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Neuronal Glucoprivation Enhances Hypothalamic Histamine Turnover in Rats

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Abstract: Histamine (HA) turnover in the rat hypothalamus following insufficient energy supply due to glucoprivation was examined after administration of insulin or 2-deoxy-D-glucose (2-DG). HA turnover was assessed by accumulation of *tele*-methylhistamine (*t*-MH), a major metabolite of brain HA, following administration of pargyline. Intraperitoneal injection of 1, 2, and 4 U/kg of insulin, which had no influence on steady-state levels of HA and *t*-MH, increased pargyline-induced accumulation of *t*-MH. Accumulation of *t*-MH due to pargyline was inversely related to the concomitant plasma glucose concentration after different doses of insulin. The level of *t*-MH accumulated by pargyline did not change compared with that of controls, when a euglycemic condition was maintained or insulin at a dose of 6 mU per rat was infused into the third cerebroventricle. Intracerebroventricular infusion of 24 μmol per rat of 2-DG, which had no influence on steady-state levels of HA and *t*-MH, increased the level of *t*-MH enhanced by pargyline. The results indicate that an increase in hypothalamic HA turnover in response to glucoprivation may be involved in homeostatic regulation of energy metabolism in the brain. **Key Words:** *tele*-Methylhistamine—Insulin—2-Deoxy-D-glucose—Hypothalamic histamine turnover.
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Our previous studies have demonstrated that neuronal histamine (HA) suppresses food intake through H_1 receptors in the ventromedial hypothalamus (VMH) and the paraventricular nucleus (PVN) (Sakata et al., 1988, 1990). The increased activity of hypothalamic HA has been shown to affect endocrine systems (Schwartz et al., 1991), metabolism of peripheral glucose (Nishibori et al., 1987), and thermoregulation (Yoshimatsu and Sakata, 1991).

In addition to these functional studies on brain HA, changes in ambient temperature (Fujimoto et al., 1990), cerebral ischemia (Adachi et al., 1991), nociceptive stimuli (Itoh et al., 1989), and glucose concentration in the medium (Nishibori et al., 1986) have been shown as factors that activate HA functions in the brain. Involvement of HA in glucose metabolism seems to be one of the important systems regulating physiological functions.

To determine whether insufficient energy supply due to reduced glucose metabolism may modulate HA neuron activity, HA function in the rat hypothalamus was examined in the present study by inducing peripheral hypoglycemia with insulin or central glucoprivation with 2-deoxy-D-glucose (2-DG). Hypothalamic HA turnover was calculated from the level of *tele*-methylhistamine (*t*-MH) that accumulated after treatment with pargyline, an inhibitor of monoamine oxidase (Oishi et al., 1984).

MATERIALS AND METHODS

Animals

Mature male Wistar King A rats (weighing 280–300 g) were housed in a soundproof room illuminated daily from 0800 h to 2000 h (a 12:12 h light–dark cycle) and maintained at 21 ± 1°C with humidity at 55 ± 5%. They were allowed free access to standard rat chow (Clea rat chow, Japan Clea) and tap water. All animal use procedures were in accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the local Animal Care Committee.

Reagents

Phosphate-buffered saline (PBS), containing 137 mmol/L of NaCl, 2.68 mmol/L of KCl, 8.10 mmol/L of Na_2HPO_4, and 1.47 mmol/L of KH_2PO_4, was used as a control solution.

The solutions of insulin (Insulin Novo Actrapid; Novo Industry, Denmark), 2-DG (Sigma, U.S.A.), D-glucose

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Abbreviations used: 2-DG, 2-deoxy-D-glucose; HA, histamine; LHA, lateral hypothalamic area; *t*-MH, *tele*-methylhistamine; PBS, phosphate-buffered saline; PVN, paraventricular nucleus; VMH, ventromedial hypothalamus.

(Sigma, U.S.A.), and pargyline hydrochloride (Sigma, U.S.A.) were freshly prepared in PBS on the day of their administration. The pH of each solution was adjusted to a range of 6.0–7.0.

Surgery

A Silastic catheter (No. 00; Shinnetsu Co., Tokyo, Japan) was chronically inserted via the right jugular vein with the inner end fixed just outside of the right atrium for blood sampling. The sampling tube was attached to a 23-gauge Multi Sampling Needle (Terumo Internationals) to prevent air from being drawn into the system (Sakata et al., 1982).

