscle. Three standard criteria were used to establish the antidromic nature of the responses of spinal neurons to adrenal nerve stimulation: 1) constant onset latency, 2) high following frequency, and 3) collision with spontaneous action potentials or those evoked by medullary stimuli (31). To perform time-controlled collision test, pulses coincident with selected neuronal action potentials were obtained from a window discriminator and used to trigger a stimulator that delivered the desired stimulus configuration at a specified delay and rate. ADR SPNs and NE ADR SPNs (4, 31), ADR SPNs were tested for 1) their responses to RVLM stimulation; 2) the relationship of their spontaneous activity to the cardiac cycle; 3) their sensitivities to baroreflex activation; and 4), in selected cases, their responses to the neuroglucopenia induced with intravenous 2-DG. Because there is a high degree of correlation within the population of ADR SPNs between a long, peak-response latency to RVLM stimulation and an excitable response to 2-DG-induced glucopenia (31), ADR SPNs that respond to RVLM stimulation with long, peak-response latencies are designated as Epi ADR SPNs and those with short, peak-response latencies are designated as NE ADR SPNs. Thus although an excitatory response to 2-DG-induced glucopenia provides the most direct test for differentiating Epi ADR SPNs, we have only applied it in some cases in the present study, relying more regularly on the long latency of RVLM stimulus-evoked responses and on the absence of baroreceptor-evoked inhibition to distinguish Epi ADR SPNs from NE ADR SPNs, which are not affected by 2-DG but exhibit a strong inhibition during baroreceptor reflex activation (31).

RVLM stimulation. A monopolar tungsten electrode (50-µm exposed tip) was used to deliver paired (6-ms interpulse interval) stimuli (50–300 µA, 1 ms, 0.25 Hz) to the region of the RVLM containing spinally projecting vasomotor neurons (25, 32, 42). The stimulating electrode was positioned 2.6 mm rostral, 2.0 mm lateral, and 2.3 mm ventral to the calamus scriptorius. For histological verification, the stimulation sites were marked with an electrophoretic deposit of fast green dye (20 µA of cathodal current for 10 min) from a micropipette stereotactically positioned at the same RVLM site.

Stimulation of aortic depressor nerve and arterial baroreceptors. The left aortic depressor nerve was identified in the neck, and the central cut end was placed across a pair of platinum hook electrodes spaced 2 mm apart. Three-pulse trains (7-ms interpulse interval, 10 µA, 1 ms, 0.25 Hz) were delivered to the ADN through a stimulus isolation unit (Grass, PSIU6). Natural stimulation of arterial baroreceptors was accomplished during the rise in AP elicited by an intravenous bolus injection of phenylephrine (5 µg/0.1 ml). To examine the effectiveness of the baroreceptor reflex activation that occurs during the brief increase in AP during systole, histograms of the activity of ADR SPNs were constructed over three to four cardiac cycles using the onset of the systolic pressure increase as the trigger. The spontaneous discharge of an ADR SPN was considered to be modulated by the systolic pressure-induced activation of the baroreceptor reflex if the systolic pressure rise was consistently followed by a period of at least 30 ms (i.e., 3 histogram bins) during which the SPN activity was less than that during the 40-ms periisystolic interval.

Histology and data analysis. At the completion of each experiment, the animal was perfused transcardially with physiological saline followed by 10% formaldehyde. The brain stem was sectioned coronally at 60-µm thickness. The locations of dye spots were identified and plotted on drawings from a rat atlas (34).

The action potentials of ADR SPNs, AP, and phrenic nerve activity were digitized at 22 kHz and recorded on videocassette recorder tape. Computer-aided data analysis consisted of peristimulus and peripheric time interval histograms of the discharges of ADR SPNs to determine the effect of the stimuli on the discharge probability of ADR SPNs and to determine whether the central respiratory generator influenced the discharge probability of ADR SPNs (19, 29), respectively. All statistical analysis was performed with Student’s t-test. Differences in mean data were considered to be significant when P < 0.05.

