Effects of Thiamine Administration on Hypothermia and Hypothalamic Histamine Levels in Dietary-Induced Thiamine Deficient Rats

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Abstract—The rats maintained on a thiamine-deficient diet for 30 days showed hypothermia, and their histamine levels increased significantly in both the anterior and posterior hypothalamus. When these rats were administered, thiamine disulfide and/or provided with thiamine-added diet for a further 30 days, the rats recovered from hypothermia, and histamine levels were decreased to the normal level. Thus, it is probable that the increased histamine levels in the hypothalamus, especially those in its anterior region, are closely related to the hypothermia in thiamine-deficient rats.

Dietary-induced thiamine deficiency is known to cause marked hypothermia in rats, which is not due to the concomitant decrease in food intake (1-3). We have recently reported that the thiamine deficiency impaired the activity of central histaminergic neurons and resulted in a significant increase in the histamine levels in the hypothalamus (4). Previous studies showed that central administration of histamine caused hypothermia in many animal species and that both H₁ and H₂ receptors in the brain seemed to be involved in the hypothermia (5-11). Stimulation of histamine H₁ receptors lowered the thermoregulatory set point, while that of histamine H₂ receptors increased the centrally induced heat loss (5, 7, 9, 10). The purposes of this study were to investigate the effect of thiamine disulfide administration on the hypothermia in thiamine-deficient rats and to investigate the relationship between the hypothermia and histamine levels in the anterior and posterior hypothalamus.

Male Wistar rats, 35 days old at the beginning of the experiment, were purchased from Funabashi Farm Co. The animals were maintained under constant temperature (22±2°C) and humidity (55±10%). The light-dark cycle was automatically controlled by a timer (with light from 7:30 to 19:30). The rats were housed individually in a mesh cage (17×25×37 cm) and divided into the following two dietary treatment groups until day 30: 1) Thiamine-deficient group (thiamine (-) diet group): The animals were fed powdered thiamine-deficient diet (Funabashi Farm Co.) containing 67.6% carbohydrate, 18% protein, 8% lipids, and necessary vitamins (without thiamine) and minerals (3, 4). 2) Thiamine-added group (thiamine (+) diet group): The animals were fed the same diet as in the thiamine (-) diet group, but containing 0.5 mg of thiamine hydrochloride per 100 g of diet. For both groups, water was supplied ad lib. The rectal temperature of each rat was measured by a thermometer probe (TX-100 model, Custom Co.) at 10:00 a.m. every day. The animals were weighed at the same time during the course of the experiments. On day 30, some of the rats were selected to test the effect of a single intraperitoneal (i.p.) administration of thiamine disulfide (10 mg/kg, Neolamin in-
jection, Nihon Kayaku Co. Ltd., Japan) on the hypothermia. Twenty-four hours after the administration of thiamine disulfide, the rectal temperature of the rats were recorded; and then these rats were immediately sacrificed by decapitation, and their brains were quickly removed on ice. The anterior hypothalamus, posterior hypothalamus and pituitary were dissected, and the histamine contents of these regions were measured by the HPLC-fluorometric method as described previously (4, 12). After the single injection of thiamine disulfide, some of the rats in thiamine (-) diet group were maintained further on the thiamine (+) diet for 30 days, and histamine levels in the hypothalamus and pituitary were measured in the same way as above at the end of the experiment. Statistical significances between the two treatment groups were assessed by Student’s t-test.

The effect of thiamine disulfide on the hypothermia induced by thiamine deficiency is shown in Fig. 1. Marked hypothermia was observed in the rats of the thiamine (-) diet group. The mean rectal temperature ±S.E.M. on day 30 was 34.4±0.1°C in the thiamine (-) diet group, while it was 36.5±0.1°C in the thiamine (+) diet group. Three hours after the i.p. administration of thiamine disulfide, the rectal temperature of thiamine (-) diet group increased significantly as compared with the saline-treated animals (P<0.01). Twenty-four hours after the administration, the average rectal temperature increased to 36.4±0.2°C in the thiamine disulfide-treated animals, while the temperature stayed at 33.9±0.2°C in the saline-treated animals.

The histamine levels on day 30 in the thiamine (-) diet group were higher than those of the thiamine (+) diet group in both the anterior and posterior hypothalamus (P<0.01, Table 1). The increased histamine levels in the thiamine (-) diet group were decreased 24 hr after the single i.p. administration of thiamine disulfide in the hypothalamus, although a statistical difference was observed only in the anterior hypothalamus when compared with the saline-treated animals (P<0.05). In addition, a further 30 days of administration of thiamine hydrochloride in the diet reversed the histamine levels in the hypothalamus to those of rats maintained on the thiamine (+) diet (Table 1). In these rats, a complete recovery from hypothermia was also observed (36.4±0.2°C, data not shown). However, the single i.p. administration of thiamine disulfide itself had neither an effect on body temperature nor the histamine levels in rats previously maintained on the thiamine (+) diet (Table 1).

