学 位 論 文 の 要 旨

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学　位　論　文　名　Proliferation of Neuronal Progenitor Cells and Neuronal Differentiation in the Hypothalamus Are Enhanced in Heat-Acclimated Rats.

発　表　雑　誌　名
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著　　者　　名
} 別紙の通り

論 文 内 容 の 要 旨

INTRODUCTION

In mammals, repeated exposure to moderate heat has been well-known to result in the development of heat acclimation that improves heat-tolerance. Such thermoregulatory changes in heat-acclimated subjects are known to be attributable to both the peripheral thermoeffector efficiency at a given level of central thermoregulatory drive and to changes in a gain of the thermoregulatory centers. The heat acclimation process has two forms, namely short-term and long-term heat acclimation, depending on a length of the heat-exposed term. Briefly, thermoregulatory changes of short-term heat acclimation are lost rapidly after the end of heat exposure, while those of long-term heat acclimation are stable and sustained. Thus, especially in long-term heat acclimation, persisting functional and/or morphological changes may be expected in the central thermoregulatory system. For the central mechanism of heat acclimation, several investigations have been made in the anterior hypothalamus from various points of views, regarding gene expression profiles and morphological changes in synaptic structures, e.g. number, thickness, curvature and complexity. These studies suggest repetitive heat exposure-induced neuronal plasticity in the thermoregulatory center and suggest a possible contribution of such hypothalamic neuronal modifications to the establishment of heat

acclimation. However, the central mechanism of heat acclimation has not been fully elucidated. In these studies, we examined the effect of heat exposure on proliferation and differentiation of neuronal progenitor cells in the rat hypothalamus.

MATERIALS AND METHODS

Male Wistar rats (5 weeks old), initially maintained at an ambient temperature (T_a) of 24°C, were subjected to a constant high T_a of 32°C (HE) or were constantly kept at 24°C (controls, CN). Bromodeoxyuridine (BrdU; 50 mg/kg/day) was intraperitoneally injected daily for 5 consecutive days after commencing heat exposure. On the 6th (HE6), 13th (HE13), 23rd (HE23), 33rd (HE33), 43rd (HE43) and 53rd (HE53) day of the heat exposure period, the brain samples were used for immunohistochemical studies. The same procedure was applied to CN without heat exposure, i.e. the brains were removed on the 6th (CN6), 13th (CN13), 23rd (CN23), 33rd (CN33), 43rd (CN43) and 53rd (CN53) days corresponding to the heat exposure period in HE. Intra-abdominal temperature (T_{ab}) of the rats was measured using a biotelemetry system. All experiments with animals in this study were approved by the Ethics Committee for Animal Experimentation of Shimane University and they were handled according to our institutional guidelines.

RESULTS AND DISCUSSION

Immunohistochemical analysis showed that the numbers of BrdU-positive (BrdU+) cells in the hypothalamus of HE were significantly and consistently greater than those of CN. In HE6, a high density of BrdU+ cells was observed in the ependymal layer of the third ventricle. In the other HE subgroups, in contrast, BrdU+ cells were broadly expressed in the parenchyma of the hypothalamic area. These results suggest that heat exposure promoted cell proliferation in the ependymal layer of the third ventricle and these cells migrated into the hypothalamic parenchyma thereafter. In HE, the number of BrdU+ cells double-stained by Neuronal nuclei (NeuN), a mature neuron marker, (BrdU+/NeuN+ cells) increased abruptly after 33 days of heat exposure by about 7 times. This result suggests that hypothalamic newborn cells differentiated to

mature neurons 33-day after commencing heat exposure, when long-term heat exposure is thought to be established. Moreover, the total counts of BrdU+ cells labeled with doublecortin (Dcx), an immature neuron marker, in the hypothalamic area in HE were significantly larger than that of CN. In contrast, BrdU+ cells expressing glial markers were rarely detected in the hypothalamus of both CN and HE. These results clearly suggest that a majority of hypothalamic newborn cells induced by heat exposure took on a neuronal fate. We additionally investigated age-dependent changes in heat exposure-induced hypothalamic neurogenesis and acquired heat tolerance in rats. In old rats (22-25 month of age), heat exposure did not promote cell proliferation and neural differentiation in the hypothalamus. Also, acquired heat tolerance by 40-day heat exposure was attenuated by aging.

CONCLUSION

Heat exposure facilitates proliferation of neuronal progenitor cells in the hypothalamus and promotes neural differentiation of newly generated cells, which may have a potential role in functional changes in thermoregulatory centers in long-term heat-acclimated rats. Also, aging may interfere with heat exposure-induced hypothalamic neurogenesis and acquired heat tolerance in rats.

別紙

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論　文　名　1.Proliferation of Neuronal Progenitor Cells and Neuronal Differentiation in the Hypothalamus Are Enhanced in Heat-Acclimated Rats.

2.Aging Attenuates Acquired Heat Tolerance and Hypothalamic Neurogenesis in Rats.

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