Pflügers Arch. 328, 320–331 (1971)

Regional Differentiation of Sympathetic Activity during Hypothalamic Heating and Cooling in Anesthetized Rabbits

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Received April 19, 1971

Summary. In anesthetized rabbits immobilized with succinyl choline, the discharges of sympathetic efferents supplying cutaneous and visceral regions were simultaneously recorded. The effects of thermal stimulation of the hypothalamic region were tested on the basis of the integrated discharges. During hypothalamic heating cutaneous sympathetic activity decreased, corresponding to increased ear blood flow, while visceral sympathetic activity increased. During hypothalamic cooling there was, on the average, no significant change of regional sympathetic activity. However, in single experimental periods an increase of cutaneous and a decrease of visceral sympathetic activity was found.

The observed responses of regional sympathetic activity were compared with findings about regional cutaneous and intestinal blood flow under the same thermal stimulus and further with corresponding former investigations on regional blood flow and regional sympathetic activity during spinal thermal stimulation. It is suggested by this comparison that regional differentiation of sympathetic activity represents a specific thermoregulatory response of the vasomotor system mediated by the hypothalamic thermoregulatory center.

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

Antagonistic changes of cutaneous and visceral blood flow as well as differentiated responses of sympathetic activity confined to these vascular regions have been observed during thermal stimulation of the spinal cord (Kullmann *et al.*, 1970; Walther *et al.*, 1970). Since the role of the spinal cord as a temperature sensor in temperature regulation is clearly established, the assumption was raised by these findings that regional differentiation of sympathetic outflow is typical for thermoregulatory vasomotor adjustments. This would imply that thermal stimulation of the hypothalamic temperature sensors also elicits this type of response. Recent observations of Schönung *et al.* (1971) on regional cutaneous and visceral blood flow during hypothalamic heating and cooling have supported this assumption. In order to confirm regional sympathetic differentiation as the possible underlying nervous mechanism, thermal stimulation of the hypothalamic region was performed in

anesthetized rabbits, and the responses of regional cutaneous and intestinal sympathetic activity were observed.

Method

The experiments were performed in 19 albino rabbits of either sex, weighing 2.1—3.0 kg, from August to December 1970. The animals were anesthetized with sodium pentobarbital [30—35 mg/kg as initial dose and subsequent continuous infusion of 1—2 mg/(kg × hr)]. For muscle paralysis succinyl choline was intravenously administered [25—50 mg per animal as initial dose and subsequent continuous infusion of 0.05—0.15 mg/(kg × min)]. Artificial ventilation with 300—400 ml/(kg × min) of air was performed by means of a Starling pump. The animals were placed on their right sides on a heating pad in order to maintain a normal body temperature. Ambient air temperature was kept constant at values between 25° C and 30° C.

Hypothalamic Heating and Cooling was performed with a wedge-shaped thermode similar to that used by Andersson and Larsson (1961). Its base was 2 mm wide, its length 6 mm and its height 5 mm. Following the coordinates of Monnier and Gangloff (1961) the thermode was inserted into the preoptic hypothalamic region in 13 animals and into the posterior hypothalamic region in 6 animals. For thermal stimulation the thermode was perfused with water of either 47—50° C or of 15—31° C at a constant temperature and at a rate of flow of 100 ml/min. The position of the thermode was controlled in each experiment by macroscopic inspection of the brains after 6% formaline fixation. The anterior and posterior thermode positions in all experiments are schematically indicated in Fig. 1 by the hatched and open squares.

