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EFFECTS OF HEATING AND COOLING THE SPINAL CORD AND MEDULLA OBLONGATA ON THERMOREGULATION IN MONKEYS

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SUMMARY

1. In the unanaesthetized monkey (*Macaca cyclopis*), heating the spinal cord or the medulla oblongata from 38 to 42–43° C produced subcutaneous vasodilatation, respiratory acceleration (frequently interrupted with a period of apnoea in the medullary experiment), bradycardia and hypotension. The animal became drowsy and had a slight decrease of body temperature. Heating the medulla oblongata often induced retching and/or emesis.

2. Cooling the spinal cord or medulla oblongata from 38 to 32–33° C produced subcutaneous vasoconstriction, slower respiration, tachycardia and hypertension. The animal became restless and had a slight increase of body temperature. Cooling the spinal cord induced shivering of the four limbs, while cooling the medulla oblongata induced only shivering of the jaws.

3. The effects of heating or cooling of the spinal cord or the medulla oblongata were antagonized by simultaneous application of temperature displacement of the opposite nature in the same areas or *vice versa*.

4. The data suggest that some thermosensitive elements possibly responsible for thermoregulation reside in the spinal cord and the medulla oblongata.

INTRODUCTION

Current interest is concerned with whether the spinal cord and medulla contain a temperature-sensitive mechanism similar to that of the hypothalamus and the skin. Indeed, the medulla oblongata has been found to be a structure sensitive to heating and cooling (Chai & Mu, 1963; Chai, Mu & Brobeck, 1965; Chai & Wang, 1970; Holmes, Newman & Wolsten-

croft, 1960). In unanaesthetized dogs and rabbits, thermoregulatory responses have been elicited by the heating and the cooling of the spinal cord. The responses closely resembled those following the same thermal stimulation of the rostral hypothalamus (Jessen, 1967; Simon, 1968; Kosaka & Simon, 1968*a*; Iriki, 1968). In addition, evidence of a functional connexion between the spinal cord and rostral hypothalamus for temperature integration have been demonstrated. Neurones that are sensitive to both heating the hypothalamus and spinal cord have been found in the rostral hypothalamus (Guieu & Hardy, 1970*b*). A synergetic effect on increased oxygen consumption subsequent to individual cooling of the spinal cord or hypothalamus has been observed during simultaneous cooling of these two structures (Jessen, Simon & Kullmann, 1968). Similar synergism has been observed in polypnoea during simultaneous heating of the spinal cord and rostral hypothalamus (Guieu & Hardy, 1970*a*).

To our knowledge, not much information is available on the thermal activation of the medulla oblongata and spinal cord in the primate with special reference to the change of body temperature.

The present investigation was, therefore, undertaken to explore whether in a primate, temperature displacement of the medulla and spinal cord induce thermal response and whether these responses are related to temperature regulation.

METHODS

Fifteen chronically prepared monkeys (*Macaca cyclopis*) of either sex, weighing between 3·5 and 5·5 kg, were used. Each monkey was trained to sit quietly in a primate chair for a period of at least 10 hr at a room temperature of $25 \pm 0{\cdot}5°$ C before every experiment. This environmental temperature was also maintained throughout the whole course of the experiment. The evening before the experiment, the animal was deprived of food but water was given without restriction.

Thermal stimulation. The thermode used for stimulation of the spinal cord was prepared by winding a section of P.E. 90 polyethylene tubing, 24 cm in length, to a hairpin-like shape under hot water. The thermode used for stimulation of the medulla oblongata was prepared by winding a section of P.E. 10 polyethylene tubing, 12 cm in length, into a spiral coil. Implantation of the thermode was performed according to the method of Kosaka, Simon, Thauer & Walther (1969) with only minor modifications. In brief, the animal was anaesthetized with sodium pentobarbitone, 30 mg/kg I.V. For those animals subjected to thermal stimulation of the spinal cord the subarachnoid space of the animals was opened between the 3rd and 4th cervical vertebrae and the U-shaped end of the spinal thermode was inserted into the subarachnoid space to as far as the first or second lumbar vertebra. For those upon which medullary activation was carried out, the cisterna magna of the animal was opened. The spiral coil of the medullary thermode was inserted into the fourth cerebral ventricle at the space between the medullary stria and the obex of the medulla oblongata. Experiments were carried out at least 1 week after surgery, and only when the animal had completely recovered from the operation.