A cannula was also chronically implanted into the third cerebroventricle. Under pentobarbital sodium anesthesia (0.18 mmol/kg, i.p.), rats were fixed in a stereotaxic apparatus (Narishige Co., Japan). A stainless steel cannula (23 gauge) containing an inner infusion cannula (29 gauge) was inserted intracerebroventricularly. Details of the surgical procedure have been described elsewhere (Sakata et al., 1981).

Procedure

One hundred ten rats were divided into three testing groups. Each rat was pretreated with an intraperitoneal injection of 0.33 mmol/kg of pargyline or PBS. Ten minutes later, one of the test solutions was administered by intraperitoneal injection or intracerebroventricular infusion.

To investigate the effect of peripheral administration of insulin in the first group, a 1-ml volume of 1, 2, or 4 U/kg of insulin or the same volume of PBS as the control was injected intraperitoneally (n = 5 for each).

For the glucose clamping procedure using the second group, rats were continuously infused with glucose solution (0.14 mmol/kg/min) through an atrial catheter 10 min after intraperitoneal injection of 2 U/kg of insulin (n = 7). A control study of this glucose clamping was carried out to infuse PBS instead of glucose after intraperitoneal injection of PBS instead of insulin (n = 7).

To determine the effects of central administration of test solutions, a 10-μl volume per rat of 6 mU of insulin, 24 μmol of 2-DG, or the same volume of PBS was infused through an intracerebroventricular cannula in the third group (n = 7 for each). The results given in the text are those for the maximal doses, although other smaller doses of insulin and 2-DG were also evaluated.

Blood for measurement of the plasma glucose level was taken 60 min after administration of the test solutions. All rats tested were decapitated immediately after the blood sampling and adjusted to be 70 min after pargyline pretreatment. The hypothalamus was immediately dissected on an ice plate according to the method of Glowinski and Iversen (1966). Details of the procedure have been described elsewhere (Sakata et al., 1984).

Measurement of HA and *t*-MH levels in the brain

HA and *t*-MH contents were simultaneously measured by the method of Tsuruta et al. (1981) as modified by Oishi et al. (1987). The hypothalamus was homogenized in 0.3 ml of 0.4 *M* perchloric acid containing 0.20 nmol of *pros*-methylhistamine as the internal standard. After centrifugation at 1,000 *g*, 0.25 ml of the supernatant was used for the assay. These amines were extracted into *n*-butanol under NaCl-saturated alkaline conditions and transferred back to 0.1 *M* HCl by shaking with benzene. After the pH was adjusted to 6.0, the extracts were applied to phosphocellulose columns (12.5 × 5 mm i.d.). The columns were washed successively with 0.01 *M* phosphate buffer (pH 6.0; 2 ml × 2), water (1 ml), and 0.12 *M* HCl (0.4 ml). The amines were eluted with 0.12 *M* HCl (1.0 ml) and, after evaporation, were subjected to a reaction with *o*-phthalaldehyde at pH 10.0 in the presence of 2-mercaptoethanol. The resulting fluorophores were then injected into a high-performance liquid chromatograph. The system was composed of an LC-6A pump (Shimazu, Kyoto, Japan), a reverse-phase column (Chemcosorb ODS-H; particle size, 5 μm; 150 × 4 mm i.d.; Chemco Scientific, Osaka, Japan), and an RF-535 fluorescence spectromonitor (Shimazu). The mobile phase was a mixture of 0.06 *M* Na_2HPO_4 and methanol (47:53 vol/vol). The excitation and emission wavelengths were set at 340 and 450 nm, respectively.

Measurement of plasma glucose level

A blood sample never exceeding 0.4 ml at one sampling, with EDTA, was withdrawn through the atrial catheter. In the glucose clamping experiment, a 0.2-ml blood sample was taken from the tail vein. Samples were taken 10 min before and 60 min after administration of a test solution. Plasma glucose was assayed by the glucose oxidase–*p*-aminophenol method (Trinder, 1969).

Statistical evaluation of the data between experimental and PBS control groups was carried out by one-way ANOVA with multiple comparisons using the method of least-significant difference. The dose–responsive curves of HA, *t*-MH, and plasma glucose after insulin injection and the relationships between plasma glucose levels after injection of insulin and levels of HA or *t*-MH in rats pretreated with pargyline were evaluated by linear regression.

