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RESPIRATORY MODULATION OF THE CUTANEOUS SOMATOSYMPATHETIC REFLEX IN NORMOTENSIVE (WKY) AND IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR): SPECIES AND STRAIN-DEPENDENT PATTERNS

M. F. CZYŻYK-KRZESKA and A. TRZEBSKI

Department of Physiology, Medical Academy
26/28 Krakowskie Przedmieście St., 00-325 Warsaw, Poland

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Abstract. In 6 normotensive Wistar-Kyoto (WKY) and 6 spontaneously hypertensive rats (SHRs) anesthetized with urethane and chloralose, paralyzed, artificially ventilated, vagotomized with carotid sinus nerves bilaterally cut, somatosympathetic reflex discharges were recorded in cervical and renal nerves by stimulating group II and III cutaneous afferents in the sural nerve. Only a long-circuited, late supraspinal component reflex discharge could be elicited. After averaging the responses evoked by random stimulation, the latency of the reflex discharge was significantly longer in the renal than in the cervical sympathetic nerve, equally in the WKY rat and in SHR. In WKY rats the peak of sympathetic discharge corresponded to early expiration, whereas in SHRs — to late inspiratory phase. The duration of the reflex discharge elicited in inspiration was greater in SHR than in WKY rats. In WKY rats stimuli applied during phrenic discharge produced a reflex response of longer latency and of reduced amplitude than those applied in expiration. In SHRs the latency of the reflex response in the sympathetic cervical nerve was shorter during inspiration than in expiratory phase. The timing of the sympathetic reflex responsiveness within respiratory cycle in SHR and in WKY rats corresponded to strain-dependent opposite respiratory synchronization pattern of the spontaneous sympathetic activity charac-

terizing each strain. No respiratory modulation of the somatosympathetic reflex was observed in the renal nerve of SHR. It is concluded that both spontaneous and evoked sympathetic activity is synchronized differently in SHR and in WKY rats and this difference is both species- and strain-dependent.

INTRODUCTION

Somatosympathetic reflexes are characterized by considerable fluctuations of their latencies and magnitude as seen from recordings of whole nerve discharge from single preganglionic and postganglionic fibers (cf ref. 16). Fluctuations of reflex responsiveness are strongly contingent upon spontaneous sympathetic discharge rhythmically modulated, among other inputs, by central respiratory activity (cf. ref. 9). Facilitation of the excitatory somatosympathetic reflex with attenuation of the post-stimulatory "silent period" was found after the electrical stimulation of afferents from the hind limb was applied during inspiratory phrenic nerve bursts in the cat (10). On the contrary, diminished effects were observed if the stimulation of hind limb afferents was timed within the expiratory phase. This pattern of respiratory modulation of the reflex was parallel with rhythmical, inspiratory-related spontaneous sympathetic discharge and expiratory-related sympathetic depression characterizing cats (9, 10). In the rat, the timing of the respiratory-modulated spontaneous sympathetic activity is different and opposite to that characterizing the cat: sympathetic activity decreases in inspiration and increases in expiration as shown in our previous study (3). In contrast, spontaneously hypertensive rats of Okamoto-Aoki strain (SHR) demonstrate inspiratory facilitation and early expiratory depression of the sympathetic discharge (4), a pattern similar to that characterizing cats (9).

In view of these species and strain dependent differences, we asked the question if responsiveness of the somatosympathetic reflexes varies over the respiratory cycle in normotensive and genetically hypertensive rats and if so, does it correspond to the timing of the respiratory-sympathetic synchronization. The problem of species-and strain-dependency of respiratory patterning of the spontaneous and evoked sympathetic activity appears interesting for studying neurogenic mechanisms of arterial hypertension. Only rats, and not cats or other animals, are available and can be used as an experimental model of genetically controlled hypertension. Besides, respiratory drive was found to be significantly increased in primary hypertension both in rats (14) and in hypertensive human subjects (22).

