Pflügers Arch. 319, 162–184 (1970)

Antagonistic Changes of Blood Flow and Sympathetic Activity in Different Vascular Beds Following Central Thermal Stimulation

II. Cutaneous and Visceral Sympathetic Activity during Spinal Cord Heating and Cooling in Anesthetized Rabbits and Cats*

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Received May 26, 1970

Summary. In anesthetized rabbits and cats immobilized with succinyl choline, the discharges of sympathetic efferents supplying cutaneous and visceral regions were simultaneously recorded. The effect of thermal stimulation of the spinal cord on regional sympathetic activity was tested on the basis of the integrated discharges.

During spinal cord heating cutaneous sympathetic activity decreased, while visceral sympathetic activity increased at the same time. During cooling the reverse reaction, i.e. increase of activity in cutaneous and decrease in visceral sympathetic efferents, was observed. This antagonistic behaviour of cutaneous and visceral efferent activity was found in all rabbits and in about half of the investigated cats.

The changes of cutaneous efferent activity were in keeping with the thermoregulatory changes of cutaneous blood flow following thermal stimulation of the spinal cord. The changes of visceral sympathetic activity offer an explanation for the adjustments of intestinal blood flow observed under the same central thermal stimulus.

It is suggested as a working hypothesis that the sympathetic nervous system may perform under special conditions a sort of "reciprocal innervation" of functionally antagonistic autonomic effector systems.

Key-Words: Temperature Regulation — Regional Sympathetic Activity — Vasomotor System.

Schlüsselwörter: Temperaturregulation — Regionale Sympathicusaktivität — Vasomotorisches System.

Antagonistic changes of blood flow in the vascular beds of the paw skin and of the intestine are evoked in dogs by thermal stimulation of the spinal cord (Kullmann *et al.*, 1970). These vascular responses correspond to the circulatory adjustments observed during external thermal

* A portion of this work was presented at the 37. Congress of the Deutsche Physiologische Gesellschaft, 10.–11. April 1970 [Pflügers Arch. **316**, R 26 (1970)].

stimulation (Rein, 1931; Grayson, 1949). This supports the conception that thermal stimuli applied to the spinal cord act upon thermosensitive structures providing a specific input for the thermoregulatory control system (Simon, 1967).

The antagonistic changes of blood flow observed during spinal cord heating and cooling do not allow definite conclusions about the mode of their central nervous control. However, they strongly suggest that an antagonistic change of vasomotor activity in the corresponding sympathetic efferents is the underlying event. A direct proof for this ability of the vasomotor system does not seem to exist. Therefore, in the present investigation the attempt was made to demonstrate in cutaneous and visceral sympathetic efferents these antagonistic changes of activity presumably governing the thermoregulatory blood flow adjustments. Spinal cord heating and cooling were regarded as the most appropriate thermal stimuli to evoke the desired responses, because the antagonistic changes of cutaneous and intestinal blood flow, especially during spinal cord heating, are distinct and occur quickly.

It seemed to be a further prerequisite for a successful investigation to record sympathetic activity from efferents supplying a skin area specifically designed for thermoregulatory changes of blood flow. According to Ström (1960), this holds true for the rabbit's ear. In the present investigation sympathetic activity could be recorded from a fine periarterial nerve strand accompanying the A. auric. post. in the rabbit. In a first series of experiments in rabbits, the discharges of this nerve were recorded together with ear temperature and were compared with the activity in a branch of the splanchnic nerve. In a second series of experiments performed in cats, the discharges of postganglionic fibers running from the superior cervical ganglion to the 1st or 2nd cervical nerves were compared with those of the spleen sympathetic. The skin areas supplied by the sympathetic portions of these cervical nerves are not so specifically designed for thermoregulatory demands in the cat, as it is the case in the rabbit's ear.

Material and Methods

The present investigations were performed in 10 albino rabbits weighing 2.0—3.1 kg and in 23 cats weighing 1.8—3.5 kg; the experiments were carried out from Jan. 1969 to Jan. 1970. The animals were anesthetized with sodium pentobarbital; the initial doses were in cats 30 mg/kg i.p. + 10 mg/kg i.m. and in rabbits 40 mg/kg i.p. + 10—20 mg/kg i.m. Eventually an additional dose of 10—20 mg/kg had to be injected after some hours. A continuous infusion of succinyl choline (0.1—0.2 mg/kg/min) prevented shivering during spinal cord cooling and disturbances by reflex movements. The animals were artificially ventilated with air (300 to 400 ml/kg/min) by means of a Starling pump.

Surgical Procedures. A Y-shaped tube was inserted into the trachea for artificial respiration. The vertebral canal was opened between the last lumbar vertebra and

the sacral bone, and a double-barreled thermode of polyethylene tubing (in cats pp. 90, in rabbits pp. 30, Portex Ltd.) was inserted into the peridural space. Its U-shaped end was carefully pushed in the cranial direction up to the lower cervical vertebrae. The position of the thermode's end was controlled after the experiment. A single-barreled, blind ending tube was placed into the peridural space containing a thermistor probe for temperature measurement. One femoral vein was cannulated for the intravenous infusion of succinyl choline. For arterial blood pressure recording a catheter was inserted into one femoral artery. Blood clotting in the catheter was prevented by continuous low volume flushing.

Preparation of "Cutaneous" and "Visceral" Sympathetic Efferents. The animals were placed on their right sides. The nerve strands to be investigated were surgically exposed. The final preparation was carried out in a paraffin pool under visual control by means of an operation microscope (Zeiss, U 1). After the nerve strands had been dissected free they were placed on fine stainless steel hooks for bipolar recording. In the *rabbit* a fine periarterial nerve twig accompanying the A. auric. post. was prepared at the proximal third of the left ear pinna. This nerve branch, which will be described in detail elsewhere (Walther and Iriki, to be published), carried postganglionic sympathetic fibers to the skin of the ear and thus represented a "cutaneous" sympathetic efferent. A branch of the left splanchic nerve was prepared extraperitoneally just below the diaphragm as a "visceral" sympathetic efferent. In the *cat* postganglionic nerve strands emerging from the superior cervical ganglion as verified by visual control were dissected free just before they fused with the 1st or 2nd cervical nerves. These nerve strands must be regarded as mainly but not exclusively consisting of "cutaneous" sympathetic efferents, which supply a skin area at the head, ear and neck (Reighard and Jennings, 1951). Only those preparations were further investigated in which a test period of spinal cord cooling had increased the discharge of the nerve strand, according to the expected cutaneous vasoconstriction. This response was missed in 5 out of 23 animals. The splenic nerve was chosen as the corresponding "visceral" sympathetic efferent. After the abdominal cavity had been opened and the hilus of the spleen had been brought into an easily accessible position, the nerve was dissected free. Some difficulties arose from the need of permanent paraffin coverage. The abdominal cavity had to be filled more or less completely with paraffin, which meant a mechanical disturbance of respiration and of circulation.