RESULTS

Levels of hypothalamic HA and *t*-MH after intraperitoneal injection of insulin

Table 1 shows changes in concentration of HA and *t*-MH in the rat hypothalamus and blood glucose levels after intraperitoneal injection of insulin. Intraperitoneal injection of 1, 2, and 4 U/kg of insulin without pargyline pretreatment showed no significant influence on steady-state HA or *t*-MH levels. After pargyline treatment, pargyline-induced accumulations of *t*-MH in the insulin groups were higher than those of the PBS-control groups [$F(3,16) = 4.351$, $p < 0.05$], and the increase was dose dependent ($y = 0.56\log x + 4.15$, $r = 0.997$, n = 5, $p < 0.05$). HA levels in rats with insulin treatment did not significantly differ from those of the PBS controls. Intraperitoneal injection of insulin in both pargyline- and PBS-pretreated groups decreased plasma glucose levels dose-dependently: $F(3,16) = 269.9$, $p < 0.01$; $y = -0.18\log x + 4.85$, $r = -0.977$, n = 5, $p < 0.05$ for pargyline pretreatment; $F(3,16) = 206.0$, $p < 0.01$; $y = -0.19\log x + 4.87$, $r = -0.998$, $n = 5$, $p < 0.05$ for PBS pretreatment. Pargyline-induced accumulation of *t*-MH was inversely related to the plasma glucose concentration ($y = -0.31\log x + 5.66$, $r = -0.715$, n = 20, $p < 0.01$). The HA level after pargyline treatment, however, had no correlation with plasma glucose concentration ($y = -0.08\log x + 3.71$, $r = -0.286$, n = 20, $p > 0.1$).

TABLE 1. *Levels of hypothalamic HA, t-MH, and plasma glucose after intraperitoneal injection of insulin*

Pretreatment, metabolite	Insulin 4 U/kg	Insulin 2 U/kg	Insulin 1 U/kg	PBS	$F(3,16)$ value
PBS					
HA (nmol/g)	3.07 ± 0.57	3.49 ± 0.43	3.01 ± 0.57	3.16 ± 0.44	0.19
t-MH (nmol/g)	1.69 ± 0.25	1.39 ± 0.34	1.46 ± 0.31	1.47 ± 0.29	0.23
Glucose (mmol/L)	2.30 ± 0.10	3.46 ± 0.08	4.29 ± 0.16	6.20 ± 0.12	206.0[a]
Pargyline					
HA (nmol/g)	3.55 ± 0.37	3.50 ± 0.46	3.13 ± 0.29	3.29 ± 0.38	0.24
t-MH (nmol/g)	4.91 ± 0.17	4.58 ± 0.54	4.13 ± 0.51	3.80 ± 0.45	4.35[b]
Glucose (mmol/L)	2.39 ± 0.08	3.50 ± 0.09	4.90 ± 0.14	6.27 ± 0.09	269.9[a]

Data are mean ± SEM values.
The $F(3,16)$ value is for the comparison among dosages of insulin and PBS controls: [a] $p < 0.01$, [b] $p < 0.05$. See the text for more details on statistical significance.

Pargyline treatment per se did not affect plasma glucose levels significantly before or after insulin injection.

In the glucose clamping experiment, the blood glucose level was maintained at a euglycemic level of 6.48 ± 0.22 mmol/L (mean ± SEM) (initial level, 6.33 ± 0.46 mmol/L). The values did not differ from either the initial level of the PBS control (6.10 ± 0.12 mmol/L) or its 60-min level of 6.04 ± 0.09 mmol/L. Under this euglycemic condition, intraperitoneal injection of insulin at a dose of 2 U/kg with pargyline did not affect HA and *t*-MH levels significantly (Table 2).

Levels of hypothalamic HA and *t*-MH after intracerebroventricular infusion of insulin or 2-DG

Table 3 shows changes in levels of hypothalamic HA and *t*-MH and blood glucose levels after central administration of insulin or 2-DG. Intracerebroventricular infusion of insulin at a dose of 6 mU per rat showed no influence on steady-state HA or *t*-MH level. Even after pargyline treatment, infusion of 6 mU of insulin per rat showed no influence on either HA or *t*-MH level. Peripheral plasma glucose levels with and without pargyline pretreatment also did not change after insulin treatment. Intracerebroventricular infusion of 2-DG showed no influence on steady-state HA or *t*-MH levels. Pargyline-induced accumulation of *t*-MH in the 2-DG group was higher than that in the PBS controls [$F(1,12) = 8.437$, $p < 0.05$], but there was no significant difference in HA levels between the 2-DG and the PBS groups. Plasma glucose levels increased after administration of 2-DG both with [$F(1,12) = 186.11$, $p < 0.01$] and without [$F(1,12) = 90.68$, $p < 0.01$] pargyline pretreatment.

