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Studies on Thermoregulatory Capability in the PO/AH Lesioned Rabbit

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Abstract: In the present series of experiments, we tried to elucidate the nature of thermoregulation in responses to environmental temperature shifts (25°C→40°C→10°C→25°C) in the rabbits devoid of pre-optic and anterior hypothalamic (PO/AH) regions. Bilateral PO/AH lesions in male rabbits were accomplished using electrolytic procedure. And thermoregulatory capabilities before and after PO/AH lesions were compared. In control rabbits, with the change in ambient temperature (Ta), the ear skin temperature (Tea) changed in the same direction. The change in rectal temperature (Tre) was small. In one-week-lesioned rabbit, the change of Tre was great when heated, but Tre was stable to cold stress. In two-weeks lesioned rabbit, Tre, inspite of Ta change, was quite stable: to the extent that it was comparable to the control rabbits. Therefore, these results should be interpreted as presenting the recovery of thermoregulatory functions after the PO/AH lesions. It is concluded that, without PO/AH participation, extrahypothalamic thermosensitive tissues were the places endowed with these thermoregulatory functions.

Key words: PO/AH lesioned rabbit, Thermoregulatory capability, Cutaneous vasodilation and vasoconstriction, Extrahypothalamic temperature regulation

INTRODUCTION

Thermal physiologists held the concept that the thermoceptive and controlling functions were to be residing in hypothalamic structures (Cooper, 1966). Thereafter, for

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about half a century the hypothalamus has been considered as the most important site of deep body temperature perception. Hypothalamic temperature had been assumed to represent the controlled variable in temperature regulation. However, when quantitative assessments were being made, the accountability of exclusive hypothalamic temperature control was questioned (Brown and Brengelmann, 1970). Various types of interaction between hypothalamus and other structures are assumed for explanation; such as shift of hypothalamic set temperature by thermal input from the skin (Fusco *et al.*, 1961, Hammel, 1965) or multiplicative interaction of cutaneous and hypothalamic temperature inputs (Stolwijk and Hardy, 1966). Moreover, the disclosure of extrahypothalamic deep body thermoception in spinal cord, mid-brain, medulla oblongata and in deep body tissues outside the CNS led to attempts to explore quantitative interactions of deep body thermosensors (Kosaka *et al.*, 1969, Simon, 1974).

In the present series of experiments, we tried to elucidate the nature of thermoregulation in response to environmental temperature shifts in animals devoid of pre-optic area and anterior hypothalamus (PO/AH) region controls.

ANIMALS AND METHODS

Animals

Male rabbits weighing about 2.6 kg were used. First, the animals were subjected to whole body temperature stress experiment. Bilateral pre-optic area and anterior hypothalamus (PO/AH) lesions were then accomplished using electrolytic procedure. After one week of the electrolysis, whole body temperature stress experiment was done again; which was repeated two weeks after. After electrolysis, the animals were put in thermoneutral room for 3 days, and body weight, rectal temperature, the amount of food and water intakes were monitored. The rectal temperature for the first 2-3 days slightly raised and food and water intakes were minimal. But after 4−5 days, the amount of food and water intakes reached normal level; rectal temperature reached around 39.5°C. After 2 weeks, a slight increase in body weight was observed.

Electrolytic procedure

Bilateral PO/AH lesion by electrolysis was accomplished by applying 5 mA direct current for 20 sec through a steel electrode with 2 mm uninsulated tip; the indifferent electrode was placed in contact with muscle in the neck or scalp. The co-ordinates of electrode placements were A −2.5, L ±1.5 and V − 3 mm (for details, see Fifková and Maršala, 1967).

Histological investigation

After general heat load experiments, rabbits were sacrificed. The brain was fixed with 10% formalin solution and hematoxylin eosin (HE) stain was performed to determine

the precise portion of the lesion. In Figure 1, a schematic representation of transverse section of the rabbit's brain is available for indicating precise portions of anterior hypothalamus (AHA), lateral hypothalamus (AHL), optic tract (TO) and third ventricle (V III). Figure 2 demonstrates a typical result of histological investigation of HE stain. In this case, PO/AH was completely omitted, and the marginal dark area indicated marked fibrotic degeneration with no blood supply, which was further surrounded by degenerative tissues with moderate vascularization.