For heating or cooling the spinal cord and medulla, hot (56° C) or cold (4° C) water was perfused through the thermode by means of a constant temperature

circulator (Haakefj, West Germany). The perfusing rate was 20 ml./min for the spinal cord and 8 ml./min for the medulla. Each perfusion was given for a period of 5 min. Within 1 min following the perfusion, the spinal cord or medulla was either heated to 42–43° C or cooled to 32–33° C.

Recordings. All recordings were made on a Grass 5B polygraph. The temperature of the brain tissue was measured with a pair of thermocouples constructed from gauge 36B & S copper and constantan wires (Thermo Electric Co., Inc. Saddle Brook, New Jersey). The tip of the copper-constantan leads was welded with open flame and coated with paint of high resistance. The thermocouples were chronically implanted into the hypothalamus (2 mm to the left of the sagittal sinus, 15 mm rostral to the zero point, and 9 mm above the interauricular line) in all the animals. Thermocouple was also implanted into the spinal cord (1–2 mm below the dorsal surface of C3–C5) or the medulla (1–2 mm below the floor of the fourth cerebral ventricle) when the respective spinal or medullary thermode was implanted. The rectal temperature was monitored by a Tri-R flexible thermistor probe (Tri-R Instruments, U.S.A.) inserted approximately 10 cm into the rectum. The temperature of the subcutaneous tissue of the tail was monitored by a Tri-R hypodermic thermistor (Tri-R Instruments, U.S.A.). Arterial blood pressure was measured according to the method of Thuránszky (1966). A length of P.E. 50 polyethylene tubing was introduced into the aorta through the right carotid artery. The end of the tubing was sealed and affixed in the occipital region. The sealed end was opened daily and the cannula was flushed with heparinized saline to prevent it from clotting. After flushing, the free end was sealed again. The pressure from the aorta was monitored by a Statham P23AC pressure transducer. Heart rate was monitored with a Grass 5P4 tachograph unit which was triggered by the arterial pulses, or estimated by counting the R waves of a e.c.g. record for a period of 20 sec. Respiratory movements were monitored with a chest pneumograph, connected to a Statham P23BC transducer.

The motor activities, shivering and piloerection were observed grossly during the experiment.

At the termination of the experiment, the animal was killed by an overdose of pentobarbitone sodium and the head of the animal was perfused with 10% formalin in saline. The position of the thermodes and thermocouples was verified by gross inspection and/or frozen section of the brain tissue at a thickness of 40 μ staining with thionin.

RESULTS

Thermoregulatory responses of the spinal cord

Table 1 summarizes the effects of heating and cooling the spinal cord upon the temperature of the spinal cord, hypothalamus, rectum and subcutaneous tissue of the tail, and respiratory and cardiovascular changes in five monkeys. Fig. 1 is prepared from a monkey SS 1 to illustrate the time course of these changes during the temperature displacement.

Heating of the spinal cord (*Fig.* 1 *and Table* 1). The spinal cord was heated to 43° C in about 1 min. About 2 min after the onset of heating, the temperature of the hypothalamus and the rectum began to decrease. The fall was slight but progressive. At the end of the 5 min heating, the temperature of the hypothalamus decreased 0·5° C while that of the rectum 0·4° C. Within half a minute after the onset of heating, the subcutaneous tem-

perature of the tail and the respiratory rate increased while the heart rate and mean blood pressure decreased. These changes reached their maximum at about two min after the onset of heating. The subcutaneous temperature of the tail increased 2·2° C. The respiratory rate increased 34 breaths/min. The heart rate decreased 62 beats/min and the mean blood pressure decreased 45 mm Hg.

During heating, the animal showed signs of drowsiness and a languid relaxation of the four limbs. Heating the spinal cord reduced the shivering, respiratory inhibition and vasoconstriction which had already been induced by cooling of the same structure.

