Prostaglandin E_2 Mediates Activation of Hypothalamic Histamine by Interleukin-1β in Rats (44349)

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Abstract. **The present study was designed to investigate the effects of peripheral interleukin-1β (IL-1β) on hypothalamic histamine (HA) systems. Intraperitoneal injection of IL-1β increased the turnover rate of hypothalamic HA, which was assessed by accumulation of *tele*-methylhistamine after pargyline treatment. IL-1β increased the activities of both histidine decarboxylase (HDC), an HA synthesizing enzyme, and HA-N-methyltransferase (HMT), an HA catabolizing enzyme. Pretreatment with indomethacin completely blocked the effects induced by IL-1β on hypothalamic HA. Infusion of prostaglandin E_2 (PGE_2) into the third cerebroventricle increased the hypothalamic HA turnover rate, and simultaneously activated both HDC and HMT dose-dependently, but intravenous infusion of PGE_2 had no effect on the dynamics of hypothalamic HA turnover. These results indicate that hypothalamic PGE_2 activated by peripheral administration of IL-1β, but not by peripheral PGE_2, may enhance synthesis and release of hypothalamic HA by activation of HDC, and may facilitate degradation of extracellular histamine by activation of HMT.** [P.S.E.B.M. 1999, Vol 220]

Interleukin-1β (IL-1β) is produced by activation of monocytes, alveolar macrophages, Kupffer's cells, and peritoneal macrophages. It plays an important role in stimulating immune cells during infection, inflammation, and injury. IL-1β has been shown to suppress food intake (1) and water intake (2), and to elevate body temperature (3) by activating hypothalamic nuclei including the ventromedial hypothalamus, the paraventricular nucleus, and the preoptic and anterior hypothalamus. The mechanisms and relationships to neuromodulators, including monoamines and neuropeptides, remain obscure.

In a series of studies, we have demonstrated that hypothalamic histamine (HA) regulates feeding and drinking behavior (4–7). Ambient thermal stimulation has been shown to modulate hypothalamic HA systems to maintain homeostatic thermoregulation (4, 8). HA also affects adaptive feeding, drinking, and ambulatory behaviors to regulate body heat production (4). These results indicate physiological significance of hypothalamic HA in processes of signal transduction and integration of thermogenic information.

Our previous report demonstrated that infusion by central administration of 1.5 pmol IL-1β into the third cerebroventricle (i3vt), which dose suppressed food intake (1), activated hypothalamic HA turnover. This effect was indicated by an increase in the pargyline-induced accumulation of *tele*-methylhistamine (*t*-MH) (8). However, there is no evidence that peripheral administration of IL-1β is sufficient to produce direct or indirect effects on hypothalamic HA systems.

To clarify the effects of peripheral administration of IL-1β, a major endogenous pyrogen, on HA systems in the hypothalamus, the present study aimed to investigate: (1) whether peripheral administration of IL-1β activates HA turnover rate directly or indirectly in the hypothalamus through the assessment of linear accumulation of *t*-MH after intraperitoneal (ip) injection of pargyline (9); and (2) whether central or peripheral prostaglandin E_2 (PGE_2) modulates hypothalamic HA, since endogenous PGs are released from the rat organum vasculosum of the lamina terminalis by circulating IL-1β (10).

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Materials and Methods

Subject. Mature male Wistar king A rats, 280–300 g, were housed in a sound-proof room illuminated daily for 12 hr (a 12:12 hr light-dark cycle) with humidity at 55 ± 5%. The temperature in each testing chamber was maintained at 21 ± 1°C except as otherwise described. The rats were allowed free access to standard pellet rat chow (Clea rat chow, #CE-2, Japan Clea) and tap water. All procedures were performed in accordance with Oita Medical University *Guide for the Care and Use of Laboratory Animals*, which was based on the NIH guide, and were approved by the Animal Care Committee of the Oita Medical University.

Surgery. A cannula was chronically implanted into the third cerebroventricle (i3vt). Under pentobarbital sodium anesthesia (45 mg/kg), each rat was fixed in a stereotaxic apparatus (Narishige Co. Ltd., Tokyo, Japan). A stainless steel cannula (23- gauge) was inserted i3vt, which was fitted with an inner infusion cannula (29-gauge).