Several controls—at least one but mostly two or more in each experiment—ensured that sympathetic activity was recorded. These controls concerned the presence of respiratory and cardiac rhythmicity in the discharge and the responses to pain stimuli, to supramaximal electric stimulation of the ischiadic nerve and to asphyxia. Similar responses, only with minor variations in quantity and time course, were observed in the nerve branches under investigation. The only one exception was the asphyctic response of the ear sympathetic in the rabbit. Here, the increase of activity during asphyxia and the postasphyctic inhibition were, in general, not observed. This finding corresponds, however, well with the special response of ear blood flow in the rabbit during asphyxia (Dastre and Morat, 1884; Chalmers and Korner, 1966) and will be discussed elsewhere (Iriki *et al.*, to be published). In the cutaneous efferents activity was completely abolished by selective preganglionic transection of the cervical sympathetic trunk, while transections of the ear sympathetic and of the splanchnic nerve branches distally from the recording points did not alter the responses to thermal and asphyctic stimulation.

Measurements and Recordings. The discharges of the cutaneous and visceral sympathetic efferents were simultaneously recorded. The potentials were fed into two differential amplifiers with impedance-matched outputs (Tönnies, No. 0329).

The amplified signals were a) recorded and b) unidirectionally integrated over intervalls of 2; 5 or 10 sec by means of a 2-channel "amplitude adder" (Tönnies, No. M 8). Since a constant amount of statistical noise was integrated together with the signals, no attempt for calibration was made and only changes of integrated activity were recognized. Arterial pressure was picked up with a pressure transducer (Statham, P 23a), which was adapted to a carrier amplifier (Tektronix, 3 C 66). Temperatures of the vertebral canal, of the rectum and—in rabbits—of both ears were measured by means of NTC miniature-thermistor probes. Sympathetic discharges and the integrated activities were recorded together with blood pressure and body temperatures on a UV-direct writing oscillograph (CEC, Galvomat). Air temperature was controlled with an electric thermometer (Ellab, Kopenhagen).

Experimental Procedures. At constant ambient air temperatures of 24—27° C, the animals were placed on a heating pad, which was perfused with water of 39 to 40° C to maintain normal body temperature. The thermode situated in the thoracolumbar peridural space was continuously perfused with water at a constant flow between 10 and 50 ml/min in cats and 10 to 15 ml/min in rabbits (method see Kosaka *et al.*, 1969). Heating and cooling was performed, in general, during 3 min by changing the perfusion temperature from neutral to hot or cold. The average intensity of heating and cooling corresponded to vertebral canal temperatures between 30.7° C and 40.5° C in rabbits and 29.1° C and 42.2° C in cats. In every experimental period the responses of the animals were observed during a pre-stimulation phase of 3 min, the stimulation phase of 3 min and two post-stimulation phases of 3 min each, the total duration of the experimental period being 12 min.

Calculations and Statistics. Mean activity of the cutaneous and visceral sympathetic efferents during the single experimental phases was determined from the integrated activity by calculating the average amplitude of the integrator deflections. The first 30 sec of each phase were excluded from the calculations, since vertebral canal temperatures changed rapidly at this time after the start and the end of thermal stimulation. Arterial blood pressure was evaluated from the recordings in 1 min-distances during the pre- and post-stimulation phases and every 30 sec during the stimulation phases. Mean pressure was calculated as $p_{\text{diast.}} + (p_{\text{syst.}} - p_{\text{diast.}}) \times 0.3$. Heart rates could be evaluated from the blood pressure recordings only, if a paper speed greater than 8.5 cm/min had been selected. The temperatures recorded in the experiments were numerically determined every minute.—For statistical calculations, one of the various cooling and/or heating periods performed in each animal was randomly selected. From these periods, the average reponses with standard deviations of mean values were calculated for the different samples of experiments: rabbits and cats—heating and cooling. The statistical significance of the changes of the various parameters during the stimulation phases, as compared with the pre- and post-stimulation phases, was controlled with the Wilcoxon matched-pairs signed-ranks test.

Results

Experiments in Rabbits

The cutaneous sympathetic nerve strand investigated in this series of experiments supplies a skin area which is known to be of special importance for the vasomotor control of heat loss. The discharges of this nerve and of a branch of the splanchnic nerve during spinal cord heating and cooling are demonstrated in Fig. 1. Their integrated activities, arterial pressure and vertebral canal and ear skin temperatures are additionally

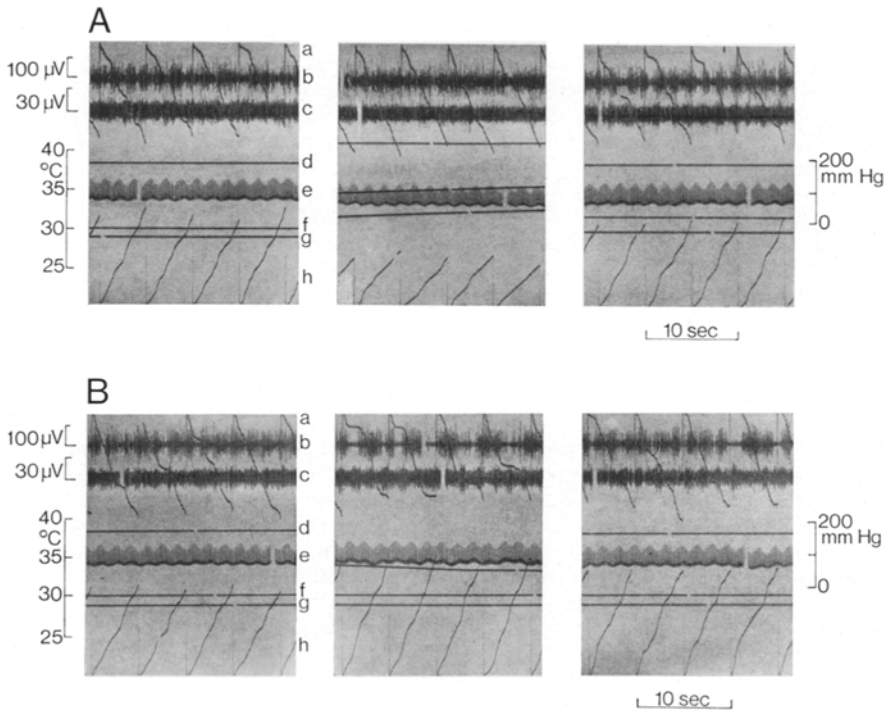

Fig. 1. Regional sympathetic activity in an anesthetized, paralyzed rabbit before (left), during (middle) and after (right) selective heating (*A*) and cooling (*B*) of the spinal cord. Sections from original recordings; *a* integrated discharges of visceral (splanchnic branch) sympathetic; *b* discharges of visceral (splanchnic branch) sympathetic; *c* discharges of cutaneous (ear) sympathetic; *d* vertebral canal temperature; *e* arterial pressure; *f* skin temperature of right ear; *g* skin temperature of left ear; *h* integrated discharges of cutaneous (ear) sympathetic

shown. During selective spinal cord heating (Fig. 1 A), a decrease of activity in the cutaneous sympathetic efferent became obvious in both the discharge recording and the deflections of the integrator signal. Rhythmic changes of activity synchronized with the respiratory cycles were observed eventually during the pre- and post-heating phases but disappeared almost completely with the waning acitivity during heating. In the visceral sympathetic efferent, activity increased during heating. Bursts of discharge synchronized with pulse and with respiration could be observed during all phases of the experiment but seemed to be superimposed during heating by additional discharges. After the end of heating the activities in both sympathetic efferents changed towards their pre-heating levels.—Antagonistic changes of activity in the cuta-