RESULTS

In 45 rats, extracellular recordings were made from 89 neurons that were antidromically activated in the intermediolateral region of spinal segments, T₁₀-T₁₂, by electrical stimulation of the left adrenal nerve (Fig. 1A). Each of these neurons was orthodromically activated by RVLM stimulation (Fig. 2, top), and, based on the criteria described above, they were separated into groups of 51 Epi ADR SPNs and 38 NE ADR SPNs.
Identification of Epi ADR SPNs and NE ADR SPNs.
Those ADR SPNs that exhibited an early inhibition and a long latency excitation (mean response latency >60 ms, Fig. 2A) following stimuli applied to the ipsilateral RVLM were designated as Epi ADR SPNs (31). Their average mean response latency was 121 ± 3 ms (range: 85–172 ms). Those ADR SPNs with monophasic responses to RVLM stimulation and short mean response latencies (Fig. 2B) were identified as NE ADR SPNs. Their average mean response latency was 34 ± 1 ms (range: 21–56 ms).

Electrical stimulation of the ipsilateral ADN produced a marked, transient inhibition (Fig. 2B) of the spontaneous discharge of all 19 NE ADR SPNs tested. The mean onset latency of the inhibition was 42 ± 5 ms, and the mean duration of the inhibition was 250 ± 31 ms. In contrast, the majority (84% of 25) of the Epi ADR SPNs tested were unaffected by baroreceptor afferent stimulation (Fig. 2A). The spontaneous activity of four (16%) Epi ADR SPNs was slightly inhibited by the stimulation of the ADN, with a mean maximum reduction of 45% control between 100 and 400 ms after the ADN stimulus. The spontaneous discharge of 14 of 19 NE ADR SPNs was synchronized to the cardiac cycle at mean AP >80 mmHg (Fig. 2B), whereas the activity of all 20 Epi ADR SPNs tested displayed no consistent modulation of their discharge probability over the course of the cardiac cycle (Fig. 2A). Similarly, the activity of all of the 15 NE ADR SPNs tested was completely inhibited by the elevations in AP produced by intravenous injection of phenylephrine (10 μg, data not shown). Only 4 of 14 tested Epi ADR SPNs, by contrast, were slightly inhibited during the pressor responses to phenylephrine injections. The remaining Epi ADR SPNs showed no change during these sustained stimulations of the arterial baroreceptors.

The antidromic latencies of the Epi ADR SPNs (mean: 32 ± 2 ms, range: 12–60 ms) were not different (Fig. 1B) from those of NE ADR SPNs (mean: 32 ± 3 ms, range: 9–67 ms). With an average distance from the spinal recording site to the adrenal nerve stimulating electrode of ~36 mm, the calculated axonal conduction velocities of the ADR SPNs were between 0.5 and 4.0 m/s. Approximately 62% of the ADR SPNs conducted at <1.0 m/s. The spontaneous discharge rate of Epi ADR SPNs (mean: 5.5 ± 0.4 Hz, range: 0.5–12 Hz) was significantly (P < 0.05) greater than that of NE ADR SPNs (mean: 4.0 ± 0.4 Hz, range: 0.7–12 Hz) at equivalent mean APs of 96 ± 3 and 97 ± 3 mmHg, respectively.

Effects on ADR SPNs of ventilation with 100% N₂. Activation of the arterial chemoreceptor reflex by ventilation with 100% N₂ for 10 s produced an increase in AP, little effect on Epi ADR SPN discharge (Fig. 3A), and a prominent excitation of NE ADR SPNs (Fig. 3B). From a control mean AP of 94 ± 2 mmHg, activation of the chemoreceptor reflex with 100% N₂ ventilation produced an average maximum increase in mean AP of 37 ± 2 mmHg (n = 91, Fig. 4A). Each of the 43 NE ADR SPNs tested was excited by this brief hypoxic stimulus (Fig. 3B), with 79% of NE ADR SPNs exhibiting a maximum increase >100% of their control discharge rate (Fig. 4A). The mean peak increase in discharge frequency of NE ADR SPNs was 216 ± 22% (Fig. 4B). In contrast, within the population of 48 Epi ADR SPNs, 10 s of ventilation with 100% N₂ had no effect on the discharge rate of 52% of the neurons (Fig. 3A), slightly inhibited 29%, and weakly excited 19% of Epi ADR SPNs (Fig. 4A). The mean peak increase in discharge frequency of Epi ADR SPNs was 14 ± 11% (Fig. 4B). The average pressor responses (Fig. 4B) to acute arterial chemoreceptor stimulation were not different between trials involving Epi ADR SPNs (37 ± 3 mmHg) and those involving NE ADR SPNs (40 ± 4 mmHg, Fig. 4B). In five cases, chemoreceptor reflex-evoked responses for Epi ADR SPNs and NE ADR SPNs were tested in the same animal.

