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Differentiation of Cutaneous and Intestinal Blood Flow during Hypothalamic Heating and Cooling in Anesthetized Dogs

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Summary. Blood flow in arteries supplying cutaneous and intestinal vascular regions were simultaneously measured with an electromagnetic flowmeter in anesthetized dogs, paralyzed with succinyl choline. The hypothalamic preoptic region was selectively heated and cooled by means of a stereotaxically inserted, water perfused thermode.

Skin blood flow increased during hypothalamic heating and was reduced during hypothalamic cooling. Conversely, intestinal blood flow decreased during heating and increased during cooling. Arterial pressure was not influenced by hypothalamic cooling and decreased slightly during heating.

The changes of blood flow distribution observed in the experiments are in keeping with the results obtained during selective spinal cord heating and cooling. It is assumed that antagonistic changes of blood flow in the cutaneous and intestinal vascular beds represent typical thermoregulatory responses of systemic circulation induced by regionally antagonistic changes of vasomotor activity.

Key-Words: Temperature Regulation — Blood Flow Distribution — Vasomotor System.

Cutaneous blood flow adjustments induced by thermal stimulation of the spinal cord in anesthetized, paralyzed dogs are accompanied by inverse changes of blood flow in visceral vascular regions (Kullmann *et al.*, 1970). Earlier observations further indicate that similar redistributions of regional blood flow may occur under external thermal stimulation (Müller and Veiel, 1910; Rein, 1931; Glaser, 1949; Grayson, 1949). Therefore, it is supposed that regional antagonism of blood flow distribution represents a special pattern of vasomotor responses in temperature regulation. Further support for this assumption may be expected from an investigation of regional blood flow during thermal stimulation of the hypothalamus. Its function as a central thermosensitive site is firmly established (Hardy, 1969). In particular, thermoregulatory adjustments of skin blood flow following adequate stimulation of this region have been described (Barbour, 1912; Prince and Hahn, 1918; Hemingway

et al., 1940; Folkow *et al.*, 1949a, b; Ström, 1950a, b; Eliasson and Ström, 1950; Freeman and Davis, 1959; Krüger *et al.*, 1959; Andersson and Larsson, 1961). However, from investigations on blood flow in vascular regions other than the skin during hypothalamic thermal stimulation, no unequivocal conclusion can be drawn with respect to a possible regional antagonism of vasomotor adjustments (Folkow *et al.*, 1949a; Ström, 1950b; Söderberg, 1956a, b). Therefore, a series of experiments was carried out in anesthetized, paralyzed dogs in which blood flow adjustments in cutaneous and intestinal vascular beds were observed during selective thermal stimulation of the anterior hypothalamic region.

Methods

The presented results were obtained from eight successful experiments carried out in mongrel dogs (18—30 kg body weight) between July and October 1970. Sodium pentobarbital (30 mg/kg) was intravenously injected. Depth of anesthesia was controlled during the experiment by observing the pupillary reflexes, and repeated small doses of the anesthetic were administered, if necessary. A tracheal cannula was inserted, and artificial ventilation was performed by means of a Bird Mark 8 respirator. For muscle paralysis succinyl choline was administered by an initial intravenous injection (100 mg) and by subsequent continuous infusion (0.5 mg/[kg × h]). Ambient temperature was thermostatically controlled between 24 and 26° C in order to maintain core temperatures of the experimental animals within the normal range.

Thermal Stimulation of the Hypothalamus. A wedge-shaped silver thermode similar to that described by Andersson and Larsson (1961) was placed into the anterior hypothalamic region. Its base was 3 mm wide, its height 6 mm and its length 6 mm. This thermode was perfused with 300 ml/min of water at various thermostatically controlled temperatures between 18 and 49° C. For insertion of the thermode the animal's head was mounted stereotaxically (stereotactor of Baltimore Instruments Ltd.) and was kept in the device throughout the experiment. The thermode, which was guided by a 3-dimensional drive, was inserted under X-ray control into the preoptic region from a point at the cortical surface about 3 mm lateral to the midline.