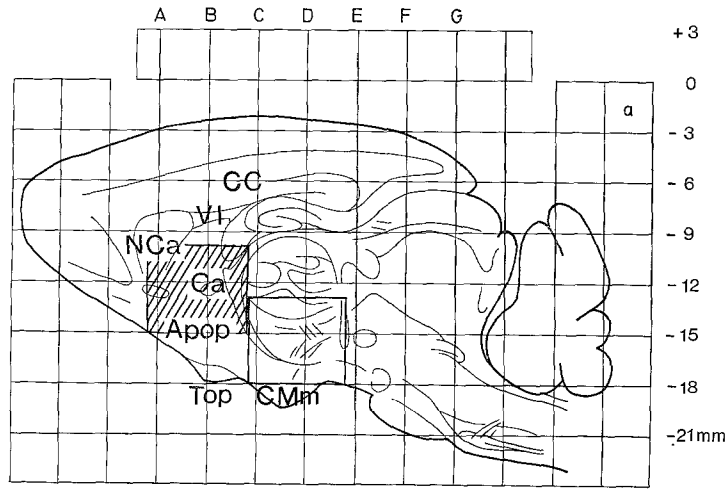

Fig. 1. Localisation of the thermodes according to the results of anatomical inspection of the formaline fixed brains of the experimental animals. Hatched area covers the anterior position of the thermode in 13 animals; open square covers the posterior position of the thermode in 6 animals. *Apop*: Area praeoptica; *Ca*: Commissure anterior; *CC*: Corpus callosum; *CMm*: Corpus mammillare mediale; *NCa*: Nucleus caudatus; *Top*: Tractus opticus; *Vl*: Ventriculus lateralis. (According to Monnier and Gangloff, 1961)

Measurements and Recordings. The discharges of a postganglionic nerve twig accompanying the left retroauricular artery (cutaneous "ear" sympathetic) and of a branch of the splanchnic nerve (visceral sympathetic) were recorded with bipolar stainless steel electrodes (for details of preparations see Walther *et al.*, 1970). The potentials were fed into differential amplifiers (Tönnies, No. 0329) and were simultaneously displayed either directly or after summation over 5 sec-intervalls (Tönnies, "amplitude adder" No. M 8) on a UV-direct writing oscillograph (CEC, Galvomat). Arterial blood pressure was measured after cannulation of one femoral artery with a Statham pressure transducer (P 23 A). Rectal temperature and skin temperatures of both ears were measured with miniature NTC-thermistors. The difference between thermode and rectal temperature was determined with a thermocouple. These temperatures and arterial pressure were recorded on the oscillograph. Ambient air temperature was controlled with an electric thermometer (Ellab, Copenhagen).

Calculations and Statistics. The courses of activities of the investigated sympathetic efferents were determined by comparing the "amplitude adder" deflections recorded during the heating or cooling phases with the average deflection amplitude during the respective pre-stimulation phases. Mean arterial pressure was calculated after numerical evaluation of the pulse pressure curve as $P_{\text{diast.}} + 0.3 \times (P_{\text{syst.}} - P_{\text{diast.}})$. Heart rate was determined from the pulse pressure recordings.—For statistical analysis of the data, one of the experimental periods performed in each animal was randomly selected. For comparison of samples of paired observations the Wilcoxon matched-pairs signed-ranks test was applied.

Results

Selective *heating of the anterior hypothalamic region* regularly induced a decrease of cutaneous sympathetic activity with a closely related rise of ear skin temperatures. Simultaneously, visceral sympathetic activity increased. The average response of 13 investigated animals is demonstrated in Tab. 1 by the mean values calculated from 13 randomly selected experimental periods, one for each animal. The antagonistic changes of regional sympathetic activity as determined from the deflections of the "amplitude adder" were statistically significant, as were the readjustments of activity during the post-heating phases. This is true also for the change of ear skin temperatures. The small but significant decrease of rectal temperature during heating is attributed to the increased conductive heat loss from the skin during hypothalamic heating.