A chronic right atrial catheter was implanted in each rat through the right jugular vein.

Reagents. The IL-1β used was a recombinant human type containing a 17-kDa protein with 153 amino acid residues (Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan). The solution of IL-1β was freshly prepared by dissolving it in phosphate buffered saline (PBS) at a concentration of 0.12 μ*M*. Pargyline hydrochloride (Sigma, St. Louis, MO), an inhibitor of monoamine oxidase B, was also freshly dissolved in PBS at a concentration of 0.10 *M*. Indomethacin (Sigma, St. Louis, MO) was freshly dissolved in 99% ethanol, and diluted to a concentration of 0.02 *M* in PBS. PGE_2 (Sigma, St. Louis, MO) was freshly dissolved in PBS containing 2% ethanol at concentrations of 0.015 m*M*, 0.030 m*M*, 0.15 m*M*, and 0.90 m*M*. The PBS contained 137 m*M* NaCl, 2.68 m*M* KCl, 8.10 m*M* Na_2HPO_4, and 1.47 m*M* KH_2O_4, pH 7.35–7.40.

Procedure. *Response to IL-1β and indomethacin.* The effects of indomethacin and IL-1β on the activities of histidine decarboxylase (HDC) and HA-N-methyltransferase (HMT) were evaluated by studying all combinations of indomethacin (dose: 0.07 mmol/kg; injection time: 1230 hr) and IL-1β (dose: 0.40 nmol/kg; injection time: 1300 hr) along with their PBS vehicles (injection time: 1250 hr). Thus four groups (i.e., PBS + PBS, PBS + IL-1β, indomethacin + PBS, and indomethacin + IL-1β) were used with five rats per group. All test solutions were administered ip at a volume of 1.0 ml.

An additional 20 rats were treated identically, but were treated with pargyline (dose: 0.30 mmol/kg; injection time: 1250 hr) instead of PBS vehicle. They were used for the measurement of *t*-MH levels.

Twenty rats were divided equally into four groups to evaluate the effects of indomethacin on activities of histidine decarboxylase (HDC) and HA-N-methyltransferase (HMT) following IL-1β injection.

In the experiment for measurement of enzyme activities, the PBS vehicle was injected instead of pargyline so that the injection procedure was identical to that for *t*-MH measurement.

Brain samples for measurement of pargyline-induced accumulation of *t*-MH and determination of HDC and HMT activities were collected by sacrifice at 1400 hr. The hypothalamus was quickly dissected on an ice plate according to the procedure of Glowinski and Iversen (11). Tissues such as the dura mater and the blood vessels were removed from the dissected hypothalamus.

Response to PGE_2. Four groups with five rats were used to test the effect of intravenous (iv) PGE_2 infusion with or without pargyline pretreatment on HA and *t*-MH levels. The rats were injected ip with 0.30 mmol/kg of pargyline or PBS vehicle 10 min before the PGE_2 infusion. Five rats in each pretreatment group were infused iv through the right atrial catheter with a 0.5-ml volume of 1.5 μmol/kg PGE_2 or PBS vehicle at 1300 hr.

Another 10 rats pretreated with PBS vehicle were divided equally into PGE_2 and the PBS control groups to evaluate the effects of PGE_2 infused iv on activities of HDC and HMT.

Thirty-two rats were used to study the effect of i3vt PGE_2 on HA and *t*-MH levels. Sixteen were pretreated ip with 0.30 mmol/kg pargyline and 16 rats with the same volume of PBS vehicle 10 min before the PGE_2 infusion. Each group of 16 rats was further divided into 4 subgroups and was infused i3vt at a rate of 1 μl/min with 0.50, 1.00, 5.00 nmol/kg PGE_2 or PBS vehicle over a period of 10 min, starting at 1300 hr.

Another 16 rats pretreated with PBS vehicle were used to evaluate the effects of PGE_2 infused i3vt on activities of HDC and HMT.

Procedures for brain sampling were the same as for the indomethacin experiment.