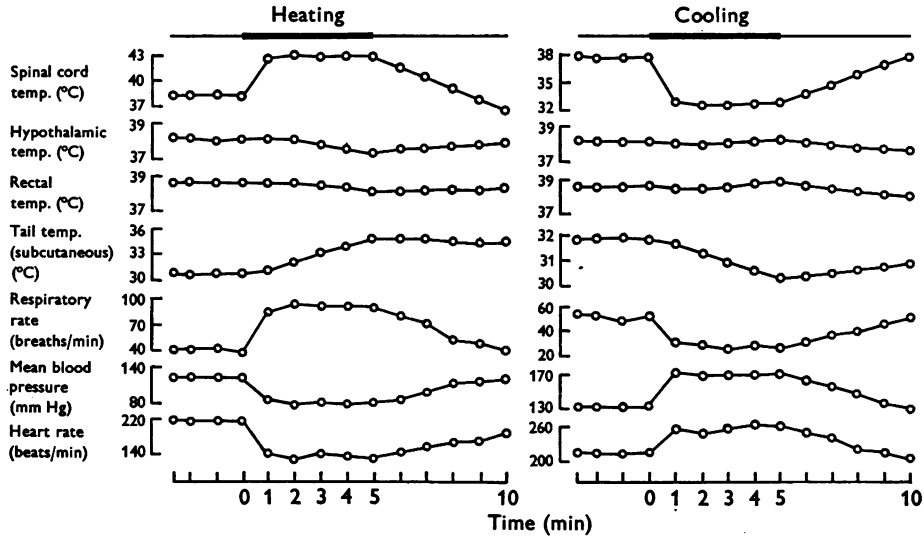

Fig. 1. Changes of the temperature of the hypothalamus, rectum and subcutaneous tissue of the tail, and respiratory and cardiovascular reactions on local change of the spinal temperature in an unanaesthetized monkey SS 1.

Cooling the spinal cord (*Fig.* 1 *and Table* 1). The spinal cord was cooled to 33° C in about 1 min. About 2 min after the onset of cooling, the temperature of the hypothalamus and the rectum began to increase and the increase was progressive throughout the cooling. The increase, however, was slight with an increase of the hypothalamus 0·4° C and that of the rectum 0·3° C. Right after the onset of cold perfusion the subcutaneous temperature and the respiratory rate decreased, while the heart rate and the mean blood pressure increased. The decrease of the subcutaneous temperature was progressive during the cooling. It reached 1·2° C at the end of the 5 min cooling. The changes of the respiratory rate, heart rate and mean blood pressure reached their maximum about 2 min after the onset of

TABLE 1. Thermoregulatory responses induced by heating and cooling of the spinal cord in five unanaesthetized monkeys

	Thermal stimulation	No. of expts.	Control	5 min after the onset of perfusion	Maximum changes	5 min after the termination of perfusion
Spinal cord temp. ° C	Heating	8	38·0 ± 0·15	41·6 ± 0·18	+ 3·6 (± 0·24)*	37·5 ± 0·12
	Cooling	8	38·0 ± 0·16	32·5 ± 0·08	− 5·6 (± 0·36)*	38·4 ± 0·16
Hypothalamic temp. ° C	Heating	8	38·0 ± 0·19	37·5 ± 0·18	− 0·5 (± 0·05)*	37·8 ± 0·15
	Cooling	8	37·9 ± 0·18	38·3 ± 0·15	+ 0·4 (± 0·04)*	38·1 ± 0·18
Rectal temp. ° C	Heating	14	38·1 ± 0·18	37·7 ± 0·20	− 0·4 (± 0·07)*	38·0 ± 0·17
	Cooling	12	38·1 ± 0·19	38·4 ± 0·21	+ 0·3 (± 0·04)*	38·2 ± 0·16
Subcutaneous temp. ° C	Heating	12	31·6 ± 0·70	33·8 ± 0·62	+ 2·2 (± 0·21)*	33·0 ± 0·58
	Cooling	14	30·8 ± 0·52	29·6 ± 0·60	− 1·2 (± 0·11)*	30·1 ± 0·48
Respiratory rate (breaths/min)	Heating	14	40 ± 1·48	74 ± 3·78	+ 34 (± 3·56)*	44 ± 1·32
	Cooling	14	44 ± 2·04	36 ± 1·35	− 8 (± 1·24)*	42 ± 2·0
Heart rate (beats/min)	Heating	10	216 ± 5·65	154 ± 9·5	− 62 (± 6·8)*	190 ± 6·25
	Cooling	10	205 ± 1·89	256 ± 5·65	+ 51 (± 6·4)*	212 ± 2·13
Arterial blood pressure, (mm Hg)	Heating	10	126 ± 2·40	81 ± 3·16	− 45 (± 3·2)*	130 ± 2·58
	Cooling	10	128 ± 2·40	168 ± 4·21	+ 40 (± 3·02)*	118 ± 1·86

Values are mean ± S.E. Asterisks (*) indicate the changes are statistically significant with P values $< 0·05$ calculated from the Student's t test.

perfusion. The respiratory rate decreased 8 breaths/min, the heart rate increased 51 beats/min and the mean blood pressure increased 40 mm Hg. Five minutes after the termination of the cooling, all parameters except the subcutaneous temperature returned to their pre-cooling level.