Whole body temperature stress experiment

An environmental chamber capable of preprogrammed control of temperature shift was used. The animal was minimally restrained for the experiment. Rectal temperature, ear skin temperature, ambient temperature were continuously monitored using thermistor probes connected to computer. The computer kept track of temperature making every minute recording and printed out. Respiratory frequency was determined from resistance changes of a strain-gauge strapped around the abdomen; recording were done with an ATAC 450 computer (Nihon Koden Co.). The ambient temperature displacements were programmed and carried out in the same manner described in the previous paper (Fujiwara

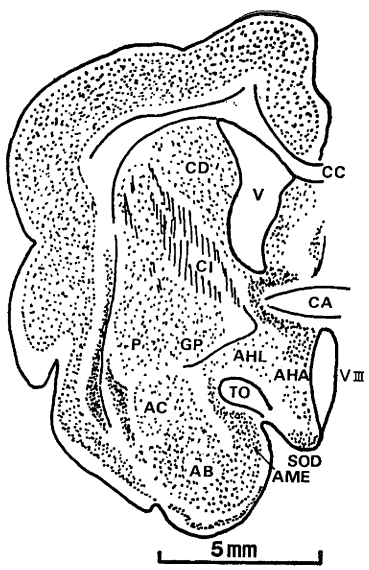

Fig. 1. A schematic representation of transverse section of the rabbit's brain (modified from Fifková and Maršala, 1967). Abbrevations; AHA: anterior hypothalamus, AHL: lateral hypothalamus, TO: optic tract, VIII: third ventricle

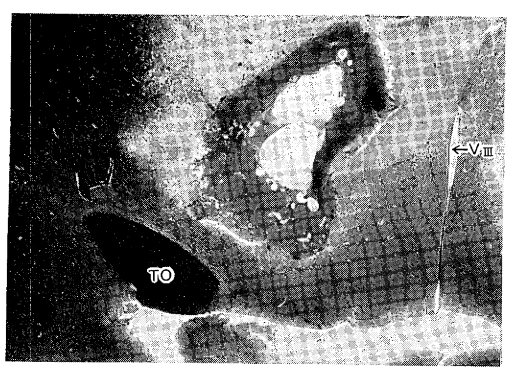

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Fig. 2. Histological investigation of the right side of preoptic area and anterior hypothalamus in the bilateral PO/AH lesioned rabbit using HE stain. Same in the left side of preparation. (For details see text)

et al., 1985), as follows; The animal was kept in the environmental chamber preset at 25°C for the first an hour. Then the temperature was brought up to 40°C within half an hour. The temperature at 40°C was maintained for half an hour. After that, temperature was again brought down to 10°C with the same rate of temperature change. It took one hour to reach at 10°C. That state continued for half an hour at 10°C. Ambient temperature was again raised to 25°C; after half an hour at 25°C, the experiment was terminated.

RESULTS

Figure 3 shows the ambient temperature (Ta) shifts, corresponding mean ear temperature (Tre) in four control rabbits. In these rabbits, for example, at the start of experiment when Ta was 25°C, mean Tea was 35.0°C and mean Tre was 38.6°C. When Ta reached 40°C, corresponding mean Tea was 36.6°C and mean Tre was 39.7°C. When Ta was lowered and reached at 10°C, mean Tea became 22.0°C and mean Tre decreased to 38.5°C, respectively. In these control rabbits, mean Tea shifted in the same direction with the change of Ta. On the other hand, change in mean Tre was small. Increase

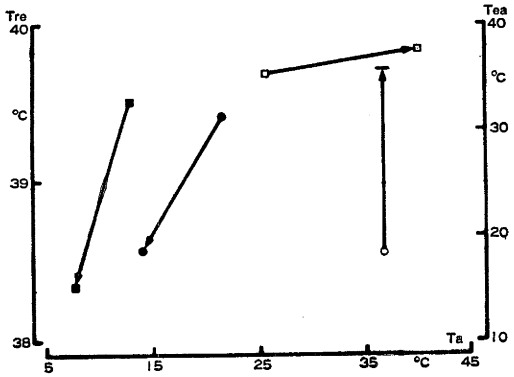

Fig. 3. Changes in mean values of rectal (Tre, squares) and ear skin (Tea, circles) temperatures due to the displacement of ambient temprature (Ta) in control rabbits (n=4). Solid and open symbols represent declining and rising phases of Ta displacement, respectively. (modified from Fujiwara *et al.*, 1985)