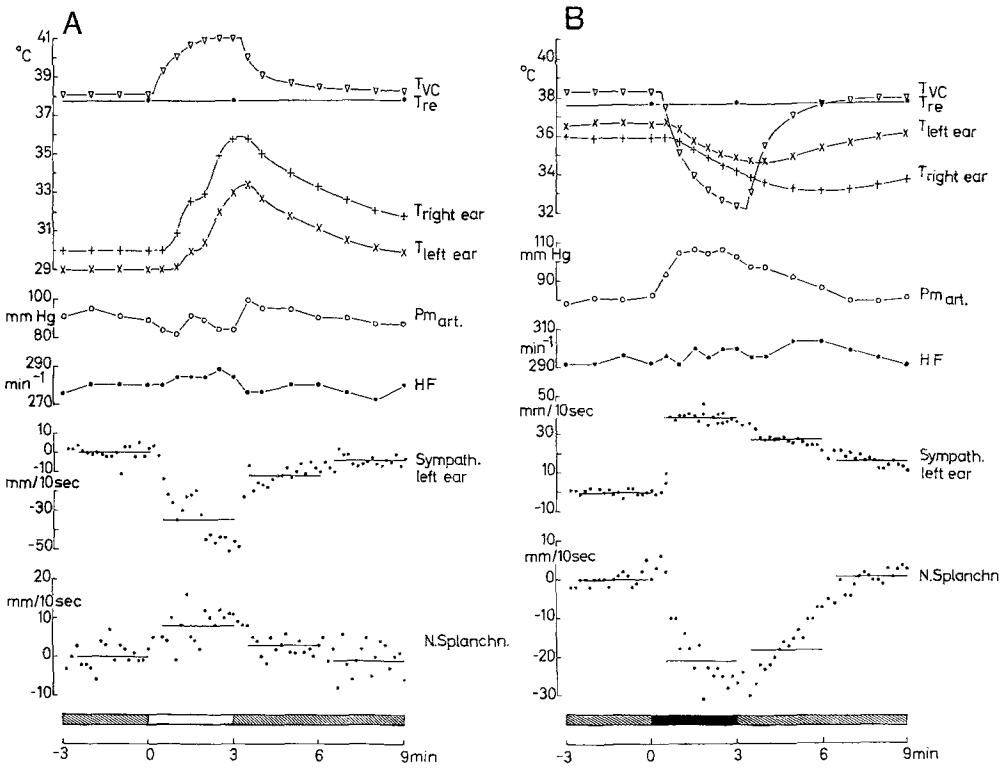

Fig. 2. Courses of regional sympathetic activity and of ear temperatures in two (*A* and *B*) anesthetized, paralyzed rabbits during experimental periods of spinal cord heating (*A* white bar) and cooling (*B* black bar). The integrated discharges per 10 sec and the mean discharge levels of the diverse experimental phases are plotted against time, reference values: mean discharge levels of the pre-stimulation phases; T_{re}: rectal temperature; T_{VC}: vertebral canal temperature; P_m art.: arterial mean pressure; *HF*: heart rate

neous and visceral sympathetic efferents, now of opposite directions, were observed during spinal cord cooling in the same animal (Fig. 1 B). A slight but significant increase of activity occurred in the cutaneous sympathetic efferent. At the same time, the activity of the visceral efferent decreased definitely. The activities of both efferents changed towards their pre-stimulation levels after cooling had been stopped. In both recordings, rhythmic changes of activity synchronized with respiration and pulse pressure were observed in all phases of this experimental period.

The courses of activity in the cutaneous and visceral sympathetic efferents during spinal cord heating and cooling are demonstrated in

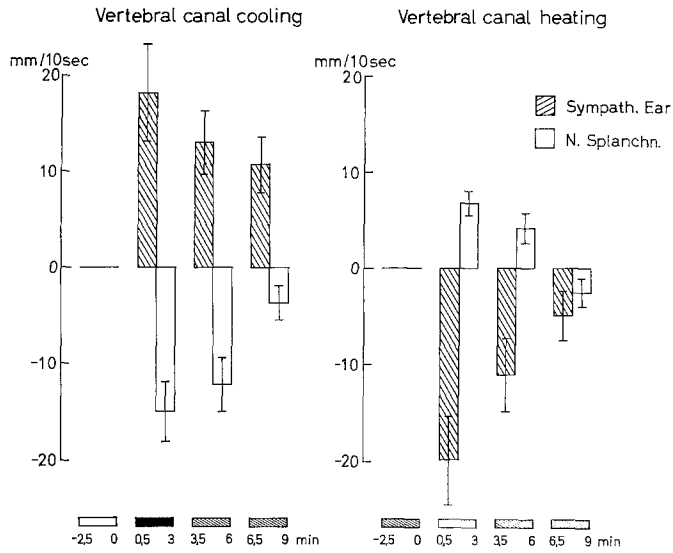

Fig. 3. Regional sympathetic activity during thermal stimulation of the spinal cord in anesthetized, paralyzed rabbits; average responses of 10 animals to spinal cord cooling (black bar) and heating (white bar). Columns: mean integrated discharges with standard deviations of mean values during the diverse experimental phases of cutaneous (hatched) and visceral (white) sympathetic efferents, reference values; mean integrated discharge levels during the pre-stimulation phases

Fig. 2 on the basis of the integrated discharges. The differences between the average integrated activity of the pre-stimulation phase, which was chosen as the reference activity, and the single integrator deflections were plotted for every 10-sec intervall. The experimental periods shown in this figure were selected to demonstrate the correlation between the cutaneous sympathetic activity and the ear skin temperatures indicating cutaneous blood flow. Apparently, ear blood flow changed in conformity with the cutaneous sympathetic activity indicating that the level of discharge in the investigated nerve strand represented the state of the total vasoconstrictor input to the ear skin vessels. In both periods the changes of visceral sympathetic activity induced by the thermal stimuli were opposite to those in the cutaneous efferents. Arterial blood pressure was not substantially affected by spinal cord heating and showed a moderate increase during spinal cord cooling.