During cooling, the animal became alert and restless and showed a marked shivering-like movement and piloerection over the four limbs. Similarly, cooling the spinal cord reduced or inhibited the heat-induced respiratory acceleration and vasodilatation.

Thermoregulatory responses of the medulla oblongata

Table 2 summarizes the effects of heating and cooling the medulla oblongata upon the temperature of the hypothalamus, rectum and the subcutaneous tissue of the tail, and respiratory and cardiovascular changes in seven monkeys. Fig. 2 is taken from one monkey MM 3 to illustrate the time course of these changes.

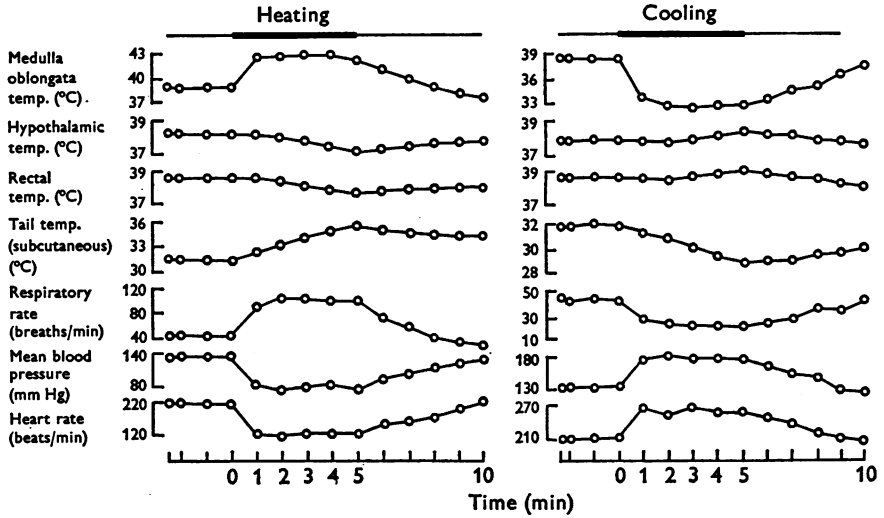

Fig. 2. Changes of the temperature of the hypothalamus, rectum and subcutaneous tissue of the tail, and respiratory and cardiovascular reactions on local change of the medullary temperature in an unanaesthetized monkey MM3.

Heating the medulla (*Fig.* 2 *and Table* 2). About 1 min after the onset of hot perfusion, the medullary temperature was elevated to a maximum of 43° C. About 2 min after the onset of heating, the temperature of the hypothalamus and the rectum began to decrease and the decrease was progressive throughout the heating. The hypothalamic temperature decreased 0·3° C while the rectal temperature decreased 0·4° C. The increase of the subcutaneous temperature was progressive. It increased 3·2° C at

TABLE 2. Thermoregulatory responses induced by heating and cooling of the medulla oblongata in seven unanaesthetized monkeys

	Thermal stimulation	No. of expts.	Control	5 min after the onset of perfusion	Maximum changes	5 min after the termination of perfusion
Medullary temp. ° C	Heating	12	38·1 ± 0·14	42·5 ± 0·20	+ 4·4 (± 0·25)*	37·6 ± 0·12
	Cooling	12	38·2 ± 0·18	32·2 ± 0·12	− 5·7 (± 0·38)*	38·6 ± 0·17
Hypothalamic temp. ° C	Heating	12	38·0 ± 0·12	37·7 ± 0·12	− 0·3 (± 0·02)*	37·9 ± 0·14
	Cooling	12	38·1 ± 0·14	38·5 ± 0·15	+ 0·4 (± 0·03)*	38·2 ± 0·15
Rectal temp. ° C	Heating	12	38·2 ± 0·16	37·8 ± 0·15	− 0·4 (± 0·02)*	38·0 ± 0·17
	Cooling	12	38·4 ± 0·10	38·7 ± 0·11	+ 0·3 (± 0·01)*	38·4 ± 0·18
Subcutaneous temp. ° C	Heating	12	28·4 ± 0·88	31·4 ± 1·11	+ 3·2 (± 0·39)*	31·2 ± 1·11
	Cooling	12	29·8 ± 0·85	28·1 ± 0·72	− 1·7 (± 0·27)*	28·8 ± 0·76
Respiratory rate (breaths/min)	Heating	20	36 ± 2·13	76 ± 4·62	+ 40 (± 4·26)*	39 ± 2·12
	Cooling	12	36 ± 3·21	27 ± 1·52	− 9 (± 1·95)*	35 ± 3·06
Heart rate (beats/min)	Heating	18	220 ± 3·05	150 ± 5·25	− 70 (± 5·20)*	210 ± 3·05
	Cooling	12	210 ± 2·62	257 ± 5·92	+ 47 (± 3·60)*	220 ± 2·70
Arterial blood pressure, (mm Hg)	Heating	12	135 ± 3·40	87 ± 5·02	− 48 (± 6·25)*	142 ± 4·10
	Cooling	12	135 ± 3·65	180 ± 5·10	+ 45 (± 4·20)*	128 ± 3·20