The changes of regional sympathetic activity in a single experimental period and of the other measured parameters are demonstrated in Fig. 2. As visualized by sections from the original recording in part A of the figure, both splanchnic and cutaneous sympathetic activity showed rhythmic bursts of discharges which were mainly related to respiration. During hypothalamic heating cutaneous sympathetic activity was greatly reduced. Splanchnic activity slightly but significantly increased. This can be derived not only from the increased amplitude adder deflec-

Table 1. *Changes of regional sympathetic activity, rectal and ear temperatures, arterial mean pressure and heart rate during heating of the anterior hypothalamic region of 6 min duration. 13 rabbits. Perfusion temperatures of thermode, 47—50° C, air temperatures 25—30° C. Sympathetic activity expressed in millimeters of integrator deflections per 10 sec: the data of the table were calculated as average values for 3 min-intervalls, reference value: discharge level during 3 min before start of warming.— $\bar{x}$: mean values, $S_{\bar{x}}$: standard deviation of mean values*

Heating			before	during		after	
Time after start of heating		min	−3—0	0—3	3—6	6—9	9—12
Sympath. left ear	mm/10 sec	$\bar{x}$	0	−14.3[a]	−27.0[a]	−14.6[a b]	−7.1[a b]
		$S_{\bar{x}}$		6.0	7.7	4.5	3.3
N. splanchn.	mm/10 sec	$\bar{x}$	0	+ 7.1[a]	+13.9[a]	+2.2[b]	−1.3[b]
		$S_{\bar{x}}$		2.8	4.7	2.2	2.2

Heating			before	during		after	
Time after start of heating		min	0	3	6	9	12
Temp. ectal	°C	$\bar{x}$	38.9	38.7[a]	38.7[a]	38.7[a]	38.8[a b]
		$S_{\bar{x}}$	0.2	0.2	0.2	0.2	0.2
Temp. left ear	°C	$\bar{x}$	30.2	33.1[a]	34.3[a]	33.4[a b]	32.4[a b]
		$S_{\bar{x}}$	0.4	0.9	0.9	0.7	0.6
Temp. right ear	°C	$\bar{x}$	29.6	33.0[a]	34.2[a]	33.2[a b]	32.0[a b]
		$S_{\bar{x}}$	0.5	0.9	1.0	0.8	0.7
Pm art.	mm Hg	$\bar{x}$	76.1	75.9	71.9	73.0	75.5
		$S_{\bar{x}}$	5.9	6.4	5.0	4.6	4.1
Heart rate	min^{-1}	$\bar{x}$	263	252 [a]	250 [a]	257	260 [b]
		$S_{\bar{x}}$	8	8	9	9	8

[a] Data significantly different from the values before warming.

[b] Data significantly different from the values at the end of warming ($P < 0.05$, Wilcoxon matched-pairs signed-ranks test).

tions but also from the broadening and the increased amplitudes of single discharge bursts during hypothalamic heating.—The time courses of all recorded parameters are demonstrated in part B of the figure. It is obvious that, in spite of the distinct changes of regional sympathetic activity and of skin blood flow, arterial pressure and heart rate remained largely unaffected during hypothalamic heating.

Several experimental periods were performed with lower heating intensities. With perfusion temperatures as low as 43° C reduction of cutaneous and concomitant increase of visceral sympathetic activity could be evoked.