METHODS

Experiments were carried out on 12 male rats. Six spontaneously hypertensive rats (SHR) and 6 matched control normotensive Wistar-Kyoto (WKY) rats aged 12-16 weeks, weighing 250-350 g were used. Anesthesia was induced first by inhalation of ether preceded by injection of atropine (0.5-1 mg/kg, i.m. Atropinum Sulfuricum, Polfa). Following this initial anesthesia a mixture of urethane (500 mg/kg) and alpha-chloralose (50 mg/kg) was administered intravenously, supplemented after 4-5 h with 30-50% of the initial dose. The adequacy of anesthesia was determined by measuring the response of the animal to pinching the hind paw. The trachea was cannulated low in the neck and catheters were placed in the femoral artery and vein in order to monitor arterial blood pressure and administer drugs, respectively. For statistical analysis the values of arterial blood pressure were taken 30 min after tracheostomy. In SHRs mean blood pressure values were 210/145 mm Hg (SE: ± 4 and ± 6) and in WKY rats 128/84 mm Hg (SE: ± 5 and ± 2), $P < < 0.001$.

All experiments were performed on paralyzed and artificially ventilated animals. For paralysis, an initial dose of 200 μg/kg of pancuronium bromide (Pavulon, Organum Hesse) was used, followed by maintenance doses of 200 μg/kg every two hours. In control conditions the respiratory pump rate was set at 90-95 cycles/min; the tracheal pressure did not exceed 5-6 cm H_2O. Animals were ventilated with room air enriched with 30% O_2 in N_2. A pneumothorax was performed and in artificially ventilated animals positive end-expiratory pressure of 0.5-1 cm H_2O was applied to prevent lung atelectasis. Rectal temperature was maintained between 36-38° C with a heating blanket controlled by a feed back circuit.

Blood gases were measured with a pH/Blood Gas Analyser (205, Plastomed). Arterial O_2 pressure (PaO_2) was 135-145 mm Hg. Blood samples of 0.1-0.2 ml each taken from the femoral artery were replaced with the same amount of donor blood or plasma.

All animals were vagotomized to abolish the effect of lung inflation on central respiratory activity and on sympathetic preganglionic neurons. Aortic nerves were cut bilaterally. Denervation of remaining arterial baroreceptors and chemoreceptors was performed by severing both carotid sinus nerves after prior visual identification. Carotid chemoreceptor denervation was verified by lack of phrenic nerve response to pure nitrogen inhalation applied for one breath.

Nerve recordings

Following a mid-dorsal incision and retraction of the scapula, the left cervical trunk and phrenic nerve were isolated, cut and their central ends placed on bipolar platinum electrodes for recording the nerve activity. The postganglionic renal nerve was identified at the kidney hilum. All nerves were kept under warm paraffin oil in a pool made of skin flaps. After amplification (bandpass 50-5 kHz) the activity of the phrenic nerve was rectified and integrated with an RC circuit (time constant of 0.1-0.2 s). Sympathetic nerve activity was integrated by the method of moving time averaging (bandpass 50-2 kHz, time constant 0.2-1 s). The level of "zero" activity of sympathetic nerves was determined by recording from the nerves after the animal had been sacrified with an overdose of Nembutal.

Nerve stimulation

Electrical stimulation of group II and III cutaneous afferents within the left sural nerve was timed at different periods of the respiratory cycle to produce a somato-sympathetic reflex discharge. After visual identification, the left sural nerve was placed on bipolar platinum electrodes and immersed in warm paraffin oil. Rectangular pulses of 0.2 ms duration and a frequency of 333 Hz were delivered though an isolation unit. The stimulator (Digitimer 4030) was synchronized with the respiratory cycle. Stimulus strength did not exceed 30 V. Stimulus threshold (T) was determined by recording the compound afferent action potential of the nerve stimulated 1 cm distal from the recording electrodes. In some cases the threshold was set by finding the minimal stimulus strength sufficient to evoke the mass reflex discharge in the sympathetic nerves.

To compare the amplitude, duration and latency of the evoked sympathetic responses in each respiratory phase, pairs of stimuli or a train of four stimuli of the same strength were applied, first during inspiration in one respiratory cycle and then during expiration in the next one. The stimuli were always applied at the same point within the respiratory cycle as measured from the onset or offset of the phrenic nerve discharge.