Effects on ADR SPNs of chemoreceptor stimulation evoked by injection of NaCN. In a manner similar to the effects of ventilation with 100% N₂, stimulation of the arterial chemoreceptor reflex with intravenous injections of NaCN (50 μg) caused an increase in AP, little effect on the activity of Epi ADR SPNs, and a dramatic excitation of NE ADR SPNs (Fig. 5A). The average
maximum increase in mean AP was 57 ± 6 mmHg ($n = 15$) from a baseline of 96 ± 2 mmHg. All of the NE ADR SPNs were excited by injections of NaCN, yielding a mean maximum increase in discharge rate of +196 ± 32% (9 ± 2 spikes/s, $n = 6$, Fig. 5, A and B), which was significantly ($P < 0.001$) greater than that of Epi ADR SPNs that had a mean maximum change in discharge rate of +6 ± 27% ($n = 9$, Fig. 5, A and B). There was no

Fig. 2. Comparison of rostral ventrolateral medullary (RVLM) stimulus-evoked, aortic depressor nerve (ADN) stimulus-evoked, and cardiac-related activity of an Epi ADR SPN and an NE ADR SPN. A: top, peristimulus time histogram of discharge of an Epi ADR SPN during paired-pulse stimulation of RVLM (time 0, 30 sweeps). Bin width: 2 ms; 0–6 ms zeroed to eliminate stimulus artifacts. Note early inhibition (duration ~ 100 ms) and late excitation (peak latency: 150 ms). Middle: peristimulus time histogram of discharge of an Epi ADR SPN during 3-pulse stimulation (time 0, 30 sweeps) of ADN. Bottom: cardiac cycle-triggered (100 sweeps) average of arterial pressure (AP) and histogram (bin width: 10 ms) of spontaneous discharge of an Epi ADR SPN. AP was mmHg. B: similar traces as in A for an NE ADR SPN. Note short-latency (peak: 25 ms) excitation of NE ADR SPN following RVLM stimuli, ADN stimulus-evoked inhibition and baroreceptor modulation of NE ADR SPN discharge during cardiac cycle (AP: mmHg).

Fig. 3. AP and ADR SPN responses to chemoreceptor reflex activation. A: chemoreceptor stimulation with inhalation of 100% N2 (horizontal bar) increased AP (top) but had no effect on spontaneous discharge (middle) or integrated rate histogram (bottom, 1-s bins) of an Epi ADR SPN. B: similar traces for an NE ADR SPN. Note chemoreceptor-evoked increase in spontaneous discharge of NE ADR SPN.
difference in the maximum increases in AP (Fig. 5A) resulting from the NaCN injections during recordings from Epi ADR SPNs (57 ± 8 mmHg) and from NE ADR SPNs (56 ± 8 mmHg; Fig. 5B).