Values are mean ± S.E. Asterisks (*) indicate the changes are statistically significant with P values $< 0{\cdot}05$ calculated from the Student's t test.

the end of the 5 min heating. The changes of the respiratory rate, heart rate and the mean blood pressure were immediate. They reached their maximum about 2 min after the onset of heating. The respiratory rate increased 40 breaths/min but was interrupted periodically with apnoea varying from 5 to 15 sec. The heart rate decreased 70 beats/min and the mean blood pressure decreased 48 mm Hg. Five minutes after the termination of the hot perfusion all parameters except the subcutaneous temperature returned to approximately the pre-heating level.

During heating, the animal became drowsy and relaxed. In addition, retching and/or vomiting occurred in ten of twelve heating experiments. Heating the medulla oblongata reduced or inhibited the apnoea and vasoconstriction induced by cooling of the same structure.

Cooling of the medulla (*Fig.* 2 *and Table* 2). About 1 min after the onset of cold perfusion, the medullary temperature was lowered to its maximum of 32·2° C. About 2 min following the onset of cooling, the temperature of the hypothalamus and the rectum began to increase and the increase was progressive. The temperature of the hypothalamus increased 0·4° C and the temperature of the rectum increased 0·3° C at the end of the 5 min cooling. Right after the onset of cooling the subcutaneous temperature and the respiratory rate decreased, while the heart rate and the mean blood pressure increased. The decrease of the subcutaneous temperature was progressive. At the end of the 5 min cooling, the subcutaneous temperature decreased 1·7° C. The changes of the respiratory rate, heart rate and the mean blood pressure reached their maximum about 2 min following the onset of perfusion. The respiratory rate decreased 9 breaths/min, the heart rate increased 47 beats/min and the mean blood pressure increased 45 mm Hg. All parameters returned to approximately their pre-cooling level within five min following the termination of the cold perfusion.

During cooling, the animal became alert and restless. In addition, marked shivering-like movements and piloerection occurred over the jaws. Similarly, cooling the medulla oblongata reduced or inhibited the heat-induced respiratory acceleration and vasodilatation.

The afore-mentioned responses on heating or cooling of the spinal cord and medulla could be reproduced in the same animal at an interval of 1 hr to several days.

In three animals thermodes were implanted merely into the occipital musculature. Similar hot or cold perfusion for a period of 5 min did not produce any response.

DISCUSSION

Body temperature is principally integrated in the preoptic anterior hypothalamic area. Its constancy is accomplished by means of the respiratory, vasomotor and other autonomic reactions to which medulla oblongata exerts an important control. The vasomotor and sympathetic pathways descend in the spinal cord. Afferent pathways of the temperature sensors from various sources also take their paths through the spinal cord and medulla. It is therefore possible that the medulla and spinal cord may relate to thermoregulation.

Indeed, current experimental evidences have suggested the existence of thermoregulatory mechanism in the neural axis other than the rostral hypothalamic-preoptic area. Panting and shivering have been elicited in unanaesthetized goats and cats with complete destruction of the preoptic region when they were exposed to hot (40–45° C) or cold (4–5° C) environment (Andersson, Gale, Hökfelt & Larsson, 1965; Jacobson & Squires, 1963; Squires & Jacobson, 1968).

The thermosensitivity of the spinal cord has been repeatedly documented. Thermal responses, i.e. cutaneous vasodilatation versus vasoconstriction, respiratory acceleration versus respiratory inhibition and shivering have been produced upon heating and cooling of the spinal cord in dogs and rabbits (Jessen, 1967; Simon, 1968; Iriki, 1968; Kosaka & Simon, 1968*a*). Similar changes of vasomotor, respiratory and somatic reactions were also observed in the present investigation during heating and cooling of the spinal cord in monkeys. These results are also consistent with those of our recent observations of similar nature in rats (M. T. Lin, Yin & C. Y. Chai, unpublished data).