Measurement of HA and *t*-MH. The HA and *t*-MH concentrations were determined simultaneously by a slight modification of the method of Tsuruta *et al.* (12). The dissected hypothalamus was homogenized in 0.3 ml of 0.4 N perchloric acid containing 0.63 μ*M pros*-methylhistamine as an internal standard. After centrifugation at 1000*g* for 10 min, 0.25 ml of the supernatant were used for the assay. The HA and *t*-MH were extracted into *n*-butanol under NaCl-saturated alkaline conditions and transferred back to 0.1 N HCl (0.4 ml) by shaking with benzene (0.45 ml). After adjusting the pH to 6.0 with 0.1 N NaOH, the extracts were applied to P-cellulose columns. The columns were washed successively with 0.01 *M* phosphate buffer (pH 6.0, 2 ml × 2), distilled water (1 ml), and 0.12 *M* HCl (0.4 ml). Amines were eluted with 0.12 *M* HCl (1.0 ml) and, after evaporation, subjected to a reaction with 0.1% *o*-phthalaldehyde (5 μl) at pH 10.0 in the presence of reaction buffer containing 0.5% 2-mercaptoethanol(0.1 ml), methanol (5 ml) and 0.4 N boric buffer (5 ml). The resulting fluorophores were then injected into an HPLC system (13). The system was composed of an LC-6 A pump (Shimadzu, Kyoto, Japan), and a

reverse-phase column (Chemcosorb ODS-H, Chemco Scientific, Osaka, Japan). The mobile phase was a solution of 0.06 *M* Na_2HPO_4 and methanol(47:53, v/v). The excitation and emission wavelengths were set at 340 and 450 nm, respectively. The retention times were 10 min for HA and 15 min for *t*-MH.

Transmethylation of HA into *t*-MH catalyzed by HMT and subsequent deamination by monamine oxidase B are the major metabolic pathway of brain HA. Linear accumulation of *t*-MH after ip injection of pargyline was used for estimation of HA turnover rate (9), to avoid the influences of mast cell HA in the hypothalamus (14).

Measurement of HDC and HMT Activities. The dissected hypothalamus was homogenized in a 1-ml volume of a solution (A) containing 0.1 *M* potassium phosphate buffer (pH 7.0), 0.01 m*M* pyridoxal-5′-phosphate, 0.2 m*M* dithiothreitol, 1.0% polyethylene glycol (average relative molecular weight, 300), 0.01 m*M* aminoguanidine, and 0.15 m*M* phenylmethylsulfonyl fluoride. The homogenates were centrifuged at 15,000 r.p.m. for 20 min at 4°C. The supernatant was dialyzed by Dialysis Merb Size 8 (Wako, Osaka, Japan) once against 50 volumes of solution A for 24 hr at 4°C. HDC activity was evaluated by measuring the HA formed from L-histidine by the dialysate (15). Loss of HA was not observed even in the absence of the HMT inhibitor, unless S-adenosylmethionine, a methyl group donor, was added to the mixture. The reaction was started by adding L-histidine (0.25 m*M*) to the dialysate (180 μl), incubating at 37°C, and stopping 2 hr later by adding 0.4 N perchloric acid containing 0.63 μ*M pros*-methylhistamine. Assay was carried out in parallel with a mixture containing 0.1 m*M* α-fluoromethylhistidine (FMH) as a blank.

HMT activity was evaluated by the amount of *t*-MH formed from HA in incubations of the dialysate (16). The reaction was started by adding HA (0.1 m*M*), pargyline(0.1 m*M*), and S-adenosylmethionine (1 m*M*) to the dialysate (100 μl), incubating at 37°C, and stopping 2 hr later by adding 0.4 N perchloric acid containing 1.26 μ*M pros*-methylhistamine. An assay was carried out in parallel without S-adenosylmethionine to serve as a blank. Activities of HDC and HMT were expressed as pmol/min/mg protein. Protein was determined by the biuret method.

Statistics. Results were expressed as mean ± SEM. The data for the effects of indomethacin or PGE_2 infused iv on HA and *t*-MH concentrations, of indomethacin on HDC and HMT activities and of PGE_2 infused iv on the concentrations of HA and *t*-MH were evaluated by Mann–Whitney *U*-tests. The dose–response curves for HA, *t*-MH, and the activities of HDC and HMT of PGE_2 infused i3vt were evaluated by linear regression. Differences were defined to be significant if the probability of the difference occurring by chance was ≤5 in 100 ($P < 0.05$).