Data collection and analysis

Nerve activity, blood pressure and intratracheal pressure were recorded and stored on the magnetic tape (Ampex, SP-300) and displayed on a polygraphic ink recorder or photographed from an oscilloscope (5103 N, Tektronix). Integrated spontaneous and evoked sympathetic

and phrenic nerve activities were averaged over 16 respiratory cycles with an averager (Anops 101) using as a trigger a single stimulus delivered from the stimulator (Digitimer 4030) at the onset or at the termination of the integrated phrenic nerve burst. Intervals between phrenic bursts were accepted as the expiratory time (T_E) and the duration of the phrenic burst was used as an index of the inspiratory time (T_T). Means (± standard errors of the mean, SE) are given for each group. Significance of the differences was calculated by one of two formulas of Student's *t*-test chosen on the basis of similarity of dispersion curves of different sets of data evaluated by F- Snedecor's test. $P < 0.05$ was accepted as significant for all tests used.

RESULTS

Averaged somatosympathetic cutaneous reflex response in cervical and renal nerves of normotensive (WKY) and spontaneously hypertensive rats (SHRs)

Reflex responses were elicited by stimulation of the cutaneous afferents in the sural nerve applied at random regardless of the respiratory

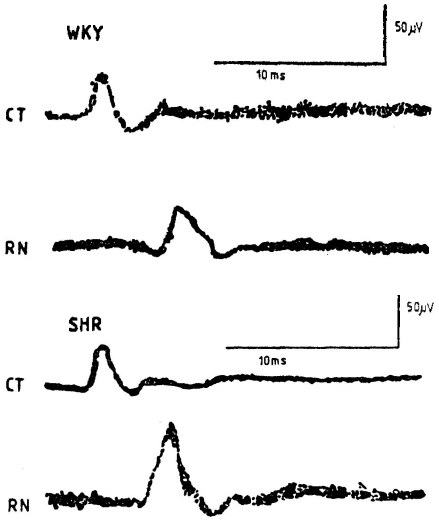

Fig. 1. Averaged somatosympathetic reflex discharge in cervical trunk (CT) and renal nerve (RN) produced by stimulation of cutaneous afferents in the sural nerve in normotensive WKY rats (1 and 2 record from the top) and in SHR (3 and 4 record from the top). Onset of the record averaged 16 times triggered by a train of four 3 T stimuli (f = 333 Hz) applied at random regardless of the respiratory phase at which stimulation was given. Latency of the reflex response in renal nerve is significantly longer than that in the cervical trunk, equally in WKY and SHR.

phase. The intensity of stimuli was 3T. A train of four pulses at frequency of 333 Hz was used. The parameters of stimulation were adjusted to excite group II and III afferents (12).

Figure 1 is an example of the cutaneous somatosympathetic reflex discharges averaged 16 times in a WKY and in a SHR. No early spinal reflex discharge component could be produced. This result is in agreement with previous findings on rat's somatosplanchnic reflex (12). The only discharge observed was a late supraspinal reflex component of mean latency in the cervical trunk 59 ± 3 ms for WKY and 53 ± 9 ms for SHR. Corresponding mean latencies in the renal nerve were 93 ± 7 ms for WKY and 86 ± 7 ms for SHR. There was no significant difference between the latencies in WKY and in SHR. In both strains of rats the latency of reflex discharge in the renal nerve was significantly longer than in the cervical trunk. Mean difference was 33 ± 4 ms and remained constant regardless of whether it was measured in normotensive or hypertensive animals and regardless of the respiratory phase at which the reflex was produced.