From the cooling and heating periods performed in each of the 10 experimental animals, one heating and one cooling period per animal were randomly selected to calculate the average reactions of the parameters measured in this series of experiments. Fig. 3 shows the mean changes

of activity in the cutaneous and visceral sympathetic efferents during the stimulation and post-stimulation phases as compared with the pre-stimulation activity. The antagonistic behaviour of these efferents proved to be statistically significant during heating and cooling (Table 1), although the pre-stimulation level of activity had not been reached

Table 1. *Changes of regional sympathetic activity during thermal stimulation of the spinal cord; average responses obtained from 10 heating and 10 cooling periods in 10 anesthetized, paralyzed rabbits. Mean values of the diverse experimental phases ($\bar{X}$), as compared with pre-stimulation activity, and standard deviations of mean values ($s_{\bar{X}}$); data significantly different: (a) from the level of activity during the pre-stimulation phase, (b) during the stimulation phase ($p < 0.05$, Wilcoxon matched-pairs signed-ranks test)*

		Integrated activity—in mm/10 sec—as compared with mean pre-stimulation activity			
		Pre-stimul.	Stimul.	Post-stimul. I.	Post-stimul. II.
	min	−2.5—0	0.5—3.0	3.5—6.0	6.5—9.0
Heating ($n = 10$)					
Cutaneous sympathetic efferent	$\bar{X}$	0	−19.9 (a)	−11.1 (b)	−4.9 (b)
	$s_{\bar{X}}$		4.6	3.8	2.6
Visceral sympathetic efferent	$\bar{X}$	0	+6.8 (a)	+4.2	−2.5 (b)
	$s_{\bar{X}}$		1.3	1.6	1.7
Cooling ($n = 10$)					
Cutaneous sympathetic efferent	$\bar{X}$	0	+18.1 (a)	+13.0 (b)	+10.7 (b)
	$s_{\bar{X}}$		5.0	3.3	2.9
Visceral sympathetic efferent	$\bar{X}$	0	−15.0 (a)	−12.2	−3.7 (b)
	$s_{\bar{X}}$		3.1	2.8	1.8

completely after 6 min in the cutaneous efferents. Some experiments with prolonged observations showed that this happened after 8—9 min. The statistical results only reflect the responses observed in the total of heating and cooling periods. Among 34 cooling periods no one failed to show the antagonistic behaviour of the cutaneous and visceral efferents. In 30 heating periods a non-antagonistic response was observed on only one occasion.

The remaining parameters measured in this series of experiments are summarized in Table 2 on the basis of randomly selected experimental periods. The changes of ear temperature shown in Fig. 2 could not be observed in every case, especially in the operated left ear, since the ear vessels were compressed sometimes by the device used to maintain the paraffin pool. A fall of ear temperature during spinal cord cooling could not be expected in those cases in which the vasoconstrictor tone was

Table 2. *Changes of temperatures and of arterial mean pressure and heart rate during thermal stimulation (3 min duration) of the spinal cord at different times of the experimental periods; average results of the same experiments as in Table 1. Mean values ($\bar{X}$) and standard deviations of mean values ($s_{\bar{X}}$); data significantly different: (a) from the values at the start and (b) from the values at the end of thermal stimulation ($p < 0.05$, Wilcoxon matched-pairs signed-ranks test)*

			Time after start of thermal stimulation (min)				
			0	1	3	6	9
Heating: perfusion temp. $\bar{X} = 49.50$; $s_{\bar{X}} = 0.30$ °C	n						
Rectal temp. (°C)	10	$\bar{X}$	37.70	—	37.70	—	—
		$s_{\bar{X}}$	0.20		0.20		
Vertebral canal temp. (°C)	10	$\bar{X}$	37.80	39.80	40.50	38.20	38.00
		$s_{\bar{X}}$	0.10	0.30	0.30	0.10	0.10
Temp. left ear (°C)	10	$\bar{X}$	30.70	30.90	31.50 (a)	31.40	31.10 (b)
		$s_{\bar{X}}$	1.20	1.20	1.30	1.20	1.20
Temp. right ear (°C)	10	$\bar{X}$	30.30	31.10 (a)	32.20 (a)	31.60	31.10 (b)
		$s_{\bar{X}}$	0.90	0.90	1.00	1.00	0.90
Arterial pressure (mm Hg)	10	$\bar{X}$	88.4	88.6	85.9	88.9	88.9
		$s_{\bar{X}}$	2.0	2.6	1.8	2.8	2.8
Heart rate (min^{-1})	10	$\bar{X}$	246	247	247	250	250
		$s_{\bar{X}}$	8.0	8.8	8.6	8.1	7.9
Cooling: perfusion temp. $\bar{X} = 10.50$; $s_{\bar{X}} = 0.00$ °C	n						
Rectal temp. (°C)	10	$\bar{X}$	37.80	—	37.80	—	—
		$s_{\bar{X}}$	0.10		0.15		
Vertebral canal temp. (°C)	10	$\bar{X}$	37.90	33.30	30.70	37.20	37.60
		$s_{\bar{X}}$	0.10	0.60	0.70	0.20	0.10
Temp. left ear (°C)	10	$\bar{X}$	29.60	29.50	29.10	29.00	29.10
		$s_{\bar{X}}$	1.00	1.00	0.70	0.80	0.90
Temp. right ear (°C)	10	$\bar{X}$	29.90	29.80	29.40 (a)	29.30	29.30
		$s_{\bar{X}}$	0.50	0.60	0.50	0.40	0.50
Arterial pressure (mm Hg)	10	$\bar{X}$	90.4	98.9 (a)	98.1 (a)	91.7 (b)	90.0 (b)
		$s_{\bar{X}}$	3.5	3.7	4.6	5.1	5.5
Heart rate (min^{-1})	10	$\bar{X}$	252	251	249	250	253
		$s_{\bar{X}}$	6.1	6.0	5.3	6.2	6.1

already high during the pre-cooling phase, i.e. if the ear temperatures were low (see Fig. 1 B). A slight increase of blood pressure was observed during spinal cord cooling. Heart rate did not change, on the average, during either heating or cooling.