Results

Effects of Indomethacin on Hypothalamic HA Turnover Modulated by IL-1β. Table I shows the concentrations of HA and *t*-MH without pargyline pretreatment (steady-state) and with pargyline pretreatment. In the absence of pargyline, no treatment significantly increased steady-state HA and *t*-MH levels. The magnitude of pargyline-induced *t*-MH accumulation after ip injection of IL-1β was the 46.1% increase ($P < 0.01$), whereas the HA concentration was not affected. The magnitude of *t*-MH accumulation was reversed by pretreatment with indomethacin, since indomethacin pretreatment decreased *t*-MH accumulation by − 1.3% compared with PBS pretreatment ($P < 0.01$). Indomethacin *per se* did not affect the concentrations of HA or *t*-MH.

Effects of Indomethacin on Activities of Hypothalamic HDC and HMT Induced by IL-1β. Table II shows the effects of indomethacin on the activities of HDC and HMT in the hypothalamus following treatment with IL-1β. The magnitude of both HDC and HMT activities increased by 100% and 68.2%, respectively, after ip injection of IL-1β ($P < 0.01$ for each). The increased activities of HDC and HMT induced by IL-1β were completely abolished by pretreatment with indomethacin (HDC, 0%; HMT, − 0.8%; $P < 0.01$ for each). Indomethacin *per se* did not affect the activity of either HDC or HMT.

Effects of i3vt or iv Infusion of PGE_2 on Hypothalamic HA. With pargyline pretreatment, iv infusion of PGE_2 did not affect the concentrations of hypothalamic HA and *t*-MH (Table III) or the activities of HDC and HMT in the hypothalamus (Table IV).

Table I. The Effect of Indomethacin on Concentrations of Rat Hypothalamic Histamine (HA) and *tele*-Methylhistamine (*t*-MH) in Response to Interleukin-1β (IL-1β)

Amine concentrations (nmol/g tissue)	PBS + PBS ($n = 5$)	PBS + IL-1β (0.40 nmol/kg) ($n = 5$)	Indomethacin + PBS (0.07 mmol/kg) ($n = 5$)	Indomethacin + IL-1β (0.07 mmol/kg) (0.40 nmol/kg) ($n = 5$)
PBS-pretreatment ($n = 20$)				
HA	4.17 ± 0.21	4.10 ± 0.12	4.10 ± 0.22	4.13 ± 0.31
t-MH	2.60 ± 0.29	2.64 ± 0.18	2.63 ± 0.27	2.69 ± 0.27
Pargyline-pretreatment ($n = 20$)				
HA	4.22 ± 0.24	4.11 ± 0.23	4.18 ± 0.23	4.22 ± 0.28
t-MH	2.93 ± 0.25	4.28 ± 0.19[a]	3.04 ± 0.25	3.00 ± 0.25

Note. All test solutions were injected intraperitoneally. Pargyline was injected at a dose of 0.30 mmol/kg. Each value, mean ± SEM. *n*, number of rats tested. PBS, phosphate buffered saline. [a] $P < 0.01$ vs. corresponding PBS + PBS group and Indomethacin + IL-1β group.

Table II. Effect of Indomethacin and Interleukin-1β (IL-1β) Alone or Together on the Activities of Histidine Decarboxylase (HDC) and Histamine-N-Methyltransferase (HMT) in the Rat Hypothalamus

Enzyme activities (pmol/min/mg protein)	PBS + PBS (n = 5)	PBS + IL-1β (0.40 nmol/kg) (n = 5)	Indomethacin + PBS (0.07 mmol/kg) (n = 5)	Indomethacin + IL-1β (0.07 mmol/kg) (0.40 nmol/kg) (n = 5)
HDC	0.33 ± 0.08	0.66 ± 0.06[a]	0.34 ± 0.03	0.33 ± 0.01
HMT	14.07 ± 1.71	23.66 ± 0.65[a]	14.28 ± 1.17	13.96 ± 1.03

Note. All the test solutions were injected intraperitoneally. Each value, mean ± SEM. n, number of rats tested. PBS, phosphate buffered saline.
[a] $P < 0.01$ vs. corresponding PBS + PBS and Indomethacin + IL-1β groups.