Timing of the synchronization of the spontaneous sympathetic activity within respiratory cycle in normotensive (WKY) and in spontaneously hypertensive (SHR) rats

In both WKY rats and SHR the amplitudes of spontaneous sympathetic discharges in cervical and renal nerves oscillated within each respiratory cycle. The timing of the maximal and minimal activity was different in SHR as compared to WKY rats. In WKY rats (Figs. 2 and 3) the peak of sympathetic discharge corresponded to early, stage I expiration, in agreement with our earlier finding (3). At the onset of inspiratory phrenic burst a prolonged depression of sympathetic activity occurred and not recovered until the peak at early expiration phase. In contrast, SHR exhibited a different pattern: short-lasting early inspiratory depression and the peak of discharge at late inspiratory phase or at inspiratory-expiratory transition (Fig. 4). At early expiration a strong inhibition of sympathetic activity appeared. These results are consistent with our earlier data analyzed in detail elsewhere (4).

Respiratory modulation of the somatosympathetic reflex in normotensive (WKY) and in spontaneously hypertensive (SHR) rats

The delivered pair of stimuli or the train of 4 stimuli at intensity of 3T were triggered at the onset or at the end of inspiration in order to compare the magnitude and latency of the reflex discharge in different respiratory phases. Figure 2 shows an evoked reflex discharge in WKY in the cervical and renal nerve of WKY rat in mid-expiration and in mid-

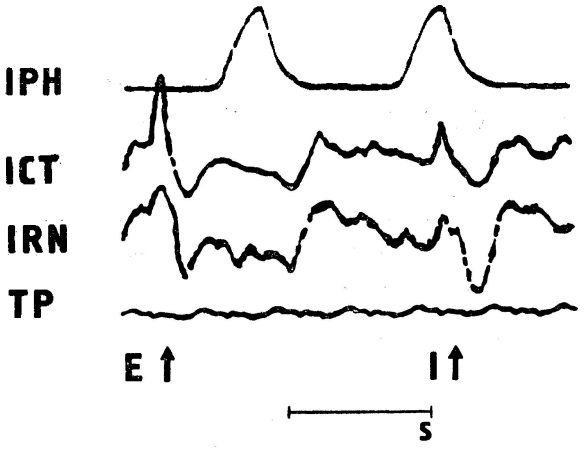

Fig. 2. Integrated and averaged reflex discharge in WKY rats recorded simultaneously in cervical trunk (ICT) and in renal nerve (IRN) produced by stimulation of sural nerve afferents during expiration (E) and during inspiration (I). Arrows mark the onset of a pair of stimuli (3 T, 333 Hz). IPH, integrated phrenic nerve record; ICT, integrated cervical trunk activity; IRN, integrated renal nerve activity; TP, tracheal pressure. Reduced amplitude of the response and a pronounced post-excitatory inhibition after the stimulus was applied in inspiratory phase.

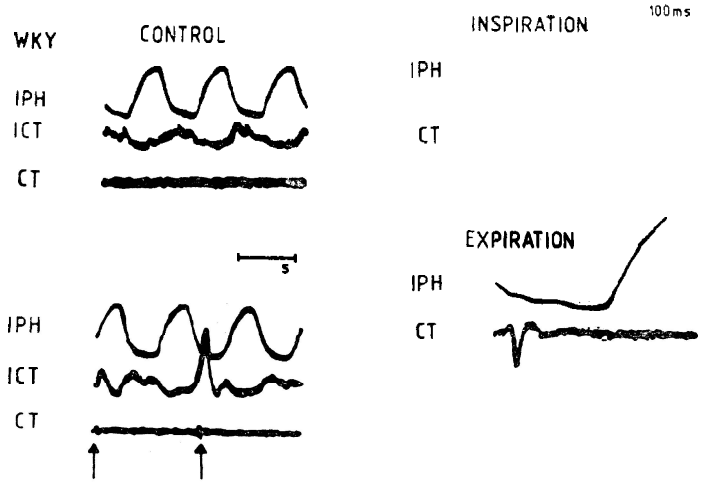

Fig. 3. Integrated phrenic nerve activity (IPH), integrated sympathetic cervical trunk activity (ICT), rough cervical trunk activity (CT) in a WKY normotensive rat. Upper record left: spontaneous activity, lower record left: somatosympathetic reflex response evoked at the onset of inspiratory phase (first arrow) and during early, stage I expiration (second arrow). Right: reflex response evoked at early inspiration (above) and at early, stage I expiration (below). Onset of the averaged record marks the application of stimulus. Significantly shorter latency and augmented amplitude (down) of the response evoked in expiration.