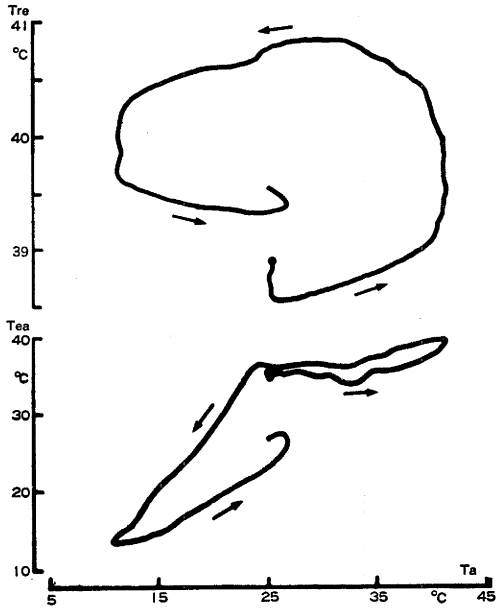

Fig. 4. Changes in rectal (Tre) and ear skin (Tea) temperatures due to the displacement of ambient temperature (Ta) in a bilateral PO/AH lesioned rabbit (recorded one day after PO/AH lesion).

in mean Tre began when Ta was 36°C (for details see previous paper; Fujiwara *et al.*, 1985).

Figure 4 shows thermoregulatory responses of a rabbit of which bilateral PO/AH were lesioned one day before with the electrolysis. And continuous changes in Tre (the upper part) and Tea (the lower part) were induced by Ta displacement of the same program as shown in the paper (Fujiwara *et al.*, 1985). In thermo-neutral at 25°C, Tea of this PO/AH lesioned rabbit was 35.5°C, and the initial Tre was 38.6°C. However, changes in Tre was suddenly induced by general heating, and Tre reached at 40.8°C in 16 minutes after the end of general heating. In time course of general cooling, Tre remained at high level. During re-heating period, Tre remained still higher than initial level of Tre.

Figure 5 shows thermoregulatory responses recorded in one week after bilateral PO/AH lesion, and it was the same rabbit in Figure 4. In general heating of 28°C to 31°C, Tea of the rabbit shifted from 32.9°C to 37.3°C. And in the time course of heating towards 35°C, Tre remained almost constant at 38.4°C. Further, Tre reached at 40.3°C in 9 minutes after the end of general heating of 40°C. In general cooling towards 17°C, Tea remained at high level, while marked decrease of Tre ensured at 25°C of Ta. In general

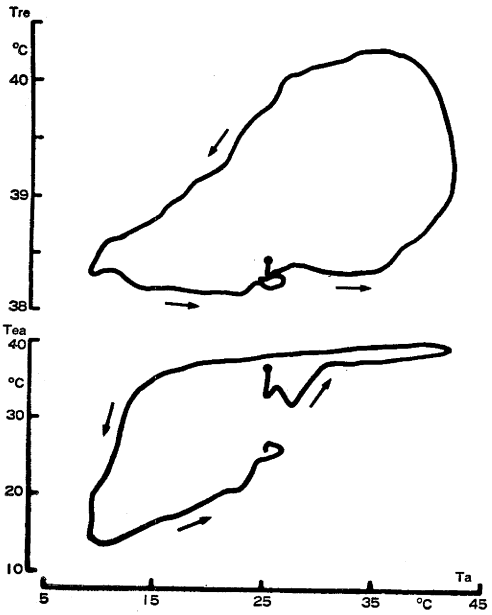

Fig. 5. Changes in rectal (Tre) and ear skin (Tea) temperatures due to the displacement of ambient temperature (Ta) in the same rabbit in Figure 4 (recorded one week after PO/AH lesion).

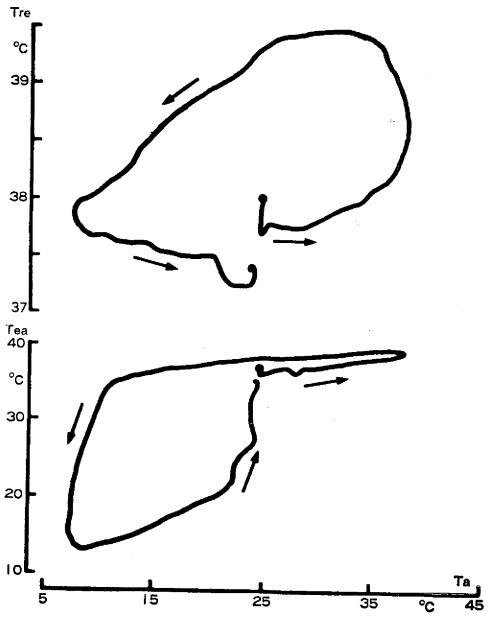

Fig. 6. Changes in rectal (Tre) and ear skin (Tea) temperatures due to the displacement of ambient temperature (Ta) in the same rabbit in rabbit in Figures 4 and 5 (recored 2 weeks after PO/AH lesion).

cooling of 13°C to 10°C, a decrease of Tre took place slowly. In this PO/AH lesioned rabbit, the range of 1.9°C in Tre variation by displacement of Ta was still wider compared with that of 1.4°C in control rabbit.