The existence of thermosensitive elements in the medulla oblongata are also evident. A fall of blood pressure and an acceleration of respiration have been produced upon heating of the carotid blood in anaesthetized and decerebrate cats (Newman & Wolstencroft, 1960). Bradycardia and respiratory inhibition have been produced by local diathermy of the lateral reticular formation of the medulla oblongata in decerebrate cats (Chai *et al.* 1965). Local cooling of the same structure has produced the opposite effects (Chai & Wang, 1970). Since all these investigations were carried out in either decerebrate or anaesthetized animals, the study of changes of body temperature was not possible. The present study used conscious monkeys. Heating the medulla oblongata to 41–43° C produced a decrease of the rectal temperature and responses of heat loss, i.e. subcutaneous vasodilatation, respiratory acceleration and responses of decreased heat production, i.e. drowsiness and decrease of motor activity. Conversely, cooling the medulla produced an increase of the rectal tem-

perature and responses of heat conservation, i.e. vasoconstriction, decrease in respiratory rate and responses of heat production, i.e. shivering and increase of motor activity.

The respiratory changes on thermal activation of the medulla in conscious monkeys are opposite to those of the anaesthetized cats observed previously (Chai *et al.* 1965). Careful examination of the previous tracings, however, revealed that during the heating, very small but fast respiratory movement was interposed during the period of respiratory inhibition. Heating and cooling of the medulla produced bradycardia and trachycardia both in conscious monkeys and anaesthetized cats. It is not known whether the cardiac changes carry any significance on thermal regulation. Changes in heart rate upon heating and cooling of the medulla may be the result of direct activation or inactivation of the vagal mechanism. A possibility of direct activation of the control mechanism for emesis in the medulla has been suggested, as heating the medulla often induced retching and/or emesis.

It is clear from the present study that heating or cooling of the spinal cord and medulla oblongata produced changes similar to those of thermal stimulation of the hypothalamus reported by various investigators (Santinoff, 1964; Hardy, 1961; Andersson, Gale & Sundsten, 1962; Spector, Brobeck & Hamilton, 1968). Because of this similarity one naturally questions whether the responses consequent to thermal stimulation of the spinal cord and medulla are results of afferent activation of the hypothalamus. One may also inquire whether the thermal responses observed are results of activation of the thermal afferents from the periphery including the dorsal root and/or the secondary order neurones inside the cord or the medulla. The importance of the thermal afferent from the periphery on the integration of body temperature has been suggested (Fusco, Hardy & Hammel, 1961). The answers for these questions await further investigation.

It should be noted that although separation of the hypothalamus from the brain stem may eliminate the mechanism for maintaining a constancy of body temperature, yet many of the thermoregulatory responses persist. For instance, in dogs, disconnexion of the hypothalamus from the neural axis did not affect the shivering induced by cooling of the spinal cord (Chatonnet, 1963; Hemingway, 1963; Kosaka & Simon, 1968*b*; Kosaka, Simon & Thauer, 1967; Simon, Klussmann, Rautenberg & Kosaka, 1966). Vasodilatation and sweating has been observed in patients with high spinal transection when the ambient temperature was elevated (Randall, Wurster & Lewin, 1966). Increase of foot blood flow has been elicited in paraplegic patients with cauda equina lesions from L1 downward upon raising the body temperature by immersion of their forearms into hot

(40–44° C) water (Cooper, Ferris & Guttmann, 1957). They found no such response to raising the body temperature in the high spinal transection patient. The respiratory and cardiovascular changes upon heating and cooling of the medulla in anaesthetized cats were not affected by decerebration (Chai *et al.* 1965; Chai & Wang, 1970). Most of these suggest that some independent mechanisms exist in the spinal cord or medulla that are sensitive to temperature displacement or that these mechanisms may share with the hypothalamus in temperature regulation.

Finally, it should be added that in the present investigation, the decrease or the increase of the hypothalamic temperature, which occurred during heating or cooling the spinal cord or medulla oblongata, is not considered to be the cause of the thermal reactions observed. Unlike that of the artificial temperature displacement of the hypothalamus, the spontaneous change of hypothalamic temperature has been found unrelated to the thermoregulatory responses (Fusco, 1963). In addition, in a neutral environment, the hypothalamic temperature may vary over a natural variation of 0·5–1·5° C, depending on the species but within this range no thermoregulatory responses were activated (Forster & Ferguson, 1952; Findlay & Ingram, 1961; Hemingway, Robinson, Hemingway & Wall, 1966; Hamilton, 1963).

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