TABLE 2. *Levels of hypothalamic HA, t-MH, and plasma glucose after intraperitoneal injection of insulin during the glucose clamping procedure in pargyline-pretreated rats*

Content	PBS + PBS	Glucose (0.14 mmol/kg/min) + insulin (2 U/kg)
HA (nmol/g)	3.58 ± 0.14	3.45 ± 0.14
t-MH (nmol/g)	3.35 ± 0.12	3.41 ± 0.11
Glucose (mmol/L)	6.04 ± 0.09	6.48 ± 0.14

Data are mean ± SEM values.

DISCUSSION

The present study demonstrates that a series of glucoprivic challenges with either insulin or 2-DG enhances pargyline-induced accumulation of *t*-MH in the rat hypothalamus. However, neither the steady-state levels of HA and *t*-MH nor the HA levels after pargyline pretreatment show any change after glucoprivic challenges. Transmethylation of HA into *t*-MH catalyzed by HA *N*-methyltransferase and subsequent deamination by monoamine oxidase are the major metabolic pathways of HA in the brain (Schwartz et al., 1971). The present results show that glucoprivic challenge increases HA turnover (its synthesis and release) in the hypothalamus.

In the present study, intraperitoneal injection of insulin produced hypoglycemia dose-dependently, which markedly enhanced pargyline-induced accumulation of *t*-MH. There was also a negative correlation between *t*-MH accumulation and plasma glucose concentration. The findings indicate that hypoglycemia may increase the HA turnover rate. However, there was a possibility that insulin may directly elevate the HA turnover rate. In fact, direct actions of insulin in the hypothalamus have been shown in several experiments. Central administration of insulin decreases food intake (Porte and Woods, 1981). Electrophoretic application of insulin increases neuronal activity in the lateral hypothalamic area (Oomura and Yoshimatsu, 1984). To determine whether insulin directly affects HA turnover rate, two experiments were performed. First, the direct effect of insulin on HA turnover was examined by a euglycemic glucose clamping procedure. The level of pargyline-

TABLE 3. *Levels of hypothalamic HA, t-MH, and plasma glucose after intracerebroventricular infusion of insulin or 2-DG*

	Insulin			2-DG		
Pretreatment, metabolite	Dose (6 mU/rat)	PBS	$F(1,12)$	Dose (24 μmol/rat)	PBS	$F(1,12)$
PBS						
HA (nmol/g)	2.64 ± 0.13	2.63 ± 0.21	0.002	2.95 ± 0.30	2.93 ± 0.28	0.002
t-MH (nmol/g)	0.94 ± 0.05	0.83 ± 0.05	1.79	1.06 ± 0.09	0.92 ± 0.11	2.29
Glucose (mmol/L)	6.14 ± 0.12	6.05 ± 0.14	0.38	8.26 ± 0.15	5.91 ± 0.15	90.7[a]
Pargyline						
HA (nmol/g)	2.97 ± 0.10	2.90 ± 0.16	0.13	4.20 ± 0.41	3.69 ± 0.33	1.81
t-MH (nmol/g)	3.76 ± 0.17	3.59 ± 0.19	0.51	4.65 ± 0.29	3.60 ± 0.36	8.44[b]
Glucose (mmol/L)	5.98 ± 0.11	6.16 ± 0.12	0.78	7.92 ± 0.13	5.83 ± 0.11	186.1[a]

Data are mean ± SEM values.

The $F(1,12)$ value is for the comparison between insulin or 2-DG and the PBS controls: [a] $p < 0.01$, [b] $p < 0.05$. See the text for more details on statistical significance.

induced accumulation of *t*-MH after intraperitoneal injection of insulin, when the plasma glucose level was maintained at a euglycemic level, did not differ from the accumulation of *t*-MH in the PBS control. Second, insulin was infused into the third cerebroventricle. Intracerebroventricular infusion of insulin did not affect the level of HA or *t*-MH with or without pargyline pretreatment. These results indicate that insulin-induced hypoglycemia, but not hyperinsulinemia, is crucial for the enhancement of HA turnover in the rat hypothalamus. Consistent with the present results, Nishibori et al. (1986) reported that in the in vitro experiments the amount of HA released from mouse hypothalamic tissue is increased by lowering the concentration of glucose in the medium.