Measurements and Recordings. Regional blood flow was determined by flow probes adapted to an electromagnetic flowmeter (Statham Multiflo M-4000). The flow probes were applied to the Arteria dorsalis pedis of the left hind leg (skin blood flow) and to the Arteria mesenterica superior (intestinal blood flow). For details of surgical procedures and calibration see Kullmann *et al.* (1970). Arterial pressure was recorded from one brachial artery with a rigid catheter connected to a Statham pressure transducer (model P 23 Dd). Arterial mean pressure was obtained by electronic integration (Hellige carrier amplifier) and was recorded together with mean cutaneous and intestinal blood flows on a UV-direct writing oscillograph (CEC Galvomat). The skin temperature of the left hind paw and the temperatures of the rectum, of the thermode and of the ingoing perfusion fluid were measured with thermocouples adapted to an electric thermometer (Ellab, Copenhagen).

Course of the Experiments. The experiments were started, when preliminary testing had shown that skin blood flow responded in an appropriate manner to hypothalamic thermal stimulation. Cooling periods of 5 min duration were performed by thermode perfusion with water of 18° C. Likewise, heating periods lasted 5 min;

in 7 animals the thermode was perfused with water of 49° C, in 1 animal perfusion temperature was 44 and 48° C. Between the various stimulation periods performed in one animal, control periods of 5—10 min duration were interposed during which the thermode was perfused with water at body temperature (37—39° C). Temperature measurements were made every 5 min. After the experiment the animals were sacrificed and the brains were fixed in 6% formaline for anatomical control of the thermode position.

Calculations and Statistics. Arterial mean pressure and regional mean flows during the single stimulation periods and the corresponding pre- and post-stimulation periods were determined from the recorded curves by planimetering. For further evaluation the values determined from the 3rd to the 5th min of every period were used. Regional vascular resistance was calculated for the respective sections from the arterial pressure and flow values. The average response of each experimental animal was calculated as the means of the data obtained for every parameter in the single stimulation periods. Final evaluation of the results obtained from the whole sample consisted in statistical comparison of the average pressure, flow, resistance, and temperature values during the stimulation periods with those of the corresponding control periods by the Wilcoxon matched-pairs signed-ranks test and in calculation of the mean values with standard deviations.

Results

Vasomotor Responses. The changes of the recorded circulatory parameters induced by hypothalamic thermal stimulation are demonstrated in Fig. 1. As shown by the section from an original recording at the left hand side, hypothalamic cooling induced a decrease of cutaneous blood flow to about half of the control value. In contrast, intestinal blood flow increased during this time. Arterial pressure was not affected. A likewise antagonistic response of cutaneous and intestinal blood flow, however of opposite direction, was observed during hypothalamic heating as shown by the recording at the right hand side obtained from another animal. In this case, cutaneous blood flow increased by 370%, whereas blood flow in the cranial mesenteric artery moderately decreased. Arterial pressure was slightly reduced. Calculations of the local vascular resistances showed that these parameters changed definitely and contributed to the regional flow changes not only in the skin but also in the intestine.

Corresponding results were obtained in all investigated animals, however, the changes of regional blood flow were, on the average, only moderate. The average courses of the measured circulatory parameters during thermal stimulation of the hypothalamus are demonstrated in Tab. 1. As indicated by the data the significant changes of regional blood flow corresponded to likewise significant changes of the regional vascular resistance. In conformity with the thermoregulatory role of hypothalamic thermosensitivity, hypothalamic heating reduced cutaneous vascular resistance, whereas cooling increased it. Intestinal vascular resistance, however, changed inversely. These changes, though only small, proved to be significant with respect to their directions as evaluated by the