Experiments in Cats

This second series of experiments was performed to demonstrate antagonistic responses of the sympathetic system to spinal thermal stimulation in animals of another species. It was of special interest to confirm this for the feline sympathetic system, which has preferably been investigated in numerous experiments. Some drawbacks mainly concerning the deteriorating influence of opening the abdominal cavity had to be put up with the experiments in cats, as mentioned above. Nevertheless, antagonistic responses of cutaneous and visceral sympathetic efferents to thermal stimulation of the spinal cord were observed, although not with the same regularity as in rabbits. Fig. 4 shows sections of recordings from a cervical postganglionic branch to the 2nd cervical nerve and from the spleen sympathetic during periods of spinal cord heating and cooling together with arterial pressure and rectal and vertebral canal temperatures. During heating—in the demonstrated case (Fig. 4 A) especially during the early phase—very prominent antagonistic changes of activity occurred. Cutaneous efferent discharge had almost completely vanished at this time; it increased during the subsequent part of the heating phase but remained below the discharge level of the pre-heating phase. Visceral sympathetic activity increased during heating. The rhythmic discharges were replaced or superimposed by a more tonic type of activity. After heating had been stopped, the discharges of both efferents gradually approached their pre-heating levels. Blood pressure dropped immediately after the start of heating but later on rose again towards its previous value. Antagonistic changes of activity in the investigated efferents, now of opposite directions, occurred during spinal cord cooling (Fig. 4 B). The distinct increase of activity in the cervical branch was accompanied by a slight decrease in the spleen sympathetic, both returning to their pre-cooling levels during the post-cooling phase. Blood pressure changed only slightly during cooling.

The courses of activity changes in cutaneous and visceral sympathetic efferents are demonstrated in Fig. 5 on the basis of the integrated discharges recorded during spinal cord heating and cooling in the same animal. The antagonistic behaviour of the investigated efferents was obvious throughout the cooling and heating phases. The graphs further illustrate the finding that the time courses of the responses could differ from case to case and between the visceral and cutaneous sympathetic.

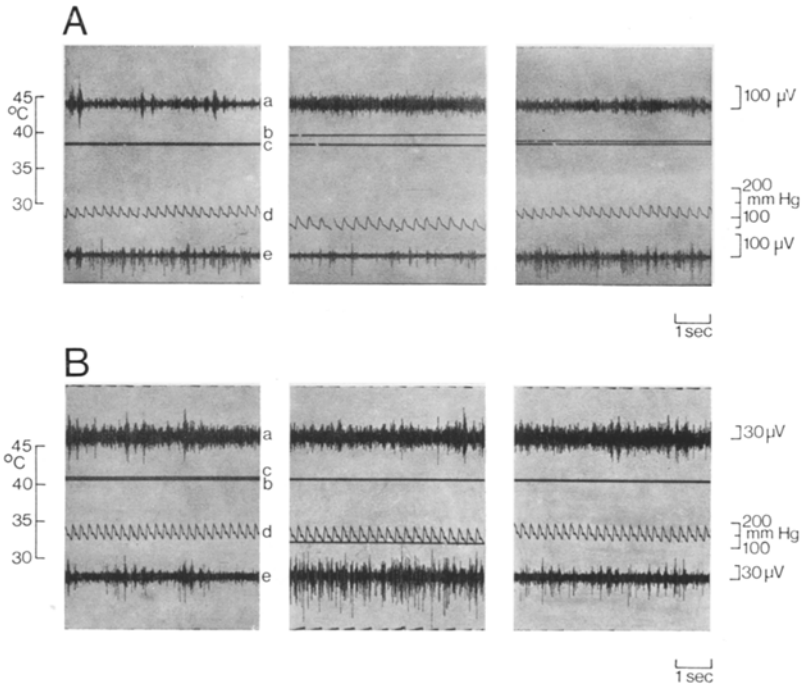

Fig. 4. Regional sympathetic activity in two (*A* and *B*) anesthetized, paralyzed cats before (left), during (middle) and after (right) selective heating (*A*) and cooling (*B*) of the spinal cord. Sections from original recordings; *a* discharges of visceral (spleen) sympathetic; *b* vertebral canal temperature; *c* rectal temperature; *d* arterial pressure; *e* discharges of cutaneous (branch to N. cerv. II) sympathetic

Sometimes, the readjustments of activity during the post-stimulation phase occurred with a temporary overshoot.

During spinal cord heating antagonistic changes of activity in cutaneous and visceral sympathetic efferents were observed only in 3 out of 8 investigated animals. High perfusion temperatures of 48—53°C corresponding to a recorded maximum vertebral canal temperature of 42.8°C had to be applied to evoke the responses. Weaker heating was without effect in the same animals. In the remaining 5 animals, which did not show the antagonistic response, the reaction to heating consisted in a uniform depression of activity in cutaneous and visceral efferents.— In contrast to this finding, the majority of the animals, 13 out of 18 cats, showed an antagonistic response to spinal cord cooling. In the remaining 5 animals the discharges of both efferents increased uniformly during cooling. Application of various degrees of cooling did not influence the direction of this response. The two types of reactions to thermal stimu-

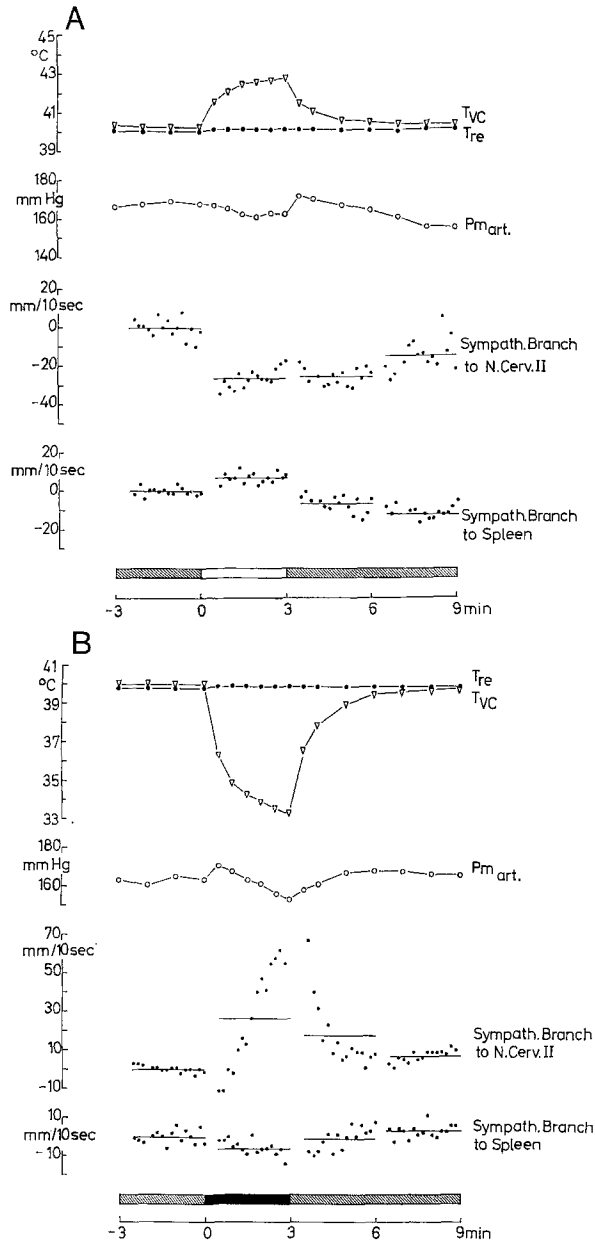

Fig. 5. Courses of regional sympathetic activity in an anesthetized, paralyzed cat during experimental periods of spinal cord heating (*A* white bar) and cooling (*B* black bar). The integrated discharges per 10 sec and the mean discharge levels of the diverse experimental phases are plotted against time, reference values: mean discharge levels of the pre-stimulation phases; T_{re} rectal temperature; T_{VC} vertebral canal temperature; P_m art.: arterial mean pressure