Table III. Effect of Intravenous Infusion of Prostaglandin E_2 (PGE_2) on Concentrations of Rat Hypothalamic Histamine (HA) and *tele*-Methylhistamine (*t*-MH)

Amine concentrations (nmol/g tissue)	PBS (n = 5)	PGE_2 (1.50 μmol/kg) (n = 5)
PBS-pretreatment (n = 10)		
HA	4.18 ± 0.15	4.22 ± 0.24
t-MH	2.63 ± 0.20	2.67 ± 0.12
Pargyline-pretreatment (n = 10)		
HA	4.21 ± 0.37	4.25 ± 0.31
t-MH	2.96 ± 0.29	3.05 ± 0.16

Note. Pargyline was injected at a dose of 0.30 mmol/kg. Each value, mean ± SEM. n, number of rats tested. PBS, phosphate buffered saline.

Table IV. Effect of Intravenous Infusion of Prostaglandin E_2 (PGE_2) on Activities of Histidine Decarboxylase (HDC) and Histamine-N-Methyltransferase (HMT) in the Rat Hypothalamus

Enzyme activities (pmol/min/mg protein)	PBS (n = 5)	PGE_2 (1.50 μmol/kg) (n = 5)
HDC	0.34 ± 0.02	0.32 ± 0.01
HMT	14.21 ± 0.51	14.02 ± 0.36

Note. Each value, mean ± SEM. n, number of rats tested. PBS, phosphate buffered saline.

As shown in Figure 1, i3vt infusion of PGE_2 did not affect the steady-state concentration of hypothalamic HA or *t*-MH (HA: $Y = 4.30–0.0310^{-1}X$, $r = 0.010$; *t*-MH: $Y = 2.63–0.0110^{-1}X$, $r = 0.010$, $P > 0.1$ for each). However, PGE_2 increased the pargyline-induced accumulation of *t*-MH in a dose-dependent manner (0.50 nmol/kg PGE_2, 9.6%; 1.00 nmol/kg, 15.6%; 5.00 nmol/kg, 46.0%. $Y = 3.14 + 0.26X$, $r = 0.860$, $P < 0.01$). The HA concentration, however, was not affected by any PGE_2 doses ($Y = 4.26 + 0.01X$, $r = 0.020$, $P > 0.1$).

The effects of i3vt PGE_2 on HDC and on HMT activities were also increased dose-dependently (HDC: 0.50 nmol/kg PGE_2, 15.2%; 1.00 nmol/kg, 48.5%; 5.00 nmol/kg, 126.0%. $Y = 0.36 + 0.06X$, $r = 0.660$; HMT: 0.50 nmol/kg PGE_2, 8.2%; 1.00 nmol/kg, 33.4%; 5.00 nmol/kg, 68.6%. $Y = 15.04 + 1.81X$, $r = 0.730$; $P < 0.01$ for each] (Fig. 2).