inspiration. Figure 3 shows an example of somatosympathetic reflex discharge, integrated yet non-averaged in the cervical trunk after a pair of afferent stimuli was delivered at early inspiration and at early expiratory phase. In WKY rats the latencies of evoked reflex discharge in cervical nerves were significantly shorter in expiration than during phrenic nerve activity. Their amplitude both in the cervical and renal nerve was significantly greater if evoked in expiration as compared to the responses produced in inspiration. There were no significant differences between the durations of the reflex discharge evoked either in the inspiratory or expiratory phase. Table I summarizes mean data.

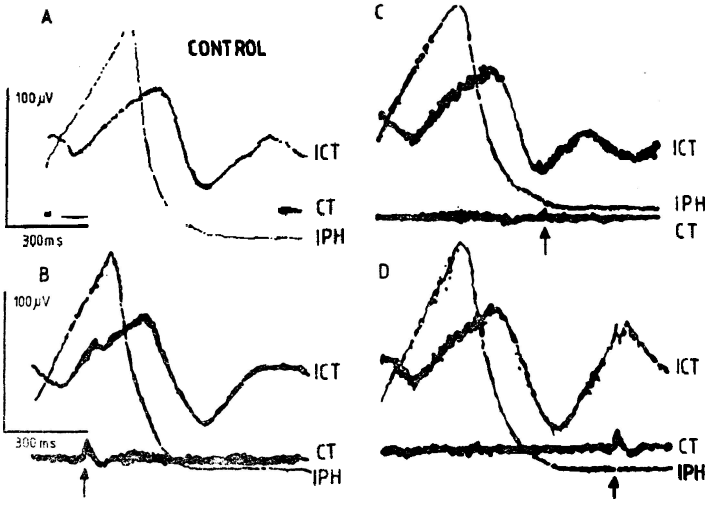

Fig. 4. Somatosympathetic reflex response in a SHR. *A*, control record. *B*, reflex discharge evoked in the late inspiratory phase. *C*, no response to stimulus applied in early, stage I expiration. *D*, a response evoked in late expiratory phase. Application of a train of afferent stimuli marked by the arrow. Abbreviations as in Figs. 2 and 3.

In SHR the respiratory modulation of the latency of evoked reflex discharge in the sympathetic cervical trunk was opposite to that in WKY rats: it was shorter during inspiration than in expiration. Stimuli of 3 T strength applied at early expiratory depression of the spontaneous sympathetic activity were ineffective in producing reflex response (Fig. 4). All other parameters studied, the latency, time duration and amplitude of reflex discharges did not significantly differ between the respiratory or expiratory phase in SHRs (Table I).

TABLE I

Mean values of latency, time duration and amplitude of the somatosympathetic reflex response incervical trunk (CT) and in renal nerve (RN) during inspiration and expiration in normotensive Wistar-Kyoto (WKY) and in spontaneously hypertensive (SHR) rats

	Latency (ms)				Duration (ms)				Amplitude (μV)			
	Inspiration		Expiration		Inspiration		Expiration		Inspiration		Expiration	
	CT	RN	CT	RN	CT	RN	CT	RN	CT	RN	CT	RN
WKY n = 6	58.6±4.5	91.7±5.7	47.5±3.5	80.6±7.9	52.4±11.4	67.6±12	63±7.7	67±7.8	25±3.4	28±4.4	48.3±9.4	54.8±11.3
	$P_1 < 0{,}001$ $t_{10} = 4{,}56$		$P_1 < 0{,}01$ $t_7 = 3{,}83$						$P_2 < 0.05$ $t_6 = 2.30$	$P_2 < 0.05$ $t_7 = 2.18$		
	$P_2 < 0{,}05$ $t_{10} = 1{,}95$											
SHR n = 6	54.7±2.8	88.5±6.9	63.9±3.4	97.9±7.7	76.1±5.4	90.8±3	71.3±2.9	87.2±2.8	20.8±2.4	35.6±6.2	21.9±3	32±4.1
	$P_1 < 0.001$ $t_7 = 4.54$		$P_1 < 0.003$ $t_7 = 4.04$		$P_1 < 0.02$ $t_8 = 2.38$		$P_1 < 0.002$ $t_{10} = 3.94$		$P_1 < 0.05$ $t_6 = 2.27$		$P_1 < 0.05$ $t_{10} = 2.15$	
	$P_2 < 0.05$ $t_{10} = 2.09$											
			$P_3 < 0.01$ $t_{10} = 3.36$		$P_3 < 0.05$ $t_{10} = 1.92$						$P_3 < 0.02$ $t_6 = 2.68$	