Table 3. *Changes of regional sympathetic activity during thermal stimulation of the spinal cord; average responses obtained from antagonistically (3 heating and 13 cooling periods) and uniformly (5 heating and 5 cooling periods) responding anesthetized, paralyzed cats. Mean values of the diverse experimental phases ($\bar{X}$), as compared with pre-stimulation activity, and standard deviations of mean values ($s_{\bar{X}}$); data significantly different from the level of activity during the stimulation phase (b) ($p < 0.05$, Wilcoxon matched-pairs signed-ranks test)*

		Integrated activity—in mm/10 sec—as compared with mean pre-stimulation activity			
		Pre-stimul.	Stimul.	Post-stimul. I.	Post-stimul. II.
	min	−2.5—0	0.5—3.0	3.5—6.0	6.5—9.0
		Antagonistic response			
Heating ($n = 3$)					
Cutaneous sympathetic efferent	$\bar{X}$	0	− 23.5	− 16.3	− 7.4
	$s_{\bar{X}}$		7.7	6.3	3.6
Visceral sympathetic efferent	$\bar{X}$	0	+ 3.0	+ 2.9	+ 2.1
	$s_{\bar{X}}$		1.9	7.7	7.3
Cooling ($n = 13$)					
Cutaneous sympathetic efferent	$\bar{X}$	0	+ 19.4	+ 2.2 (b)	+ 6.7 (b)
	$s_{\bar{X}}$		4.1	5.4	3.3
Visceral sympathetic efferent	$\bar{X}$	0	− 8.4	− 5.4	+ 2.3 (b)
	$s_{\bar{X}}$		2.4	3.5	1.8
		Uniform response			
Heating ($n = 5$)					
Cutaneous sympathetic efferent	$\bar{X}$	0	− 14.1	− 1.0	− 3.3
	$s_{\bar{X}}$		8.7	6.5	8.0
Visceral sympathetic efferent	$\bar{X}$	0	− 15.1	− 6.4	− 1.1
	$s_{\bar{X}}$		4.2	4.0	2.7
Cooling ($n = 5$)					
Cutaneous sympathetic efferent	$\bar{X}$	0	+ 10.9	+ 4.0	+ 1.7
	$s_{\bar{X}}$		4.7	2.1	3.0
Visceral sympathetic efferent	$\bar{X}$	0	+ 9.8	+ 12.1	+ 9.2
	$s_{\bar{X}}$		3.6	4.7	5.7

lation of the spinal cord are compared in Table 3 on the basis of stimulation periods randomly selected for each experiment.

Differences of the level of arterial pressure and of the time courses of its changes were observed between the animals responding antagonistically and uniformly to thermal stimulation of the spinal cord. These differences gave the impression that the regulatory performance of the

uniformly responding animals was impaired. As is shown in Table 4, the uniformly responding animals had, on the average, a lower blood pressure. During heating, these animals showed a permanent depression of arterial pressure, while in the antagonistically responding animals blood pressure fell during the early phase of heating and then rose again halfway towards the pre-heating level. A similar but more distinct observation was made during spinal cord cooling. As is shown in Fig. 6, the adjustment of arterial pressure during and after cooling seems to have occurred more quickly and more pronounced in the animals showing the antagonistic response of cutaneous and visceral sympathetic efferents.

Discussion

Antagonistic Changes in Sympathetic Efferents

The present investigation has shown that the discharge activities recorded from sympathetic efferents supplying cutaneous and visceral regions may change antagonistically. As pointed out above, the origin of the investigated nerve fibers from the sympathetic nervous system could be deduced from the discharge pattern and from the various tests performed in the experiments. With special respect to the splanchnic branches investigated in rabbits, control experiments with transections of the nerve strands distally from the recording points had ensured that possible abdominal pressoreceptor afferents as discussed, for instance, by Sarnoff and Yamada (1959) or other afferents did not produce the response. As to the spleen sympathetic investigated in the cats, the contribution of vagal efferents to the responses is excluded on the basis of the investigations of Utterback (1944) and of Greenway *et al.* (1968) and by own control experiments with vagus transection.

Cutaneous sympathetic activity responded to thermal stimulation of the spinal cord in a way which could be expected from previous observations on cutaneous blood flow (Simon *et al.*, 1963; Jessen *et al.*, 1967; Iriki, 1968; Rautenberg, 1969), if it was assumed that vasodilatation corresponded to decreased and vasoconstriction to increased vasomotor activity. This was confirmed directly in the investigations in rabbits. The efferent nerve recordings have given, so far, no support for the participation of vasodilatatory efferents in the cutaneous vascular response of the rabbit's ear. While the findings in cutaneous sympathetic efferents of both rabbits and cats were thus entirely in keeping with the prevailing conception of thermally induced cutaneous vascular responses, the present investigation has for the first time furnished direct evidence that simultaneous changes of activity antagonistic to those in the cutaneous efferents are induced in other sections of the sympathetic system

Table 4. *Changes of temperatures and of arterial mean pressure and heart rate during thermal stimulation (3 min duration) of the spinal cord at different times of the experimental periods; average results of the same experiments as in Table 3. Mean values ($\bar{X}$) and standard deviations of mean values ($s_{\bar{X}}$); data significantly different: (a) from the values at the start and (b) from the values at the end of thermal stimulation ($p<0.05$, Wilcoxon matched-pairs signed-ranks test)*

