generation of hydroxyl radicals, depending on the ratio of chelator to iron salt concentration, another chelator, deferoxamine, was investigated and was found to be a powerful inhibitor of hydroxyl radical generation at any concentration [19]. Though it was studied in three concentrations, the results were the same as those for DETAPAC, and 100 mg/kg DFO tended to increase the ulcerogenicity of DDC.

On the basis of the present findings, it appears that the superoxide radical and hydrogen peroxide play a more important pathogenetic role in DDC-induced antral ulcer in the rat than does the hydroxyl radical.

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Hypothalamic histamine modulates adaptive behavior of rats at high environmental temperature

K. Fujimoto, T. Sakata, K. Ookuma, M. Kurokawa, A. Yamatodani* and H. Wada*

*Department of Internal Medicine I, Faculty of Medicine, Kyushu University, Fukuoka 812 (Japan), and * Department of Pharmacology II, Faculty of Medicine, Osaka University, Osaka 530 (Japan)*
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Summary. Histamine content in the rat hypothalamus was lower at 4 °C and higher at 31 °C compared to that at 21 °C. Pretreatment with α-fluoromethylhistidine, a 'suicide' inhibitor of histidine decarboxylase, attenuated both the increased level of hypothalamic histamine and rat adaptive behavior at 31 °C. Increase of histamine content in the hypothalamus appears to be an important factor contributing to rat adaptive behavior to high environmental temperature.
Key words. Histamine; hypothalamus; environmental temperature; adaptive behavior.

To adapt to high environmental temperature, rats decrease food intake and ambulation, and increase water intake [1-3]. These behavioral changes help to maintain their body temperature [1-3]. Administration of histamine into the rat central nervous system has been shown to increase water intake [4, 5], decrease food intake [6], and lower body temperature [7, 8]. Although these findings suggest that brain histamine may contribute to the adaptation of the rat to a heated environment, the function of brain histamine in adaptation to environmental change in temperature is still obscure. The present experiment was aimed at investigating the relationship between hypothalamic histamine and behavioral adaptation to high environmental temperature.

Materials and methods

Subjects. Mature male Wistar King A rats, 270–320 g, were used. They were in a sound-proof room illuminated daily from 08.00–20.00 h (a 12:12 h light-dark cycle) with humidity at 45 ± 5%. Room temperature was maintained at 21 ± 1 °C unless otherwise described. The rats used were reared under these conditions from the prenatal period.

Analytical procedure for histamine and catecholamines in the brain. Rats were sacrificed by decapitation at 19.00 h. The hypothalamus and frontal cortex were isolated and homogenized [9]. The homogenates were centrifuged at 10,000 × g, and the histamine content in the clear deproteinized supernatants was assayed using high-performance liquid chromatography (HPLC) [10]. Catecholamines in the supernatant were also analyzed in a fully automated HPLC-fluorometric system (Model HLC-8030 Catecholamine Analyzer, Tosoh, Japan) using the diphenylethylenediamine condensation method [11]. Samples were taken from 9 rats maintained at 21 ± 1 °C room temperature as the control group, from

8 rats at 4 ± 1 °C, and from 9 rats at 31 ± 1 °C. The lower and higher temperatures were maintained for 11 h after the shift from 21 °C. Additional samples were taken at 31 ± 1 °C from 9 rats pretreated with an intraperitoneal injection of 100 mg/kg α-fluoromethylhistidine (FMH) 8 h before sampling. The data were evaluated by the Welch test.