Relationship of ADR SPN discharge to the central respiratory cycle. To determine if central respiratory generating circuits influence the discharge of ADR SPNs, the onset of the inspiratory phase of the phrenic nerve activity was used to trigger histograms of the spontaneous activity of antidromically identified ADR SPNs (n = 20) recorded in vagotomized animals. The RVLM stimulus-evoked responses (Fig. 6A) of eight ADR SPNs indicated that they could be classified as Epi ADR SPNs (31). As illustrated in the phrenic-triggered histogram in Fig. 6A, there was no discernible modulation of the discharge probability of seven of eight Epi ADR SPNs over the time course of the central respiratory cycle as monitored by the phrenic nerve discharge. In contrast, as shown in the examples in Fig. 6, B and C, the discharge probabilities of all 12 ADR SPNs with short-latency RVLM stimulus-evoked excitations indicative of NE ADR SPNs were strongly synchronized to the central respiratory cycle. The discharge of 75% of the NE ADR SPNs was reduced during the inspiratory phase of the phrenic activity (Fig. 6B), while the remaining NE ADR SPNs were excited during inspiration (Fig. 6C).

DISCUSSION

The major finding of the present study is that acute activation of the arterial chemoreceptor reflex produces a marked excitation of the ADR SPNs controlling noradrenaline secretion but little change in the activity of ADR SPNs proposed (31) to regulate adrenal medullary epinephrine release. The increases in both respiratory and sympathetic vasomotor outputs in cats (21, 23, 28) and in rats (1, 16) produced by brief N2 inhalation or bolus injection of sodium cyanide are
dependent on intact carotid sinus nerves, indicating that these results and those of the present study are due to activation of arterial chemoreceptors in the carotid body rather than to an effect of hypoxia on the central nervous system. Similarly, the spontaneous discharge of Epi ADR SPNs showed little or no modulation over the course of the central respiratory cycle, whereas the discharge probability of NE ADR SPNs exhibited large fluctuations synchronized to the inspiratory phase of the phrenic nerve activity. Together, these results indicate that neither acute fluctuations in arterial oxygen tension nor changes in central respiratory drive play a significant role in determining adrenal epinephrine secretion. Adrenal norepinephrine release, in contrast, is strongly influenced by both of these variables, in a manner paralleling their effects on sympathetic tone to visceral, muscle, and cutaneous vasoconstrictor targets (15, 17, 18, 24, 25).

Data from several labs (14, 24, 26, 30) indicate that activation of sympathetic premotor neurons in the RVLM is essential for both the sympathoexcitatory response to chemoreceptor reflex stimulation and the respiratory modulation of vasoconstrictor sympathetic outflow. Although anatomical findings (42, 50, 53) point to the RVLM as a potential location of sympathetic premotor neurons controlling the discharge of Epi ADR SPNs and this conclusion is supported by the significant increases in plasma epinephrine that result from activation of neurons in the RVLM (33, 36), there is, however, no direct evidence indicating that neurons in the RVLM project specifically to Epi ADR SPNs. Within this framework, two scenarios are suggested by our data indicating marked differences between Epi ADR SPNs and NE ADR SPNs in their sensitivity to chemoreceptor reflex activation and in the degree to which central respiratory networks modulate their spontaneous discharges. If, in the first case, we assume that Epi ADR SPNs are monosynaptically excited by premotor neurons in the RVLM, the premotor neurons with inputs to Epi ADR SPNs must be different from those projecting to NE ADR SPNs or to vasoconstrictor SPNs, because both of the latter groups exhibit a marked sensitivity to arterial chemoreceptor stimuli and a strong modulation of their spontaneous discharge during the central respiratory cycle. This scenario would extend the conclusion drawn from our previous studies in which the existence of a unique population of adrenal epinephrine-regulating sympathetic premotor neurons in the RVLM was suggested by the absence of baroreceptor reflex-evoked effects on the discharge of Epi ADR SPNs (31) and by the failure of interruption of the baroreceptor reflex pathway to alter plasma epinephrine levels (33). Indirect support of this model comes from the correspondence between