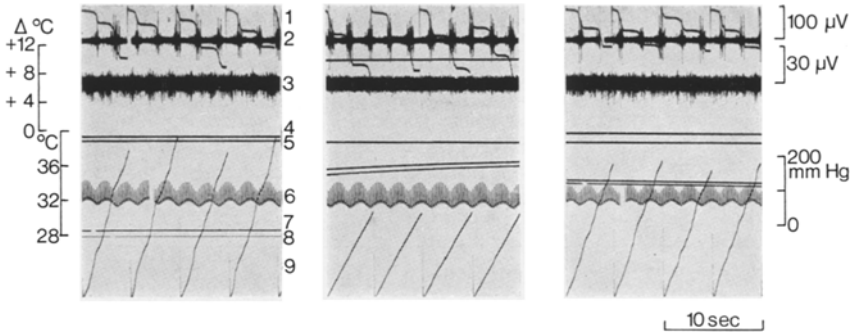

Fig. 2 A

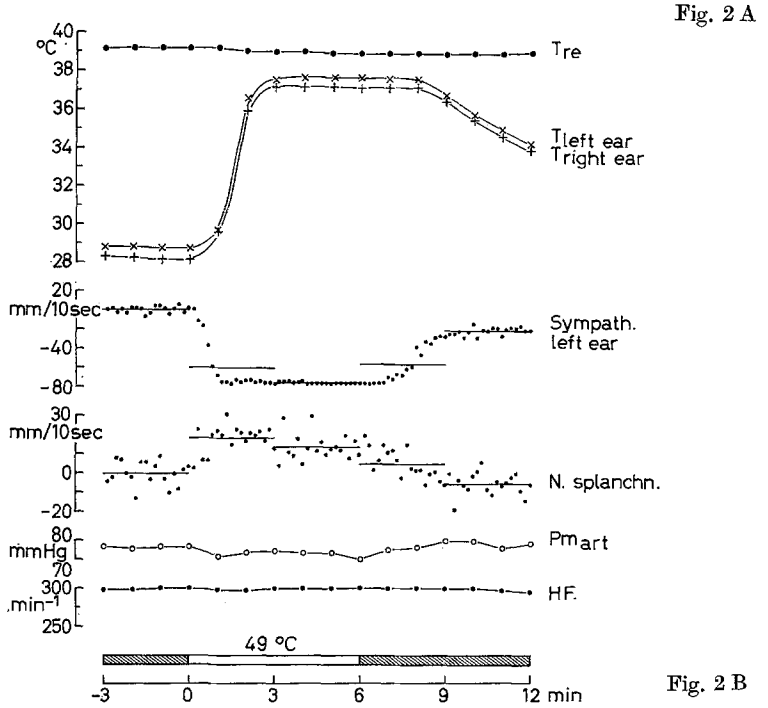

Fig. 2 B

Fig. 2. Regional sympathetic activity during heating of the anterior hypothalamic region of 6 min duration in an anesthetized paralyzed rabbit. A: Sections from the original recordings before (left), during (middle) and after (right) heating. Integrated discharges (*1*, downward deflections) and discharges (*2*) of the visceral sympathetic, discharges of the cutaneous sympathetic (*3*), temperature difference between hypothalamic thermode and rectum (*4*, scale ▵ °C), rectal temperature (*5*), arterial pressure (*6*), skin temperatures of the left (*7*) and right (*8*) ears, integrated discharges of the cutaneous sympathetic (*9*, upward deflections). B: Time courses of regional cutaneous (*Sympath. left ear*) and visceral (*N. splanchn.*) sympathetic activity as influenced by heating (white bar). The integrated discharges per 10 sec and the mean discharge levels during 3 min-intervals are plotted against time; reference value: mean discharge level during the last 3 min before thermal stimulation. Further parameters: Ear skin temperatures (*T right ear*, *T left ear*), arterial mean pressure (*Pm art*), heart rate (*HF.*). Perfusion temperature of thermode 49°C; air temperature 26.5°C