It is still unclear whether systemic hypoglycemia or local glucoprivation in the brain is essential for activation of HA turnover. To answer this question, 2-DG was injected into the third cerebroventricle. This synthetic glucose analogue has been found to be an effective inhibitor of glucose utilization by competitively blocking both glucose transport into the cells (Horton et al., 1973) and intracellular glucose metabolism (Sols and Crane, 1954). Administration of 2-DG causes intracellular glucoprivation in the CNS (Epstein et al., 1975) and a peripheral hyperglycemic response through catecholamine secretion from the adrenal medulla (Yoshimatsu et al., 1991). The present study showed that intracerebroventricular infusion of 2-DG increased HA turnover despite its systemically hyperglycemic effect. The findings indicate that the hypothalamic glucoprivation due to 2-DG, but not from systemic hypoglycemia, increases the HA turnover rate.

The reciprocal feeding responses to 2-DG and HA, i.e., elicitation by 2-DG (Booth, 1972) and inhibition by HA (Sakata et al., 1988, 1990), seem to be inconsistent with the present result, because administration of 2-DG increases HA turnover. A series of studies on glucose analogues demonstrated that administration of glucose analogues such as 2-DG (Tsutsui et al., 1983) and 1-deoxy-D-glucosamine (Fujimoto et al., 1986) produced biphasic responses: initial elicitation of feeding followed by its prolonged inhibition. The later phase of feeding suppression induced by 2-DG (Sakata et al., 1994) and 1-deoxy-D-glucosamine (Kang et al., 1993) was abolished by depletion of hypothalamic HA using α-fluoromethylhistidine, a suicide inhibitor of the HA-synthesizing decarboxylase enzyme, but not the initial elicitation of feeding. These findings suggest that 2-DG may induce feeding at the initial phase through its direct glucoprivic action on feeding-related neurons in the lateral hypothalamic area (LHA) and feeding inhibition at the delayed phase through HA activation by 2-DG in the VMH. In fact, the LHA was shown to be a main locus of 2-DG action on behavioral and autonomic responses (Katafuchi et al., 1985). Microinfusion of 2-DG into the LHA induced feeding behavior (Balagura and Kanner, 1971), and activation of sympathoadrenal function (Yoshimatsu et al., 1991). LHA neurons were anatomically shown to project to the cell bodies of the histaminergic neurons, which are localized in restricted areas of the posterior hypothalamus (Panula et al., 1984; Ericson et al., 1991). Taken together, glucoprivic information received by LHA neurons seems to activate histaminergic neurons in the posterior hypothalamus through this neuronal projection. Another possible explanation for the action of 2-DG is that 2-DG may directly stimulate histaminergic neurons, most likely the cell bodies in the posterior hypothalamus or the nerve terminals in those target nuclei. In fact, histaminergic neuronal projections and their receptors are known to distribute densely to several hypothalamic nuclei, including the VMH and the PVN, but their density is relatively sparse in the LHA (Palacios et al., 1981; Inagaki et al., 1988). In addition, histaminergic modulation of feeding behavior has been shown to be mediated by the VMH and the PVN (Sakata et al., 1988, 1990; Ookuma et al., 1989).

Glycogen is stored predominantly in glial cells of the hypothalamus (Nahas and Abdul, 1989). Glycogenolysis in the brain is quite active (Magistretti, 1988) and is triggered by several neuromodulators, including

noradrenaline (Quach et al., 1978, 1988), adenosine (Quach et al., 1978), vasoactive intestinal peptide (Magistretti et al., 1981), and serotonin (Quach et al., 1982). HA also has potent glycogenolytic action in brain tissue (Quach et al., 1980). In addition to this local effect of HA in the brain, HA produces systemic hyperglycemia through the hypothalamus via an increase in catecholamine secretion from the adrenal medulla (Nishibori et al., 1987; Yoshimatsu et al., 1992). These studies suggest that HA may play an important rôle in glucose supplementation in the brain under energy-deficient conditions.

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