Behavior and rectal temperature. A rat in a 30 × 25 × 25 cm testing chamber, equipped with a pellet-sensing eatometer, a drinkometer and photosensing counters to measure ambulation (Astec Co. Ltd, Japan), was allowed free access to standard pellet rat chow (mean weight, 46.3 ± 0.3 mg) and tap water (mean droplet volume, 43.1 ± 0.3 µl). Food pellets and water droplets consumed, and ambulation, were automatically recorded in a computer [12, 13]. Cumulative food intake and ambulatory activity were measured at 24 h intervals. The ratio of 24-h cumulative water intake to food intake (ml/g) was calculated. Rectal temperature of the rat was measured at 13.30 h. These data were recorded at 21 ± 1 °C for two successive days. After recording, the room temperature was raised to 31 ± 1 °C at 08.00 h. Matched on the basis of the data at 21 °C, 16 rats were equally divided into two groups. One group was injected intraperitoneally with 100 mg/kg FMH at 11.00 h on the first day after elevation of room temperature to 31 ± 1 °C. Another was injected at the same time with 0.15 M saline as controls. Ten additional rats at 21 ± 1 °C were injected with the same doses of FMH or saline. Statistical evaluation of the data was based on two way analysis of variance with replications in which orthogonal decomposition for linear comparison was carried out.

Results

Contents of histamine, noradrenaline and adrenaline in the hypothalamus at three different environmental temperatures are shown in the table. Histamine content was significantly decreased by cooling the environmental temperature from 21 °C to 4 °C ($t = 2.4$, $p < 0.05$). The histamine level at the higher temperature of 31 °C was significantly higher than that at 21 °C ($t = 2.3$, $p < 0.05$). Noradrenaline and adrenaline levels did not change when the temperature was changed. Histamine level in the cortex was not different at the three different environmental temperatures (21 °C: 0.25 ± 0.02 nmol/g, 4 °C: 0.23 ± 0.01 nmol/g, 31 °C: 0.24 ± 0.01 nmol/g) (not shown in table).

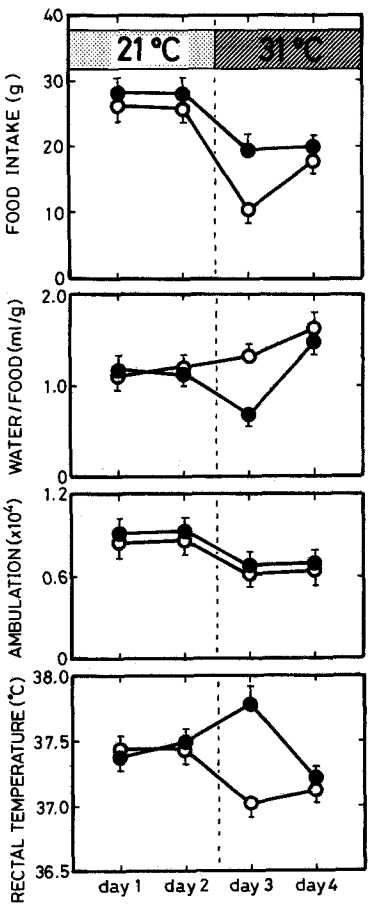
The table shows the effect of FMH on the content of hypothalamic histamine. Elevation of hypothalamic histamine at 31 °C was significantly attenuated by FMH pretreatment ($t = 5.6$, $p < 0.01$). FMH did not affect hypothalamic contents of noradrenaline and adrenaline.

The figure indicates the effects of FMH on changes in ingestive behavior and rectal temperature at 31 °C. Food intake decreased with elevation of the environmental temperature ($F(3,56) = 32.2$, $p < 0.01$), and this was significantly attenuated by decrease of hypothalamic histamine due to FMH ($F(1,56) = 11.1$, $p < 0.01$). The attenuation was observed on the first day after injection ($F(1,56) = 71.3$, $p < 0.01$). FMH also decreased the ratio of water intake to food intake at 31 °C on the first day after the treatment compared to that in the untreated controls ($F(1,56) = 5.6$, $p < 0.05$). The ratio increased in both groups on the second day after elevation to 31 °C, compared to that at 21 °C ($F(1,56) = 19.4$, $p < 0.01$).

Histamine, noradrenaline, and adrenaline contents of the rat hypothalamus at 19.00 h. Mean ± SEM; n = number of rats tested; i.p, infusion into peritoneum.