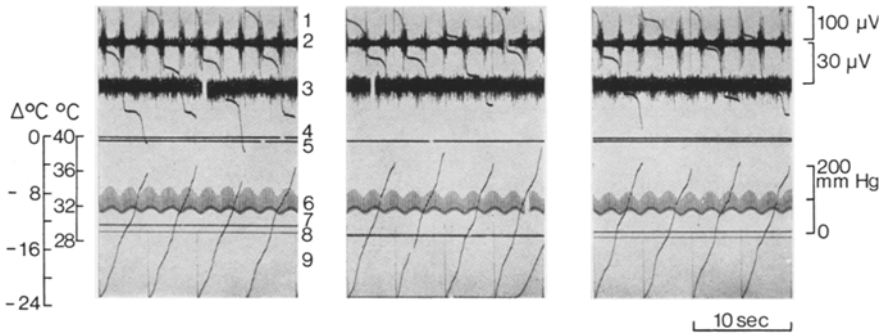

Fig. 3 A

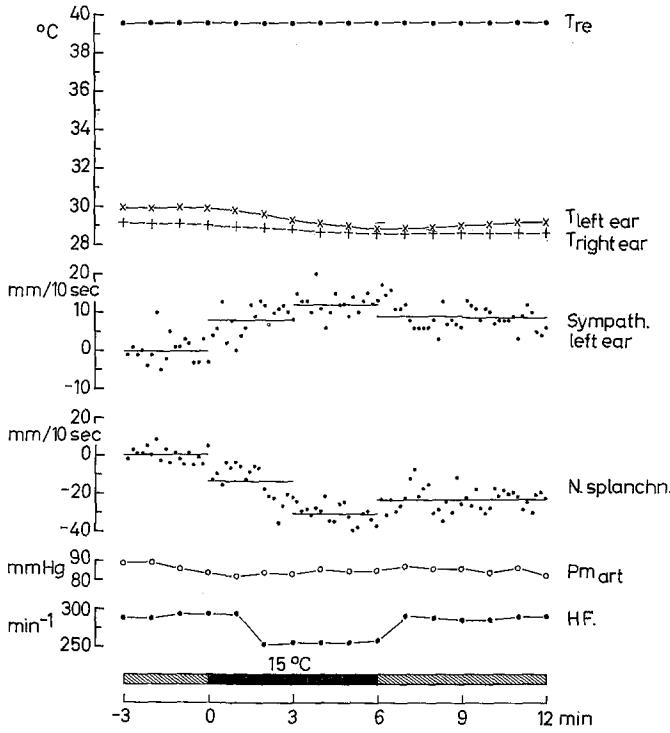

Fig. 3 B

Fig. 3. Regional sympathetic activity during cooling of the anterior hypothalamic region of 6 min duration in an anesthetized paralyzed rabbit. A: Sections from the original recordings before (left), during (middle) and after (right) cooling. Parameters as in Fig. 2A. B: Time courses of regional sympathetic activity as influenced by cooling (black bar). Parameters as in Fig. 2A. Perfusion temperature of the thermode 15°C; air temperature 26.5°C

Table 2. *Changes of regional sympathetic activity, rectal and ear temperatures, arterial mean pressure and heart rate during cooling of the anterior hypothalamic region of 6 min duration. 13 rabbits. Perfusion temperatures of thermode, 15—31°C, air temperatures 26—29°. Parameters as in Table 1*

Cooling			before	during		after	
Time after start of cooling		min	−3—0	0—3	3—6	6—9	9—12
Sympath. left ear	mm/10 sec	$\bar{x}$	0	+1.2	+2.1	+ 0.7	− 0.9
		$S_{\bar{x}}$		1.6	2.3	2.1	2.4
N. splanchn.	mm/10 sec	$\bar{x}$	0	−3.6	−6.4	−10.9[a]	−13.7[a b]
		$S_{\bar{x}}$		3.2	3.9	4.4	4.8

Cooling			before	during		after	
Time after start of cooling		min	0	3	6	9	12
Temp. rectal	°C	$\bar{x}$	38.8	38.8	38.8	38.8	38.8
		$S_{\bar{x}}$	0.3	0.3	0.3	0.3	0.3
Temp. left ear	°C	$\bar{x}$	30.3	30.2	29.8[a]	29.5[a]	29.5[a]
		$S_{\bar{x}}$	0.5	0.5	0.6	0.4	0.4
Temp. right ear	°C	$\bar{x}$	30.2	29.9	29.5[a]	29.3[a]	29.4[a]
		$S_{\bar{x}}$	0.7	0.6	0.5	0.4	0.4
Pm art.	mm Hg	$\bar{x}$	71.9	70.4	72.5	71.5	73.2
		$S_{\bar{x}}$	4.0	4.2	3.7	4.0	4.3
Heart rate	min^{-1}	$\bar{x}$	263	258	259	264	264
		$S_{\bar{x}}$	12	12	12	12	12