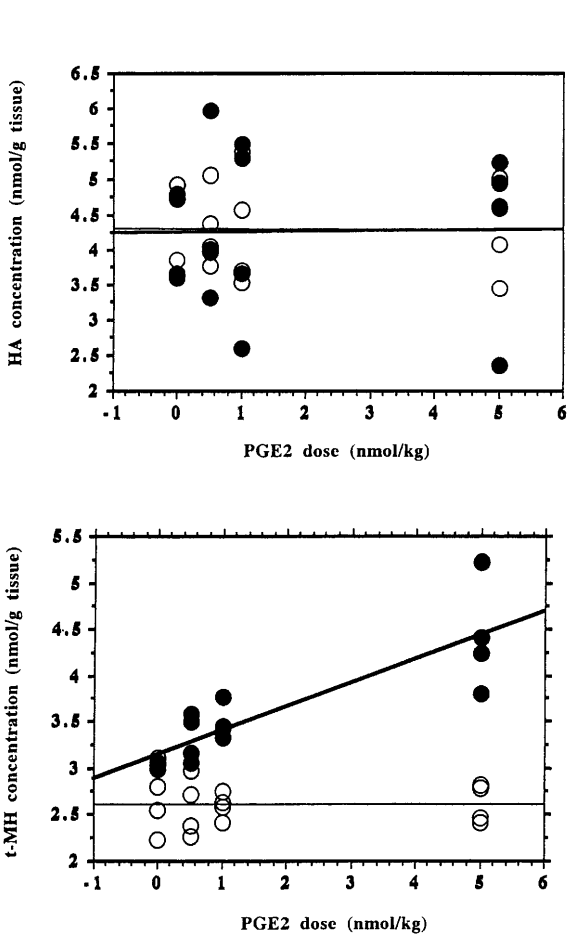

Figure 1. Effect of intra-3rd-cerebroventricular infusion of 0.50, 1.00, and 5.00 nmol/kg prostaglandin E_2 (PGE_2) on concentrations of rat hypothalamic histamine (HA) and *tele*-methylhistamine (*t*-MH). (A) The effect of PGE_2 on HA concentration (phosphate buffered saline (PBS) pretreatment group, $Y = 4.30–0.0310^{-1}X$, $r = 0.010$, $P > 0.1$. Pargyline pretreatment group, $Y = 4.26 + 0.01X$, $r = 0.020$, $P > 0.1$). (B) The effect of PGE_2 on *t*-MH concentration (PBS pretreatment group, $Y = 2.63–0.0110^{-1}X$, $r = 0.010$, $P > 0.1$. Pargyline pretreatment group, $Y = 3.14 + 0.26X$, $r = 0.860$, $P < 0.01$). Open circle, PBS pretreatment + PGE_2 group. Closed circle, Pargyline pretreatment + PGE_2 group.

Discussion

In the present study, peripheral administration of IL-1β has been shown to increase the accumulation of *t*-MH after pargyline treatment, but not the steady-state level of HA or *t*-MH. Thus, peripheral IL-1β increases the hypothalamic HA turnover rate. This activation of HA turnover was con-

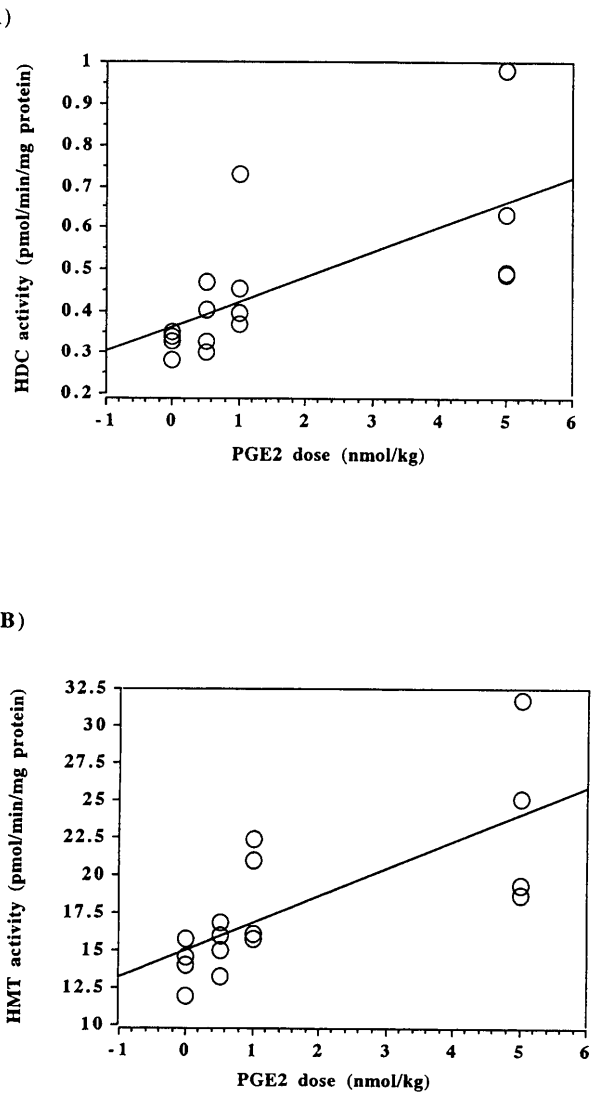

Figure 2. Effect of intra-3rd-cerebroventricular infusion of 0.50, 1.00, and 5.00 nmol/kg prostaglandin E_2 (PGE_2) on activities of histidine decarboxylase (HDC) and histamine-N-methyltransferase (HMT) in the rat hypothalamus. (A) The effect of PGE_2 on HDC activity ($Y = 0.36 + 0.06X$, $r = 0.660$, $P < 0.01$). (B) The effect of PGE_2 on HMT activity ($Y = 15.04 + 1.81X$, $r = 0.730$; $P < 0.01$).

