学 位 論 文 の 要 旨

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学　位　論　文　名　　Contribution of the Suprachiasmatic Nucleus to the Formation of a Time Memory for Heat Exposure in Rats

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論 文 内 容 の 要 旨

INTRODUCTION

When rats or humans are subjected to heat exposure limited to about 5 h at a fixed time daily, and then transferred to a constant thermoneutral ambient temperature (T_a), the pattern of day-night variations in their core temperature (T_{cor}) alters so that T_{cor} falls for 3 to 4 h around the period when they were previously exposed to heat. We therefore hypothesized that a time memory for heat exposure can be formed in rats and humans due to daily heat exposure limited to a fixed time once a day, and according to this memory, thermoregulatory function may be modified during the specific period so that their T_{cor} drops. However, the central mechanism for the formation and retention of such a time memory is totally unknown. The suprachiasmatic nucleus (SCN) of the hypothalamus is known to be important for genesis of circadian rhythms of T_{cor}. Thus, the present study investigated a contribution of the SCN to the formation of a time memory of heat exposure time in rats acclimated to heat given at a fixed time daily. For this purpose, we examined the pattern of nocturnal variations of Fos expression, as a marker of neuronal activation, in the SCN and the effects of SCN lesions on nycthemeral changes of T_{cor} in heat-acclimated rats.

MATERIALS AND METHODS

Animals and heat exposure schedule: Male Wistar rats (240 - 260 g) were housed individually in cages at a T_a of 24.0℃ with access to food and water ad libitum. Main lighting was controlled on a 12:12 h cycle. To produce heat-acclimated rats (HA), the T_a inside the animal room, initially set at 24.0℃, was raised to 32.0℃ over 30 min, starting in the middle of the dark phase. The high T_a was maintained for the subsequent 5 h, then returned to 24.0℃ over 30 min; thus, rats were exposed to heat only during the last half of the dark phase. Heat exposure was repeated for 10 consecutive days. After the 10-day heat exposure schedule, the rats were maintained at a constant T_a of 24.0℃. Control rats (CN) were kept at a T_a of 24.0℃ throughout the study.

Fos expression in the SCN: After the 10-day heat exposure schedule, HA were anesthetized at 0900 h (n=6), 1200 h (n=6) or 1500 h (n=5), the time corresponded to the middle of the first half of the dark phase, the middle of the dark phase and the middle of the last half of the dark phase, respectively. CN were anesthetized at the same times of day as HA (n=4 at each point). They were then perfused transcardially with buffered fixing solution. Their brains were removed and used for Fos immunohistochemical study. In the SCN, Fos immunoreactive (Fos-IR) neurons were counted in two subdivisions, i.e. dorsomedial (dSCN) and ventrolateral (vSCN) SCN, in the middle plane where the area of the SCN was the largest. For each region we counted both sides of three sections and calculated the average of the six areas.

Effects of SCN lesion on daily T_{cor} changes: The SCN were electrically lesioned bilaterally in 5 rats under anesthesia. Sham-operation was performed in 5 rats. In each rat, additionally, temperature transmitter was implanted in the peritoneal cavity to remotely measure intraperitoneal temperature (T_{ab}) as an indicator of T_{cor}. After a 3-week recovery period, the rats were acclimated to heat. Their T_{ab} and spontaneous body movements (BM) estimated by the times that the rats crossed infrared beam placed at the side of the cage were sampled every 150 sec for over 24 h before and after heat acclimation.

RESULTS AND DISCUSSION

The number of Fos-IR neurons of CN did not vary during the dark phase in either the dSCN or vSCN, whereas in HA, there were significant nocturnal variations of the number of Fos-IR cells in the two regions. In the dSCN, the Fos-IR cell number of HA at 1500 h, when HA had been previously exposed to heat, was significantly smaller than that of HA at 0900 h and that of CN at 1500 h. In the vSCN, neurons appeared to be activated at 1500 h in HA. Since an attenuation of neuronal activities in the dSCN may be related to induction of hypothermia, the results may suggest a significant contribution of the SCN to a specific fall in T_{cor} during the period of previous heat exposure time in HA.

In sham-operated rats, there were clear day-night variations of T_{ab} and BM throughout the measurements. Heat acclimation induced characteristic falls in T_{ab} in the last half of the dark phase. In SCN-lesioned rats, T_{ab} and BM exhibited arrhythmicity regardless of the acclimation condition. The pattern of daily variations of T_{ab} was significantly influenced by heat acclimation, i.e. the levels of T_{ab} obviously decreased after the 10-day heat exposure schedule. However, there were no specific falls in T_{ab} in the last half of the dark phase when SCN-lesioned rats had previously been exposed to heat. Thus, the SCN seems to be the dominant brain structure forming and retaining a time memory for timed daily heat stress and then establishing a new pattern of circadian T_{cor} variations in heat-acclimated rats. Since heat acclimation generally induces hypothermia, the SCN may have a minimal role in the process of heat acclimation, at least with regard to a T_{cor} shift in rats.

CONCLUSION

The SCN may be a crucial structure in establishing and retaining a time memory for timed heat stress in the central nervous system, while it may not have a significant role in the process of heat acclimation in rats.