In contrast to heating, selective *cooling of the anterior hypothalamic region* did, on the whole, not result in an unequivocal differentiated response of regional sympathetic activity. As shown in Fig. 3, differentiated sympathetic responses were occasionally observed which were consistent with the expected thermoregulatory changes of skin blood flow. In the demonstrated case both, the discharge recordings and the "amplitude adder" deflections revealed that cutaneous sympathetic activity increased and splanchnic activity decreased during hypothalamic cooling. Further, ear skin temperatures showed a slight fall during cooling. However, as shown in part B of the figure, there was a tendency of sustained deviation of regional sympathetic activity from the prestimulation level also after the end of cooling. Further, in this case heart rate was definitely affected.

As shown in Tab. 2 by the mean values of 13 experimental periods, each one randomly selected from one experimental animal, no significant changes of regional sympathetic activity could be established during

hypothalamic cooling. There seemed to be a tendency towards an increase of cutaneous sympathetic activity. A slight decrease of ear skin temperatures corresponds to this finding. Splanchnic activity showed a tendency towards a decrease during cooling which became, however, significant only during the post-cooling phase. Thus, a sustained suppression of splanchnic activity seems to have resulted from hypothalamic cooling. Likewise, the decrease of ear skin temperatures was prolonged over the end of thermal stimulation. Blood pressure and heart rate rose in some animals and fell in others with no significant change, on the average.

In 6 animals the responses to *thermal stimulation of the posterior hypothalamic region* were observed. During heating, regional antagonistic changes of cutaneous and visceral sympathetic activity of the same directions as during anterior hypothalamic heating occurred. However, as estimated from the changes of ear skin temperatures, the vasodilatatory responses were smaller than during anterior heating—on the average + 0.6°C instead of + 4.1 to + 4.6°C within 6 min of heating. During posterior hypothalamic cooling the responses were mainly at variance with an adequate thermoregulatory response. Various combinations of antagonistic and synergistic changes of splanchnic and cutaneous sympathetic activity occurred. Ear skin temperature showed, on the average, a slight decrease.

Discussion

The present observations made during hypothalamic heating in anesthetized rabbits have unequivocally shown that antagonistic changes of regional sympathetic activity are induced by this type of central heat stimulation. This corresponds to the antagonistic changes of blood flow in cutaneous and intestinal vascular beds observed in anesthetized dogs during selective hypothalamic heating (Schönung *et al.*, 1971). Since the role of the hypothalamus as a thermosensitive, especially heat sensitive region is firmly established (Hardy, 1969), the described vasomotor responses are regarded as thermoregulatory adjustments of regional circulation. On the other hand, the results obtained during hypothalamic cooling remained equivocal, although appropriate antagonistic changes of regional sympathetic activity were occasionally observed. This contrasts to the definite results obtained during spinal cord cooling in anesthetized rabbits (Walther *et al.*, 1970). In view of the results of Schönung *et al.* (1971), however, which strongly suggest a regional differentiated response of sympathetic activity during hypothalamic cooling for the dog, it seems justified to apply more significance to the positive results obtained in the present series of experiments during hypothalamic cooling.

Several factors may have accounted for the vagueness of the results obtained during hypothalamic cooling in the rabbit. Firstly, as indicated by the long lasting controversy about a possible hypothalamic cold sensitivity (Ström, 1950; Krüger *et al.*, 1959; Freeman and Davis, 1959; Brendel, 1960; Hammel *et al.*, 1960; Rauten-

berg *et al.*, 1963, and others) it is more difficult to evoke definite cold defence responses by cooling than heat defence responses by heating of the hypothalamus. This seems reasonable, if it is assumed that such cold defence responses are elicited by activation of hypothalamic cold sensitive units, since they seem to be less in number than heat sensitive units (Hardy *et al.*, 1964). Traumatization of the hypothalamic thermosensitive area by the insertion of the thermode could have further reduced the chance of getting positive responses. Unspecific side effects of cooling, which are indicated by the varying responses to posterior as well as anterior hypothalamic cooling, might additionally have obscured the result. Finally, observations of Krüger *et al.* (1959) and of Rautenberg *et al.* (1963) seem to indicate that cerebral cold sensitivity is more easily affected by anesthesia than extracerebral central cold sensitivity.