Fig. 6. Relationship of ADR SPN discharge to central respiratory cycle. A: average of integrated phrenic nerve activity (top trace) and histogram of spontaneous discharge of an Epi ADR SPN triggered by the onset of the inspiratory phase (45 sweeps). Inset, peristimulus time histogram of the discharge of this Epi ADR SPN during stimulation of the RVLM. Arrowhead, mean response latency. Note the early inhibition and late excitatory response to RVLM stimulation, but the absence of any synchronization between this Epi ADR SPN’s spontaneous discharge and phrenic nerve activity. B: same traces as in A for an NE ADR SPN that has its probability of discharge reduced during inspiratory phase of phrenic nerve discharge. Average and histogram constructed from 60 sweeps. Note short latency excitation of this NE ADR SPN during RVLM stimulation. C: same traces as in B for an NE ADR SPN that has its probability of discharge increased during inspiration. Average and histogram constructed from 40 sweeps.
the calculated conduction velocities of the potential RVLM-spinal pathways activating Epi ADR SPNs (0.58 m/s) and NE ADR SPNs (2.0 m/s) and those (0.4–0.8 and 2–8 m/s) of the two populations of antidromically identified RVLM-spinal vasomotor neurons (32, 40, 44). However, although it is reasonable to propose that NE ADR SPNs are excited by rapidly conducting RVLM-spinal vasomotor neurons because both are sensitive to baroreceptor and chemoreceptor inputs, it seems unlikely that Epi ADR SPNs receive a significant excitatory input from the previously characterized, slow-conducting, sympathetic premotor neurons in the RVLM, because these premotor neurons are not different from their more rapidly conducting counterparts with respect to their baroreceptor and chemoreceptor reflex sensitivities. Thus if the RVLM does contain premotor neurons controlling Epi ADR SPN discharge, they remain to be identified. In the alternative scenario, RVLM stimulus-evoked excitation of Epi ADR SPNs (31) would be mediated indirectly through activation of sympathetic premotor neurons outside of the RVLM. The absence of an influence of chemoreceptor or baroreceptor reflex activation on this population of sympathetic premotor neurons could then explain the reduced sensitivity of Epi ADR SPNs to these reflex inputs.

The effects of hypoxemia on adrenal catecholamine release are equivocal and are complicated by the different models used and by the influences of barometric pressure and the duration and severity of the hypoxic stimulus. In addition, the significant contribution to the plasma levels of norepinephrine from the norepinephrine spillover from the terminals of sympathetic ganglion cells indicates that only measurements of adrenal venous NE can provide a useful measure of the effect of hypoxia on adrenal norepinephrine release. Further factors complicating the direct assessment of the relationship between our results and those employing other models and stimuli include 1) the fact that although the acute hypoxic stimuli used in the present study were of sufficient strength to activate the central components of the arterial chemoreceptor reflex pathway, they were likely too brief to produce much of an effect on plasma epinephrine levels; 2) the difficulty in assessing the “severity” of the chemoreceptor stimulation achieved with NaN₄ administration; and 3) the absence of an assessment of the level of hypoxia achieved during our 10-s N₂ inhalations. Inhalation of an hypoxic gas mixture for 2 h that yielded a mixed expiratory O₂ concentration of 7% produced no change in plasma epinephrine in conscious dogs (35) during the first 80 min but did produce a significant increase by the end of the second hour. A similar absence of effect on plasma epinephrine was seen in several studies on human responses to acute hypoxia (37). In awake rats, exposure to 10.5% O₂ for 1 day or 7.5% O₂ for 6 h increased urinary epinephrine (22). Similarly, breathing 10% O₂ increased adrenal catecholamine metabolism in the rat after 7 days, but this effect was also seen in animals with sectioned carotid sinus nerves (8). Evidence has also been presented for a nonneurogenic mechanism capable of eliciting hypoxia-stimulated release of adrenal catecholamines (41). A 45-s exposure of anesthetized rats to an hypoxia that resulted in a mixed expiratory O₂ concentration of 6% produced an increase in both adrenal sympathetic nerve activity and in adrenal venous adrenaline and noradrenaline effects that were abolished by severing the carotid sinus or the splanchic nerves (1). Although our results indicating an hypoxic excitation of NE ADR SPNs are consistent with this finding, it is unclear whether the differences in duration and method of chemoreceptor reflex activation between the present study and that of Biesold et al. (1) are responsible for the divergence in the Epi ADR SPN-mediated responses to hypoxic stimuli in the two studies.

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REFERENCES