			Time after start of thermal stimulation (min)				
			0	1	3	6	9
			Antagonistic response				
Heating: perfusion temp. $\bar{X} = 49.67$; $s_{\bar{X}} = 0.88$ °C	n						
Rectal temp. (°C)	3	$\bar{X}$	39.23	—	39.27	—	39.27
		$s_{\bar{X}}$	0.44		0.47		0.48
Vertebral canal temp. (°C)	3	$\bar{X}$	39.30	40.63	41.47	39.67	39.50
		$s_{\bar{X}}$	0.50	0.81	0.75	0.47	0.50
Arterial pressure (mm Hg)	3	$\bar{X}$	135.9	115.2	125.3	135.4	133.0
		$s_{\bar{X}}$	16.2	25.7	18.7	15.8	12.6
Cooling: perfusion temp. $\bar{X} = 10.97$; $s_{\bar{X}} = 0.76$ °C	n						
Rectal temp. (°C)	13	$\bar{X}$	38.16	—	38.16	—	38.17
		$s_{\bar{X}}$	0.23		0.23		0.23
Vertebral canal temp. (°C)	13	$\bar{X}$	38.86	31.69	29.14	37.97	38.48
		$s_{\bar{X}}$	0.16	0.92	0.91	0.19	0.17
Arterial pressure (mm Hg)	13	$\bar{X}$	124.0	129.6 (a)	126.6	123.2	124.3
		$s_{\bar{X}}$	6.7	7.1	7.1	6.3	6.8
Heart rate (min^{-1})	10	$\bar{X}$	212	211	200 (a)	208	211
		$s_{\bar{X}}$	10.6	11.3	9.3	11.3	12.3
			Uniform response				
Heating: perfusion temp. $\bar{X} = 49.80$; $s_{\bar{X}} = 0.97$ °C	n						
Rectal temp. (°C)	5	$\bar{X}$	37.80	—	37.82	—	37.88
		$s_{\bar{X}}$	0.24		0.26		0.29
Vertebral canal temp. (°C)	5	$\bar{X}$	38.66	41.32	42.16	39.08	38.88
		$s_{\bar{X}}$	0.20	0.56	0.59	0.23	0.23
Arterial pressure (mm Hg)	5	$\bar{X}$	112.4	101.0	101.0	116.2	115.2
		$s_{\bar{X}}$	5.0	13.0	10.0	5.9	6.2

Table 4 (Continued)

			Time after start of thermal stimulation (min)				
			0	1	3	6	9
Cooling: perfusion temp. $\bar{X} = 18.46$; $s_{\bar{X}} = 3.50$ °C[a]	n						
Rectal temp. (°C)	5	$\bar{X}$	37.16	—	37.14	—	37.06
		$s_{\bar{X}}$	0.87		0.88		0.88
Vertebral canal temp. (°C)	5	$\bar{X}$	38.66	34.02	32.14	37.76	38.26
		$s_{\bar{X}}$	0.51	0.78	0.99	0.65	0.59
Arterial pressure (mm Hg)	5	$\bar{X}$	105.0	110.4	108.2	105.0	104.0
		$s_{\bar{X}}$	3.2	3.6	2.1	3.0	3.4
Heart rate (min^{-1})	3	$\bar{X}$	228	234	228	230	230
		$s_{\bar{X}}$	0.0	0.0	3.5	2.0	2.0

[a] The higher average perfusion temperature is due to the application of various degrees of cooling in the uniformly responding animals.

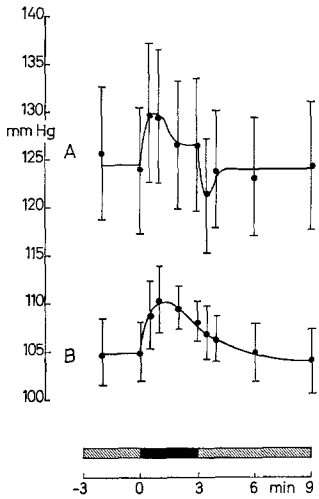

Fig. 6. Courses of arterial mean pressure during experimental periods of spinal cord cooling (black bar) in anesthetized, paralyzed cats. Mean values with standard deviations of mean values in 13 antagonistically (*A*) and 5 uniformly (*B*) responding animals

by the same stimulus. This result coincides with the observations of Kullmann *et al.* (1970) that antagonistic changes of blood flow in the cutaneous and intestinal vascular beds are induced by thermal stimulation of the spinal cord.

In cats, the antagonistic responses of cutaneous and visceral efferents could not be observed with the same regularity as in rabbits. This might be due to an impaired regulatory performance which was indicated by the course and the level of arterial pressure in the uniformly responding animals. As mentioned above, this might have been caused by the more severe surgical procedures and by the instillation of large amounts of paraffin oil in the abdominal cavity.—Finally, species differences between rabbits and cats must be taken into consideration.

Indirect Evidence for Antagonistic or Differentiated Responses of the Sympathetic Nervous System

As pointed out by Kullmann *et al.* (1970), effects of peripheral thermal stimulation on different vascular beds are reported in the literature which may be interpreted as indicating qualitatively differentiated regional responses of the sympathetic system. With respect to own observations on the control of palm and fore-arm blood flow in man, Barcroft (1960) concluded that the thermoregulatory responses of the skin vessels are not consistent with the idea of a "widespread diffuse action of the sympathetic system". Webb-Peploe (1969) investigated the responses of cutaneous and visceral capacity vessels to thermal stimulation and came to a similar conclusion in stating that there was "evidence that the neurons controlling the capacity sections of diverse vascular beds exhibit considerable functional differentiation".

In contrast to these findings, the analysis of the reactions evoked by electric stimulation of afferent nerve fibers does not seem to indicate an ability of the sympathetic system for qualitatively different responses in its diverse sections. Mainly uniform changes of activity were concluded from the observations of, for instance, Sell *et al.* (1958) and Weidinger *et al.* (1961). Only occasionally, indirect hints suggesting a differentiated sympathetic response, e.g. an observation of Fedina *et al.* (1966), are found in the literature. Reports of Feigl (1964) and of Kahn and Mills (1967) concerned with differentiated vasomotor responses to electric stimulation of the medulla are open to the objection that diverse efferent pathways affected by the stimulus may be differently responsive with respect to the stimulation parameters (Peiper *et al.*, 1967).

As pointed out recently (Schmidt and Schönfuss, 1970), the variable and partly conflicting results of the stimulation experiments indicate the great influence of the stimulation parameters and of other experimental conditions on the reactions observed. These authors suggest that tnly natural stimulation experiments might help to clarify the effects of ohe various types of afferents on the sympathetic system. With regard to the present investigation, one ist tempted to assume that it was the appli-

cation of a comparatively natural and specific stimulus which has enabled the demonstration of the differentiated sympathetic response.

In an attempt to find further indications for differentiated vasomotor responses, the effects of natural or adequate stimuli known to influence the vasomotor system should, therefore, preferably be considered. In fact, observations of Rushmer *et al.* (1961) concerning blood flow distribution during exercise seem to indicate differentiated vascular adjustments. The vasomotor effects of baro- and chemoreceptor stimulation (Löfving, 1961; Browse *et al.*, 1966) were discussed by the authors under this point of view. Especially, however, reports on regional vascular responses to asphyxia and hypoxia—from the early observations of Zuntz (1878) and Dastre and Morat (1884) to the recent findings of Chalmers and Korner (1966)—may be considered as indicating qualitatively differentiated responses of regional vasoconstrictor activity. Own observations (Iriki *et al.*, to be published) have confirmed that, in fact, these stimuli evoke antagonistic responses in different sections of the sympathetic system.