Environmental temperature	Histamine (nmol/g)	Noradrenaline (nmol/g)	Adrenaline (nmol/g)
No pretreatment			
21 ± 1 °C (n = 9)	3.89 ± 0.29	6.84 ± 0.18	0.090 ± 0.006
4 ± 1 °C (n = 8)	2.98 ± 0.22[a]	6.59 ± 0.97	0.088 ± 0.004
31 ± 1 °C (n = 9)	4.70 ± 0.32[a]	7.01 ± 0.26	0.092 ± 0.005
Pretreatment with α-fluoromethylhistidine (100 mg/kg, i.p.)			
31 ± 1 °C (n = 9)	2.63 ± 0.17[b]	6.95 ± 0.29	0.090 ± 0.005

[a] $p < 0.05$ vs appropriate values at 21 °C; [b] $p < 0.01$ vs values in the controls at 31 °C.



Effects of α-fluoromethylhistidine (FMH) on changes in ingestive behavior, ambulation, and rectal temperature in environmental temperature elevated from 21 °C to 31 °C. Environmental temperature was 21 ± 1 °C on days 1 and 2, and 30 ± 1 °C on days 3 and 4. Closed circles, rats treated with 100 mg/kg FMH at 11.00 h on day 3. Open circles, rats treated with the same volume of 0.15 M saline at the same time.

Ambulatory activity was decreased by elevation of room temperature ($F(3,56) = 7.0$, $p < 0.01$), but no difference was found between the FMH and control groups ($F(1,56) < 1$, n.s.). Rectal temperature increased significantly in the FMH group at 31 °C on the first day after injection compared to that in the control group ($F(1,56) = 21.9$, $p < 0.01$). FMH had no effect on ingestive behavior or rectal temperature at 21 °C room temperature (not shown in figure).

Discussion

The present study demonstrated an increase in histamine content in the rat hypothalamus at an elevated environmental temperature. FMH is known to be a specific 'suicide' inhibitor of histidine decarboxylase and to decrease neuronal histamine content, specifically and selectively[14,15]. Both previous studies[16,17] and the current study of the saline-treated rats demonstrated that rats can adapt to a change in environmental temperature from 21 °C to 31 °C. Adaptive behavior of rats to 31 °C environmental temperature was attenuated during decrease of endogenous hypothalamic histamine by FMH. These findings imply that increase of hypothalamic histamine content may be important in rat adaptive behavior at high environmental temperature.

Our previous studies demonstrated that neuronal histamine acted through H1-receptors in the hypothalamus to suppress food intake, and changes in hypothalamic histamine content might modulate daily fluctuation of food intake[18–21]. Together with these findings, the present results verify one of the physiological functions modulated by brain histamine.

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The influence of cold or isolation stress on resistance of mice to West Nile virus encephalitis

D. Ben-Nathan[a] and G. Feuerstein[b]

[a] *Department of Virology, Israel Institute for Biological Research, P. O. Box 19, 70450 Ness-Ziona (Israel), and* [b] *Department of Pharmacology, Smithkline Beecham, P. O. Box 7929, L-524, Philadelphia (Pennsylvania 19101, USA)*
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Summary. The effect of cold or isolation stress on mortality rate and brain virus level were investigated in mice infected with West Nile virus (WNV). Exposure of mice for 5 min/day to cold water (1 ± 0.5 °C) for 8–10 days resulted in 92% mortality as compared to 47% in control mice ($p < 0.001$). Mice housed in individual cages (isolation stress) were also more susceptible to WN viral infection, as shown by increased mortality rate reaching 85% as compared to 50% in mice housed 6 per cage ($p < 0.01$). Cold or isolation stress increased blood brain and spleen virus levels as early as 2 days after inoculation. After 8 days of isolation or cold stress, mice inoculated with WNV had 8.9 and 9.0 $\log_{10}$ plaque forming units in the brain, respectively, as compared to 6.9 in the control ($p < 0.01$–0.001). Furthermore, lymphoid organs such as spleen and thymus showed severe mass loss. These data suggest that physical or non-physical stress situations enhance WNV encephalitis by accelerating virus proliferation and increase mortality in mice.

Key words. West Nile virus; stress; isolation; cold stress; encephalitis.