P_1, significance of differences between responses in cervical and in renal sympathetic nerves separate for each group, WKY rats and SHR.
P_2, significance of differences between responses produced in inspiration and in expiration separate for each group, WKY rats and SHR.
P_3, significance of differences between responses in WKY rats and in SHR recorded either in inspiration or in expiration for each group. Differences not-significant ($P > 0.05$) are not presented.

DISCUSSION

Somatosympathetic responses produced in the cervical and in renal sympathetic nerves by the stimulation of cutaneous somatic myelinated group II and III afferents are of long latency and mediated by long-circuited, late supraspinal component of the reflex discharge. This finding is consistent with the results of Nosaka et al. (1980) who observed only late, supraspinal component of reflex discharge in the splanchnic nerve by stimulation of sural nerve afferents in the rat. Early, spinal component of about 9 ms latency could be produced only by stimulating the afferents in the intercostal nerve on the respective segmental level (12). Both those and present data indicate some interesting species difference in the organization of somatosympathetic reflexes in the rat as compared to the cat. In the latter, an early spinal reflex discharge component may be elicited by stimulation of remote limb afferents and appears before the late, supraspinal discharge (7, cf. ref. 16). In the rat, a spinal organization is restricted to segmental inputs as the stimulation of remote somatic afferents produces only a generalized, non-segmental supraspinal somato-sympathetic reflex discharge.

The longer latency of the evoked response in the renal than in the cervical sympathetic nerve is apparently due to a longer spinal descending pathway from the medulla to preganglionic sympathetic neurons. Some minor contribution of the ganglionic transmission may also account for a longer delay of the response in the postganglionic renal nerve than in the preganglionic cervical trunk. Conduction velocities in both nerves do not differ, however, as in the rat the preganglionic cervical sympathetic nerve contains mainly non-myelinated preganglionic C-fibers (6, 13). If ganglionic transmission to renal nerve is ignored, then 33 ms difference in latency could be used to calculate an approximatively estimated conduction velocity in the spinal pathway defined as between segment T_1 and T_{12}, the latter being a major orgin of preganglionic neurons for paravertebral ganglion cells supplying renal nerve (5, 18). The value calculated in this way is in the range of 2 m/s, not very much dissimilar from a mean value 5.5 m/s characterizing spinal pathway of the somatosympathetic reflex (20) or 1.6-7.9 m/s range of conduction velocity within the bulbospinal excitatory pathways (2) in the cat.

Spontaneous sympathetic activity varied over the respiratory cycle with an inspiratory-related depression and an early expiratory discharge in normotensive WKY rats. On the contrary, in SHRs, the pattern was characterized by a late inspiratory peak of sympathetic discharge and an early expiratory inhibition. This species-and strain-specific dif-