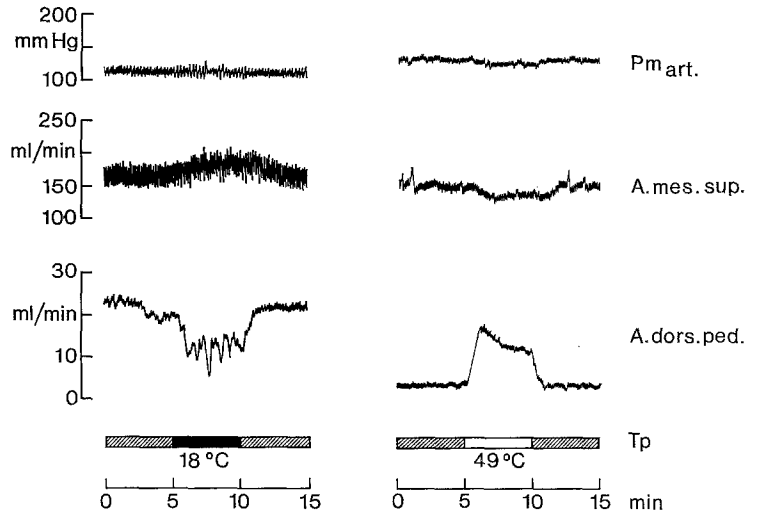

Fig. 1. Arterial mean pressure (Pm_{art}) and blood flow in cutaneous (*A.dors.ped.*) and intestinal (*A.mes.sup.*) vascular beds during thermal stimulation of the anterior hypothalamus in anesthetized, paralyzed dogs. The cooling and heating period were recorded in different dogs.—T_p Perfusion temperature. Hatched bars: Neutral perfusion temperature

Wilcoxon matched-pairs signed-ranks test and thus revealed an antagonistic behaviour of the two investigated vasomotor regions.

The results of the temperature measurements are shown in Tab. 2. Hypothalamic heating was accompanied by a slight but significant rise of paw skin temperature, hypothalamic cooling induced a slight fall. Rectal temperature was falling in response to hypothalamic heating and rising during hypothalamic cooling with a slowing of the rise in the post-cooling phase.

Location of the Thermode. Macroscopic inspection of the formaline fixed brains showed that in 4 animals the position of the thermode was exactly in the median plane and in the remaining 4 animals up to 3 mm lateral from the median plane. The location of the thermode projected on a parasagittal plane is shown in Fig. 2. The hatched area shows the region stimulated by the thermode in 7 out of the 8 investigated animals, which corresponds well to the thermosensitive region as described by Eliasson and Ström (1950) and by Andersson *et al.* (1956). In one animal the thermode reached only the anterior commissure. In this case weak responses were observed which were, however, consistent with those of the other animals.

Table 1. *Comparison of systemic arterial pressure, blood flow and regional vascular resistance in cutaneous and intestinal vascular regions during thermal stimulation of the hypothalamus. Mean valus ($\bar{X}$) with standard deviations (s) of 8 experiments. ($\neq$) significant differences between data ($p < 0.05$) as determined by the Wilcoxon matched-pairs signed-ranks test*

		Thermal stimulation of the hypothalamus					
		Neutral	Cooling 18° C	Neutral	Neutral	Heating 49° C	Neutral
Arterial mean pressure (mm Hg)	$\bar{X}$	134.92	133.88	133.04	134.72 $\neq$	129.65 $\neq$	133.94
	s	19.69	19.22	21.01	20.27	19.53	19.25
Flow of A.dors.ped. ($ml \times min^{-1}$)	$\bar{X}$	14.86 $\neq$	10.85 $\neq$	14.98	14.01 $\neq$	18.19 $\neq$	13.97
	s	8.1	6.64	6.89	7.64	6.81	8.09
Resistance to flow of A.dors. ped. ($10^5 dyn \times sec \times cm^{-5}$)	$\bar{X}$	10.98 $\neq$	15.18 $\neq$	10.47	11.99 $\neq$	6.71 $\neq$	11.57
	s	8.71	12.92	8.19	9.95	2.74	8.55
Flow of A.mes.sup. ($ml \times min^{-1}$)	$\bar{X}$	265.32 $\neq$	283.0 $\neq$	255.85	225.96 $\neq$	209.67 $\neq$	225.25
	s	117.37	124.4	118.9	76.2	73.05	74.8
Resistance to flow of A. mes.sup. (10^5 dyn $\times$ sec $\times cm^{-5}$)	$\bar{X}$	0.47 $\neq$	0.44 $\neq$	0.49	0.52 $\neq$	0.55 $\neq$	0.52
	s	0.17	0.16	0.21	0.15	0.15	0.15

Table 2. *Temperatures measured at the end of the stimulation periods and the corresponding pre- and post-stimulation periods. Mean values ($\bar{X}$) with standard deviations (s) of 8 experiments. ($\neq$) significant differences between data of the rectal temperatures and the hind-paw temperatures ($p < 0.05$) as determined by the Wilxocon matched-pairs signed-ranks test*