Thermoregulatory capabilities of the same rabbit in Figure 4 and 5 were examined in 2 weeks after bilateral PO/AH lesion, and the results are demonstrated in Figure 6. In thermo-neutral state at 25°C, Tea of the rabbit remained at 36.0°C. Further in general heating towards 40°C, Tea increased gradually up to 37.7°C. Rectal temperature increased slowly, and reached at 39.5°C in 6 minutes after end of general heating. In Ta displacement of 40°C to 14°C, Tea remained considerably high level. Remarkable decrease of Tea was induced at general cooling of 12°C.

DISCUSSION

As a summary of results, in control rabbits, with the change in Ta, Tea changed in the same direction. The change in Tre, on the other hand, was minimal. In one day after bilateral PO/AH electrolysis, Tea of the rabbit considerably depended on displacement of Ta, therefore, the functions of heat dissipation and conservation due to cutaneous vasomotion trended to be suppressed. The range of 2.3°C in Tre shift of the PO/AH lesioned rabbit induced by ambient thermal stimulation was a large variation compared with 1.4°C of control rabbits. And this finding suggests that the ability of thermoregulation in the PO/AH lesioned rabbit is considerably poor in one day after lesions. In one week after bilateral PO/AH lesions, the range of variation in Tre by displacement of Ta of 25°C→40°C→10°C→25°C in this rabbit was 1.9°C. It suggests that recovery of thermoregulatory function was not enough to control the body temperature at constant. However, though the changes of Tre seemed to be great when heated, Tre seemed to be quite resistant to cold stress. In two weeks after bilateral PO/AH lesions, Tre in spite of Ta changes, was quite stable; to the extent that it was comparable to the control rabbits, as shown in Figure 6. By use of proton irradiation to attain complete destruction of pre-optic region, Andersson *et al.* (1965) reported that the responsiveness to hyperthermia with a certain degree of polypnoea in goats was retained. It did not become permanently poikilothermic against heat. As second line of defense against over-heating residing more posteriorly in the brain was postulated. When exposed to cold, these goats had a slightly lower body temperature (36−37°C) after which further drop was arrested and even then shivering brought a certain rise in body temperature. It is clear that PO/AH lesions cause decreased ability to maintain normal body temperature in heat and in cold in rats and that some rats (with less lesion, presumably) are able to regulate against high and low Ta. Various autonomic thermoregulatory responses induced by general heating and cooling of skin in the PO/AH impaired rabbits closely resemble those observed in PO/AH intact animals (Kosaka *et al.*, 1984).

As regards to ear skin vasodilation, there is no significant difference observed between control and PO/AH lesioned rabbits which imapired PO/AH one month before by X-ray irradiation (Kosaka *et al.*, 1984). In intact rabbits, exposure to heat of 35°C for one hour caused ear skin vasodilation; Tea increase 5.5°C and increase in respiratory rate; with little increase in Tre. In decerebrate animals, there was less active response when subjected to the same heat load. Increase in respiratory rate was slight, the rise in Tea was less (3.9°C) and therefore Tre increased considerably (1.8°C) (Chai and Lin, 1973). It is the same in case of cold stress. In the results of these experiments presented here, Tre changes observed in the rabbits one day after and one week after PO/AH lesion were accentuated. On the other hand, those in control rabbits and 2 weeks lesioned rabbit, were less marked. Ear skin temperature changes in intact and 2 weeks lesioned rabbits had steep slope and wide gap between initial position and the peak (or pit) during thermal stress. Recording activity of single neurons in PO/AH region during local heating, Nakayama *et al.* (1963) and Hardy (1964) reported that a small percentage of these responsed to changes in brain temperature. It was suggested that thermoreceptors in skin, sensitive to increasing ambient temperature also play an important role (Lim and Grodins (1955)), and they had demonstrated a lower threshold for thermal polypnoea for whole body heating as opposed to local heating in the anesthetized dog. Murakami *et al.* (1967) asserted that peripheral warm stimulation did not modify any of the PO/AH units activities studied in the dog. According to Wit and Wang (1968), a large majority of neurons encountered in PO/AH area were unresponsive to increase in Ta or body temperature. Therefore, the results obtained in the present experiments should be interpreted as presenting the return of thermoregulatory function after bilateral PO/AH lesions to a certain extent. The structures other than PO/AH might have the capacity to carry out the regulatory responses appropriate to the change. The magnitude and direction of the responses were appropriate for attainment of a fairly well regulated position. It is assumed that without PO/AH participation, brain stem and spinal cord were the places endowed with these functions.