ference is consistent with our previous results (3, 4) which showed an opposite timing of respiratory-related synchronization of the sympathetic activity in the rat as compared with the cat and also a difference between SHR and WKY strains of Wistar rats. Along with oscillations of the spontaneous sympathetic activity, also the reflex responsiveness varied respectively over the respiratory cycle in WKY rats. A significant shortening of the reflex latency, and an increase in amplitude of the reflex response during expiration, as compared to inspiratory phase, suggest that augmented expiratory-related spontaneous discharge facilitates neuronal pathways mediating somatosympathetic reflex. This conclusion is supported by the findings that neuronal population in the rostral ventrolateral medulla, an area responsible for the descending tonic drive to sympathetic spinal preganglionic neurons in the rat (19, cf. ref. 1), mediates the somatosympathetic reflex response (11, 21). One can assume that neurons active in expiration, and responsible for augmented spontaneous sympathetic discharge, excite some otherwise silent units yet the excitation is below firing threshold. If another convergent excitatory input arrives from somatic afferents, sympathoexcitatory neurons will fire and consequently a componud somatosympathetic reflex discharge will be augmented and of shorter latency in expiration than in inspiration. The timing of the reflex responsiveness is species-specific for the rat, as it is opposite to the pattern described in cats (cf. ref. 9, 10).

Respiratory-related modulation of the somatosympathetic reflex responsiveness appeared to be less pronounced in hypertensive than in normotensive rats. Only in the sympathetic cervical trunk, but not in the renal nerve, a shortening of the reflex latency was observed during inspiration as compared to expiratory time. Stimuli effective if applied during inspiration were sub-threshold in early expiratory phase. The pattern of rhythmical fluctuations of reflex responsiveness in the cervical trunk in SHRs follows therefore an inverse pattern of the strain-specific timing of the respiratory modulation of the spontaneous sympathetic activity characterizing SHRs. However, no respiratory-related modulation of the reflex responsiveness appeared in the renal nerve despite of strong, previously observed (4) respiratory synchronization of the spontaneous sympathetic activity in this nerve. The mechanism of reduced respiratory modulation of the somatosympathetic reflex in SHR as compared to WKY rats is obscure. One of the possible explanations may be an augmented over-all sympathetic tonic drive well known in SHRs (e.g. 8, 17). Such a tonic drive may continuously recruit some silent neurons and make it therefore more difficult to demonstrate any

rhythmical depression of reflex response. Some support to this interpretation provides our finding that the time duration of somatosympathetic reflex discharges elicited during inspiration is significantly greater in SHR that in WKY rat (Table I). A reduced amplitude of the somatosympathetic reflex response in the cervical nerve during expiration in SHRs as compared to normotensive rats (Table I) is not at variance with this explanation. One may assume that some neurons utilized by the central pathway of the somatosympathetic reflex are spontaneously active in expiration. If the spontaneous sympatho-excitatory drive is strong enough in expiration in SHRs, an occlusion mechanism may reduce the reflex response on the background of high tonic activity. In contrast, in inspiration a relative contribution of the tonic sympathetic drive versus respiratory related phasic excitation may be smaller thus any occlusion-dependent reduction of the reflex magnitude may be less pronounced (see Table I). Another, less probable, explanation may be that the reflex pathway utilized by the somatosympathetic reflex in SHR is different from that in WKY rats as it does not involve central sympathoexcitatory neurons modulated by rhythmical respiratory drive. The results of this study do not provide sufficient data to conclude on the mechanism involved. Further research is needed in order to identify central neuronal populations, controlled possibly by different subpopulations of respiratory neurons (15), and responsible for the respiratory-related modulation of the somatosympathetic reflex in normotensive rats and its attenuation in SHRs.

In conclusion, our results showed that in the rat a somatosympathetic reflex from limb skin afferents is a long circuited supraspinal response of late latency. In normotensive WKY rats reflex responsiveness, its latency and amplitude, is strongly modulated over the respiratory cycle along with respiratory synchronization of the spontaneous sympathetic activity. The temporal pattern of this modulation of reflex responsiveness is species-specific and opposite to the timing known in the cat. In spontaneously hypertensive rats (SHR) the respiratory modulation of the somatosympathetic reflex is attenuated, as compared to the WKY rat and appears only in the sympathetic cervical, but not in the renal nerve. The pattern of slight rhythmical modulation of the latency of somatosympathetic reflex response in SHRs is strain-specific, as it is different from the pattern characterizing WKY rats and follows a strain-specific respiratory-related synchronization of the spontaneous sympathetic activity typical for SHRs.

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