The less distinct responses during heating of the posterior hypothalamic region fit in the conception that the anterior hypothalamus is the most effective warmth sensor within the brain (Hardy, 1969). Although both heat and cold sensitive units have also been discovered in the posterior hypothalamic and midbrain regions (Cabanac *et al.*, 1968; Cabanac and Hardy, 1969; Nakayama and Hardy, 1969), their influence on temperature regulation seems to be of minor importance (Adair and Stitt, 1971).

The hypothalamus is known as a central nervous region, from where differentiated vasomotor responses may be induced by electric stimulation (Eliasson *et al.*, 1951; Feigl, 1964). In the dog and the cat, increase of muscle blood flow with concomitant vasoconstriction in other vascular areas and increase of heart rate during stimulation of the hypothalamic "defence area" are attributed to simultaneous activation of sympathetic vasodilatator and vasoconstrictor efferents. Quantitative differentiation of the adrenergic outflow to e.g. the heart and to vascular regions, which must additionally be assumed in this situation, is explained by the interference of the hypothalamic drives with the pressoreceptor afferents at the medullary level (Djojosugito *et al.*, 1970). Identical vascular defence responses to hypothalamic stimulation were, however, observed also in animals which are supposed to lack sympathetic vasodilatatory fibers (Folkow and Rubinstein, 1966). This indicates a qualitatively differentiated response of the vasoconstrictor outflow (Lisander, 1970).

The antagonistic responses of regional sympathetic activity during central thermal stimulation represent a further, different pattern of vasomotor differentiation which is characterized by its qualitative aspect, namely a kind of "reciprocal innervation" of functionally different vascular regions. Mediation by the hypothalamic thermoregulatory control center of the vasomotor effects of hypothalamic as well as spinal thermal stimulation seems most likely, at least under the conditions of intact connections between spinal cord and hypothalamus. Afferent conduction of both spinal heat and cold stimuli to supraspinal, probably hypothalamic levels was demonstrated (Wünnenberg and Brück, 1968, 1970; Kosaka *et al.*, 1969; Simon and Iriki, 1970). Further, cooperation of spinal with hypothalamic temperature sensors was shown to be achiev-

Table 3. *Qualitative differentiation of cutaneous and intestinal sympathetic activity or, respectively, blood flow during central thermal stimulation.* "+" *experimental series with statistically significant observations on regional differentiation.* "(+)" *experimental series withouth statistically significant results, however, with single positive experiments*

central thermal stimuli	heat stimulation	cold stimulation
hypothalamic stimulation		
dog (Schönung *et al.*, 1971)	+	+
rabbit (this investigation)	+	(+)
spinal cord stimulation		
dog (Kullmann *et al.*, 1970)	+	(+)
rabbit (Walther *et al.*, 1970)	+	+
cat (Walther *et al.*, 1970)	(+)	+

ed in a manner strongly suggesting a common hypothalamic thermoregulatory center (Jessen and Simon, 1971).

If the reactions of cutaneous and intestinal blood flow and of regional sympathetic activity during hypothalamic and spinal thermal stimulation are compared, as shown in Table 3, a satisfactory agreement of the experimental results may be stated. Thus, regional qualitative differentiation of the sympathetic vasoconstrictor outflow appears to be involved in temperature regulation as a specific vasomotor response which enables regulation of heat transfer from the body core to the skin with the least possible alterations of general circulatory homeostasis.

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