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REFERENCES

1) Andersson, B., Gale, C. C., Hokleft, B. and Larsson, B. (1965): Acute and chronic effects of preoptic leisons. Acta physiol. scand., 65, 45−60.

2) Brown, A. C. & Brengelmann, G. L. (1970): The interactions of periphral and central inputs in the temperature regulation system. pp 684−702. *In*: J. D. Hardy, A. Gagge & J. A. J. Stolwijk (ed.). Physiological and behavioural temperature regulaion. Thomas Springfield.

3) Chai, C. Y. & Lin, M. T. (1973): Effects of thermal stimulaion of medulla oblongata and spinal cord on decerebrate rabbits. J. Physiol., 234, 409−419.

4) Cooper, K. E. (1966): Temperature regulation and the hypothalamus. Br. Med. Bull., 22, 238−242.

5) Fifková, E. & Maršala, T. (1967): Stereotaxic atlases for the cat, rabbit and rat. pp 653−731. *In*: J. Bureš, M. Petráň & J. Zachar (ed.). Electrical methods in biological research. Academic Press, New York.

6) Fujiwara, M., Ohwatari, N. & Kosaka, M. (1985): Studies on thermoregulatory mechanisms in heat-acclimated rabbits. J. Physiol. Soc. Japan, 47, 616.

7) Fusco, M. M., Hardy, J. D. & Hammel, H. T. (1961): Interaction of central and peripheral factors in physiological temperature regulation. Am. J. Physiol., 200, 572−580.

8) Hammel, H. T. (1965): Neurons and temperature regulation. pp 71−97. *In*: W. S. Yamamoto & J. R. Brobeck (ed.). Physiological controls and regulation. Saunders, Philadelphia.

9) Hardy, J. D., Hellon, R. F. & Sutherland, K. (1964): Temperature sensitive neurones in the dog's hypothalamus. J. Physiol., 175, 242−253.

10) Kosaka, M., Ohwatari, N., Fujiwara, M., Inomoto, T. & Tsuchiya, K. (1984): Study on temperature regulation in preoptic anterior hypothalamus impaired rabbits. pp 75−78. *In*: J. R. S. Hales (ed.). Thermal Physiology. Raven Press, New York.

11) Kosaka, M., Simon, E., Thauer, R. & Walther, O.-E. (1969): Effect of thermal stimulation of spinal cord on respiratory and cortical activity. Am. J. Physiol., 217, 858−864.

12) Lim, P. K. & Grodins, F. S. (1955): Control of thermal panting. Am. J. Physiol., 180, 445−449.

13) Murakami, N., Stolwijk, J. A. J. & Hardy, J. D. (1967): Responses of preoptic neurons to anesthetics and peripheral stimulation. Am. J. Physiol., 213, 1015−1024.

14) Nakayama, T., Hammel, H. T., Hardy, J. D. & Eisenman, J. S. (1963): Thermal stimulation of electrical activity of single units of the preoptic region. Am. J. Physiol., 204, 1122−1126.

15) Simon, E. (1974): Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev. Physiol. Biochem. Pharmacol., 71, 1−76.

16) Stolwijk, J. A. J. & Hardy, J. D. (1966): Temperature regulation in man: A theoretical study. Pflügers Arch., 291, 129−162.

17) Wit, A. & Wang, S. C. (1968): Temperature sensitive neurons in preoptic anterior hypothalamic region: effects of increasing ambient temperature. Am. J. Physiol., 215, 1151−1159.

視床下部破壊ウサギの体温調節能に関する研究

Ye-Win（ビルマ・ラングーン第2医学研究所・生理学教室），小坂光男，大渡　伸，藤原真理子，土屋勝彦，岩元　純，范　育仁（長崎大学熱帯医学研究所・環境生理）

両側視床下部破壊ウサギに環境温度刺激（25°C→40°C→10°C→25°C）を加えて誘発される体温調節反応から体温調節機序の解明を試みた．前視床下部（PO/AH）の破壊には直流を用い，破壊後の体温調節能の推移を検索した．無傷ウサギの耳介皮膚温度変化は環境温度変化と同じ方向に推移し，その直腸温度変化は微少であった．PO/AH 破壊1週間後のウサギの直腸温は加温刺激時で大きく変動をみたが，冷却刺激には，かなりの抵抗を示した．破壊2週間後には，環境温度刺激に対する直腸温変化は無傷ウサギの直腸温変化に近似となった．この実験結果はPO/AH 破壊ウサギの体温調節能には回復がみられる事を示唆しており，視床下部外温度感受性組織（脳幹や脊髄）による体温調節機能の修飾が推察される．

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