Origin of the Antagonistic Sympathetic Responses

The fact that thermal stimulation of the spinal cord evokes a pattern of responses involving all known thermoregulatory effectors (Simon, 1968; Hales and Jessen, 1969) strongly suggests that the changes of activity in the visceral as well as in the cutaneous sympathetic efferents are an essential part of the blood flow adjustments controlling conductive heat loss. The incidence of antagonistic changes of cutaneous and intestinal blood flow not only during spinal but also during external thermal stimulation, as discussed by Kullmann *et al.* (1970), supports this hypothesis. The discrimination in the sympathetic outflow described in the present investigation might, therefore, be regarded as a special regulatory response of the vasomotor system.

The antagonistic responses most probably were not produced by peripheral mechanisms. The relay function of the peripheral sympathetic ganglia (Langley, 1904; Hillarp, 1960) is assumed not to be modified by facilitatory or inhibitory processes (Eccles, 1935) to an extent great enough to account for the responses observed. The identical findings obtained from the preganglionic splanchnic (rabbit) and the postganglionic splenic (cat) visceral efferents speak against this possibility, as well as the coincident changes of activity in preganglionic and cutaneous postganglionic filaments of the cervical sympathetic observed in control experiments (Fig. 7A).

Further, no indication was found that sympathetic efferents emerging from different sections of the spinal cord could have responded differently

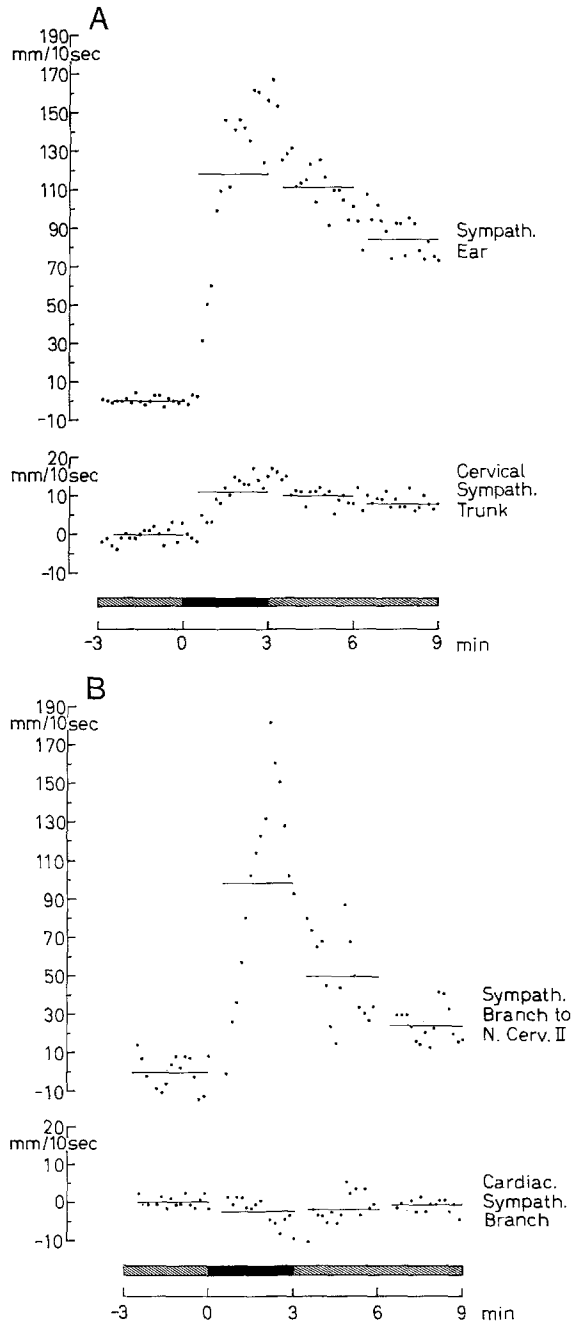
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Fig. 7

to the spinal thermal stimulus. As shown by the experiment of Fig. 7B, in which the discharges of the cutaneous and of the cardiac sympathetic nerves were simultaneously recorded, antagonistic changes of activity were induced by spinal cord cooling in these efferents originating both from the same upper thoracic segments (Langley, 1903). This finding additionally offers an explanation for the decrease of heart rate (see Table 4) observed in cats and dogs during spinal cord cooling (Simon, 1969a, b; Kullmann *et al.*, 1969).

At present, only a tentative hypothesis can be suggested for the origin of the antagonistic responses of the sympathetic nervous system. It may be assumed for the segmental sympathetic outflow that single preganglionic neurons or groups of neurons can be influenced separately from each other by a variety of supraspinal or segmental inputs. The sympathetic outflow would then be differentiated or uniform, respectively, according to the pattern of the input signals arriving at the preganglionic neuron pools. With respect to the present observation, this pattern might be produced primarily as a central nervous thermoregulatory performance. It might likewise be, in part, a secondary phenomenon induced by the medullary vasomotor centers as a reflex response to primarily isolated thermoregulatory changes of cutaneous blood flow. The differentiated responses would be initiated in both cases by the central integrative structures providing body temperature regulation. These structures are, most likely, identical with the thermoregulatory centers located in the hypothalamus (Jessen *et al.*, 1968). However, the spinal segment by itself may be able to transform thermal stimuli into adequate thermoregulatory responses. This was demonstrated for the effector mechanism of cold shivering (Simon *et al.*, 1966; Kosaka and Simon, 1968) and is assumed also for the thermoregulatory vasomotor responses (Walther *et al.*, 1969). Consequently, segmental integrating systems might have contributed to the antagonistic reactions of the sympathetic nervous system.

Conclusion

The present investigation has shown that antagonistic changes of activity are evoked in cutaneous and visceral sympathetic efferents by

Fig. 7. Courses of regional sympathetic activity in anesthetized, paralyzed animals during experimental periods of spinal cord cooling (black bars). *A* (rabbit): activity in the preganglionic cervical sympathetic trunk and in a postganglionic cutaneous (ear) sympathetic nerve branch; *B* (cat): activity in cardiac and cutaneous (branch to N. cerv. II) sympathetic efferents. The integrated discharges per 10 sec and the mean discharge levels of the diverse experimental phases are plotted against time, reference values: mean discharge levels of the pre-stimulation phases

heating and cooling the spinal cord. They may be regarded as thermoregulatory responses of the sympathetic vasoconstrictor system to the central thermal stimulus. A similar vasomotor response might account, in part, also for changes of blood flow distribution following external thermal stimulation. Indirect evidence reported in the literature and own observations further seem to indicate that other adequate stimuli likewise might evoke differentiated responses. It is suggested as a working hypothesis that the sympathetic nervous system may perform under special conditions a sort of "reciprocal innervation" of functionally antagonistic autonomic effector systems.

We express our gratitude to Prof. Dr. U. Peiper, Würzburg, for helpful discussions on the topics of this investigation.

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