		Thermal stimulation of the hypothalamus					
		Neutral	Cooling 18° C	Neutral	Neutral	Heating 49° C	Neutral
Rectal temperature (° C)	$\bar{X}$	38.79 $\neq$	38.85	38.87	38.81 $\neq$	38.77	38.76
	s	0.38	0.38	0.39	0.43	0.43	0.42
Hind-paw temperature (° C)	$\bar{X}$	36.0 $\neq$	35.69 $\neq$	35.76	35.77 $\neq$	36.19	36.08
	s	4.62	4.72	5.23	5.63	4.99	4.44
Thermode temperature (° C)	$\bar{X}$	38.72	18.85	38.69	38.72	48.47	38.71
	s	0.41	0.55	0.43	0.48	0.44	0.52
Ambient air temperature (° C)	$\bar{X}$	24.94	24.95	25.0	24.97	24.96	24.94
	s	0.7	0.69	0.69	0.65	0.66	0.67

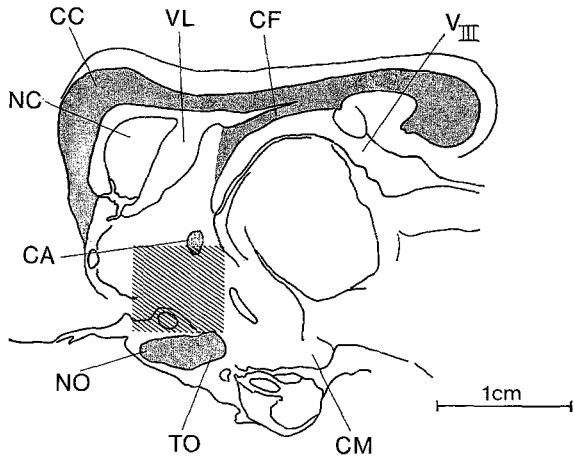

Fig. 2. Location of the thermode (hatched area) in 7 experiments, projected on a parasagittal section through the hypothalamus of the dog (Singer, 1962). — V_{III} Ventriculus tertius; *CF* Crus fornicis; *VL* Ventriculus lateralis; *CC* Corpus callosum; *NC* Nucleus caudatus; *CA* Commissura anterior; *NO* Nervus opticus; *TO* Tractus opticus; *CM* Corpus mammillare

Discussion

As shown by the evaluations of the recorded circulatory parameters, the antagonistic changes of cutaneous and intestinal blood flow during hypothalamic heating and cooling were caused by changes of regional vascular resistance, i.e. presumably by neural influences. Thus, the regional blood flow adjustments induced by thermal stimulation of the hypothalamus correspond to those observed during thermal stimulation of the spinal cord (Kullmann *et al.*, 1970). Hypothalamic and spinal temperature sensors have been confirmed to provide the prevailing central sensory input for the thermoregulatory control system in the dog (Jessen and Mayer, 1971). Therefore, the present findings contribute further evidence that regional antagonism of cutaneous and other, central vascular regions represents a typical pattern of thermoregulatory vasomotor adjustments.

The antagonistic responses of cutaneous and intestinal blood flow to hypothalamic thermal stimulation are not confined to the special conditions given by anesthesia and muscle immobilization. The same response has recently been observed during hypothalamic and spinal thermal stimulation in the conscious dog (Schönung *et al.*, 1971).

According to the anatomical controls of the thermode positions, the changes of local temperature induced by thermode perfusion probably

involved the whole thermosensitive hypothalamic region in 7 out of the 8 investigated animals. Testing in one animal with 44°C perfusion revealed a typical vasomotor response in skin and intestine at this weak stimulation. With the higher perfusion temperatures generally applied, even in case of unilateral destruction of the thermosensitive region by thermode insertion, a stimulation of the intact side, sufficiently strong to evoke a response could be expected from the gradient measurements of Andersson and Larsson (1961) and of Gale *et al.* (1970).