firmed by enzyme assay, in which peripheral IL-1β enhanced activities of both HDC, an essential enzyme for the synthesis of neuroneal HA at the nerve terminal (17), and HMT, an enzyme that degrades neuronal HA in the extracellular space (18) with the increases in 100% and 68.2%, respectively. These findings lead to the conclusion that peripheral administration of IL-1β stimulates not only synthesis and release of hypothalamic HA but also its degradation. IL-1β increased pargyline-induced *t*-MH accumulation by 46.1% and HMT activity by 68.2%. This 22% difference between the values may reflect influence of other neuromodulators, including norepinephrine, dopamine, serotonin, and corticotropin-releasing hormone, on the dynamics of neuronal HA (19, 20).

A question can be raised as to whether peripheral IL-1β may modulate the dynamics of hypothalamic HA directly, or indirectly *via* PGs directly or indirectly. In the previous study, we demonstrated that i3vt infusion of IL-1β increased hypothalamic HA turnover (8). The present study demonstrated that indomethacin, an inhibitor of PGs-forming cyclooxygenases, of which dose was sufficient to abolish IL-1β-induced physiological responses to food and water intake completely (2, 21), potently blocked the IL-1β-induced activities of both HDC and HMT which mediate HA turnover, while the present results were not derived from a direct assessment of PGE_2. Thus, IL-1β appears to act on the hypothalamus indirectly *via* cyclooxygenase products including PGs. Neither indomethacin nor PGE_2 appears to interfere with the enzymatic assays.

IL-1β, one of the endogenous pyrogens, has been reported to increase synthesis of PGs in brain elements including the organum vasculosum of the lamina terminalis (10) and astrocytes (22), and in peripheral cells including fibroblasts (23). PGE has been shown to be elevated in the cerebrospinal fluid of rabbits that have a fever or that have been exposed to bacterial pyrogens (24). PGE_2 is also involved in IL1β-induced feeding (25) and drinking suppression (2). In the present study, i3vt infusion of PGE_2 at the maximum dose increased pargyline-induced *t*-MH accumulation by 46.1%. The value of *t*-MH confirmed the result from HA turnover rate (46.1%) enhanced by IL-1β. On the other hand, i3vt infusion of PGE_2 increased activities of HDC and HMT dose-dependently, which resulted in a dose-dependent increase in HA turnover. Iv infusion of PGE_2 does not affect HA even in doses reported to be sufficient to have a central pharmacologic action (26). Since PGE_2 is rapidly inactivated in the peripheral circulation (27), iv infusion may be an ineffective route of administration. Endogenous PGs are released from the rat organum vasculosum of the lamina terminalis in response to circulating IL-1β (10), and this structure is the most sensitive site for synthesis of PGs (28, 29). Therefore, peripheral administration of IL-1β may stimulate PGE_2 synthesis in the organum vasculosum of the lamina terminalis, which in turn affects hypothalamic HA neuron systems directly or indirectly because PGE_2 releases hypothalamic feeding-related chemical substances (30).

Hypothalamic HA is known to suppress food intake and facilitate water intake, which effectively prevents body temperature elevation (4–7). In addition, stimulation of H_1-receptors in the hypothalamus has been shown to lower the thermoregulatory set point, and stimulation of H_2-receptors has been shown to activate an efferent heat loss pathway (31). Our previous study demonstrated that elevation of body temperature by IL-1β was potently accelerated after depletion of hypothalamic HA (32). Thus, one physiological role of hypothalamic HA systems under inflammatory conditions may be to suppress excessive elevation of body temperature induced by circulating IL-1β, but the HA systems are insufficient to restore normal body temperature.

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