The present results on rectal temperature showed that a single administration of thiamine disulfide had a rapid and profound effect on the recovery from the hypothermia induced by thiamine deficiency. Therefore, the abnormality of thermoregulation in thiamine-deficient rats could be considered to be a consequence of the thiamine deficiency.

The present biochemical data that thiamine
Table 1. Effects of thiamine disulfide administration on histamine levels in thiamine-deficient rats

| Group            | Treatment      | Time after treatment | Body weight (g) | Histamine levels (ng/g) | Anterior hypothalamus | Posterior hypothalamus | Pituitary |
|------------------|----------------|----------------------|-----------------|-------------------------|-----------------------|------------------------|-----------|
|                  |                |                      |                 |                         |                       |                        |           |
| Before feeding   | None           | 0                    | 78.7±2.2 (10)   | 254.7±29.8 (7)          | 281.5±27.3 (7)        | 106.3±12.0 (7)         |           |
| Thiamine (+) diet| A) None        | 0                    | 247.1±8.0 (6)   | 291.5±12.0 (6)          | 309.3±15.2 (6)        | 129.6±8.2 (6)          |           |
|                  | B) Saline i.p. | 24 hr                | 251.7±4.4 (10)  | 318.6±25.5 (5)          | 346.7±32.6 (5)        | 131.7±4.5 (5)          |           |
|                  | C) Thiamine disulfide i.p. | 24 hr | 252.0±7.0 (5) | 253.8±17.0 (5) | 323.3±33.1 (5) | 171.2±23.7 (5) |           |
| Thiamine (-) diet| D) None        | 0                    | 94.8±2.6** (8)  | 526.8±43.3** (8)        | 512.1±44.4** (8)      | 159.6±14.1 (8)         |           |
|                  | E) Saline i.p. | 24 hr                | 91.7±9.2** (8)  | 636.8±51.6** (8)        | 577.5±28.3** (8)      | 217.1±29.5* (6)        |           |
|                  | F) Thiamine disulfide i.p. | 24 hr | 113.5±3.6** (8) | 464.1±30.3** (5) | 472.6±63.7 (5) | 174.2±24.5 (5) |           |
|                  | G) Thiamine (+) diet | 30 days | 304.3±2.5## (7) | 282.3±21.2# (7) | 324.1±17.9## (7) | 136.5±9.1# (7) |           |

Each value represents the mean±S.E.M. Numbers in parentheses indicate the number of determinations. Statistical difference between A and D (**P<0.01). Statistical difference between B and E (*P<0.05, ##P<0.01). Statistical difference between B and F (##P<0.01). Statistical difference between E and F (*P<0.05). Statistical difference between E and G (##P<0.01).
deficiency resulted in a marked increase in histamine levels of both the anterior and posterior hypothalamus are consistent with our previous report (4). It was notable that the histamine levels in the anterior hypothalamus were higher than those in the posterior hypothalamus in the thiamine (-) diet group. Furthermore, the administration of thiamine disulfide effectively reversed the increased histamine levels. Twenty-four hours after the administration of thiamine disulfide, a statistically significant decrease of the histamine levels was observed in the anterior hypothalamus of the thiamine deficient rats, but this decrease was not sufficiently recovered to the normal levels. It is of interest that the rectal temperature of this group was not fully recovered to the normal range, either. The reason for this incompleteness is unknown, although it is reported that the thiamine levels in the blood and brain in rats treated with thiamine disulfide were higher than those treated with thiamine hydrochloride, and these higher levels were maintained for more than 8 hr after the administration (13). After the single administration of thiamine disulfide and the thiamine hydrochloride in the diet for thirty consecutive days, the histamine levels in both the anterior and posterior hypothalamus of this group were reversed to the normal range in parallel with the complete recovery from hypothermia.

These data suggest that there exists a close relationship between the thermoregulation and central histamine although further experiments will be needed to clarify the mechanism of hypothermia in thiamine-deficient rats especially the relationship between histaminergic and other neuron systems such as serotonergic, dopaminergic and noradrenergic systems (1, 11).

Because the hypothalamus is rich in the histaminergic nerve fibers emanating from the tuberomammillary nucleus (14), if neuronal histamine of the brain was involved in the thermoregulation, then activation of the histaminergic system by histidine load or centrally administered histamine should lead to hypothermia, while the reduction of histamine synthesis by α-fluoromethylhistidine (FMH), etc. should increase body temperature. In fact, centrally administered histamine and/or histidine lowers the body temperature in many animal species (5–11). Conversely, phencyclidine elicits a marked hyperthermic effect in mice pretreated with FMH, but in moderate doses, it does not affect body temperature in mice (15). These results and our present data support the hypothesis that endogenous histamine is involved in thermoregulation in animals.

In conclusion, it is probable that the increased histamine levels in the hypothalamus, especially the one in the anterior region, are closely related to the hypothermia in thiamine-deficient rats.

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