However, the changes of skin blood flow induced by hypothalamic thermal stimulation, though unequivocally characterized as thermoregulatory responses by their directions, were small as compared to the vascular responses in awake or anesthetized animals during spinal cord cooling and heating. One of the possible reasons for the minuteness of the observed responses may be partial damage of the hypothalamic thermosensitive structures by the insertion of the rather coarse thermode. A further reason might be the greater susceptibility of hypothalamic temperature sensors against the anesthetic as indicated by observations of Krüger *et al.* (1959) and of Rautenberg *et al.* (1963). Observations in rabbits indicate that the changes of cutaneous and intestinal blood flow during hypothalamic thermal stimulation are induced by corresponding changes of regional vasoconstrictor outflow (Iriki *et al.*, 1971). As far as the effects of hypothalamic cooling in the dog are concerned, it may be concluded that reduction of cutaneous blood flow was induced by increased vasoconstrictor tone, and increase of intestinal blood flow by a decreased vasoconstriction. With respect to hypothalamic heating in the dog, participation of vasodilatatory fibers supplying the skin of the paws must be taken into consideration (Calvelo *et al.*, 1970). It may be inferred, however, that a possible activation of vasodilatatory fibers by hypothalamic heating was accompanied not only by an increase of vasoconstrictor activity in the intestinal vessels but also by a decrease of vasoconstrictor tone in the skin. Accord ng to Lisander (1970), vasodilatatory drives mediated by vasodilatatory fibers would easily be canceled by a simultaneous activation of vasoconstrictor fibers confined to the same region. Further, own preliminary observations in the dog have confirmed that activity in sympathetic branches supplying the ear skin is reduced by spinal cord heating.

The great susceptibility of the thermoregulatory vasomotor response in the skin during hypothalamic heating to any vasoconstrictor influence, and hence the necessity of a reduction of cutaneous vasoconstrictor activity for generation of cutaneous vasodilatation, is demonstrated further by the observation shown in Fig. 3. In this lightly anesthetized dog a typical vasodilatation in the skin with concomitant vasoconstriction in the intestine had been induced by hypothalamic heating. A sudden

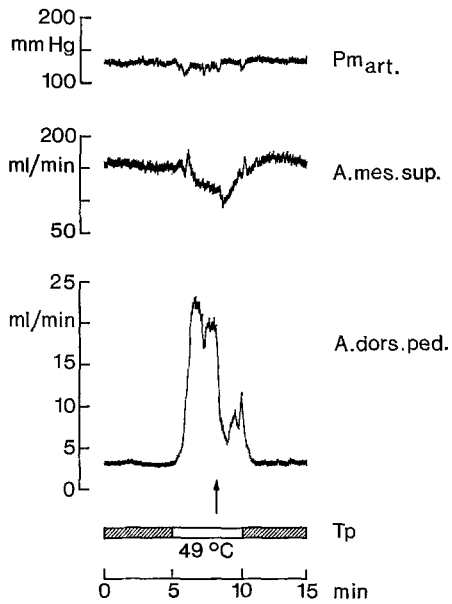

Fig. 3. Arterial mean pressure (Pm_{art}) and blood flow in cutaneous (*A.dors.ped.*) and intestinal (*A.mes.sup.*) vascular beds during heating of the anterior hypothalamus of a lightly anesthetized, paralyzed dog.—T_p Perfusion temperature. Hatched bars: Neutral perfusion temperature. (↑) Acoustic stimulus

general vasoconstrictor impulse induced by an intense acoustic stimulus was able to completely override cutaneous vasodilatation, although its effect on intestinal circulation was comparatively small. From this experiment it may be inferred that most probably not only no increase but rather an appropriate decrease of cutaneous vasoconstrictor activity must have accompanied a possible activation of cutaneous vasodilatatory fibers during hypothalamic heating.

If it is assumed that regional differentiation of vasoconstrictor activity is the underlying mechanism of the observed regional blood flow antagonism, the role of the baroreceptors in this regional differentiation must be considered, since they are supposed to contribute to this phenomenon under certain conditions (Djojosugito *et al.*, 1970). In agreement with observations of Folkow *et al.* (1949a) and of Ström (1950b), hypothalamic heating induced a slight decrease of arterial pressure in the present investigation. On the other hand, spinal cord heating caused a moderate elevation of arterial pressure (Kullmann *et al.*, 1970). However, both stimuli gave rise to the same regional vasomotor response. This indicates that the proprioceptive circulatory control loop, though essential for

circulatory homeostasis, is not involved as a basic mechanism in the generation of the regional vasomotor antagonism.

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