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Centrally administered histamine evokes the adrenal secretion of noradrenaline and adrenaline by brain cyclooxygenase-1- and thromboxane A_2-mediated mechanisms in rats

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Abstract

Plasma adrenaline is originated from adrenal medulla, while plasma noradrenaline reflects the release from sympathetic nerves in addition to the secretion from adrenal medulla. The present study was designed to characterize the source of plasma catecholamines induced by centrally administered histamine, with regard to the brain prostanoids. Intracerebroventricularly (i.c.v.) administered histamine (1, 5 and 10 μg/animal) elevated plasma noradrenaline and adrenaline (noradrenaline<adrenaline) in a dose-dependent manner. Ketoprofen (a selective inhibitor of cyclooxygenase-1) (100, 250 and 500 μg/animal, i.c.v.) dose-dependently reduced the histamine (5 μg/animal, i.c.v.)-induced elevation of both catecholamines, while NS-398 (a selective inhibitor of cyclooxygenase-2) (250 and 500 μg/animal, i.c.v.) had no effect. The histamine-induced response was dose-dependently attenuated by furegurelate (an inhibitor of thromboxane A_2 synthase) (250 and 500 μg/animal, i.c.v.), and abolished by acute bilateral adrenalectomy. These results suggest that centrally administered histamine evokes plasma noradrenaline and adrenaline from adrenal medulla by brain cyclooxygenase-1- and thromboxane A_2-mediated mechanisms in rats.

Keywords: Histamine; Cyclooxygenase-1; Thromboxane A_2; Catecholamines; Adrenal medulla

1. Introduction

Centrally administered histamine has been shown to elevate plasma noradrenaline and adrenaline (Knigge et al., 1990). We also reported that centrally administered bombesin-induced elevation of plasma noradrenaline and adrenaline was attenuated by central pretreatment of pyrilamine, a histamine H_1 receptor antagonist, in rats (Okuma et al., 1996, 1997). These findings suggest that the brain histaminergic neurons play a role in the activation of the central sympatho-adrenomedullary outflow in rats.

It is generally accepted that plasma noradrenaline reflects the activity of the sympathetic nervous system, while plasma adrenaline reflects the activity of the adrenomedullary system. Noradrenaline and adrenaline have overlapping, but essentially distinct roles: noradrenaline is the more potent vasoconstrictor, while adrenaline is responsible for metabolic actions (such as raising the blood glucose levels) in addition to cardiovascular effects. Hypoglycemia causes the elevation of plasma adrenaline (Young et al., 1984; Fujino and Fujii, 1995; Vollmer et al., 1997), while hypotension elevates both catecholamines (noradrenaline>adrenaline) (Brown and Fisher, 1984; Vollmer et al., 2000). However, plasma noradrenaline reflects the secretion from adrenal medulla in addition to the release from sympathetic nerves (Folkow and von Euler, 1954; Vollmer et al., 1997; Yokotani et al., 2002; Okada et al., 2003). In the adrenal medulla, noradrenaline and adrenaline are localized in separate populations of chromaffin cells, noradrenaline-containing NA cells and adrenaline-containing A cells (Verhofstad et al., 1985). These two populations are centrally regulated by separate groups of preganglionic neurons in the spinal cord (Edwards et al., 1996; Vollmer et al., 2000).

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Recently, we reported that centrally administered bombesin and vasopressin elicit adrenal secretion of both noradrenaline and adrenaline via brain prostanoid TP receptors, while centrally administered corticotropin-releasing factor (CRF) elicits sympathetic noradrenaline release and adrenal adrenaline secretion through brain prostanoid EP_3 and TP receptors, respectively, in rats (Okada et al., 2003; Yokotani et al., 2005). In the present study, therefore, we aimed to clarify the source of plasma catecholamines elevated by centrally administered histamine in regard to the brain prostanoids using anesthetized rats.

2. Materials and methods

2.1. Experimental procedures

Male Wistar rats weighing about 350 g were maintained in an air-conditioned room at 22–24 °C under a constant day–night rhythm for more than 2 weeks and given food (laboratory chow, CE-2; Clea Japan, Hamamatsu, Japan) and water ad libitum. Under urethane anesthesia (1.2 g/kg, i.p.), the femoral vein was cannulated for infusion of saline (1.2 ml/h), and the femoral artery was cannulated for collecting blood samples. In some experiments, acute bilateral adrenalectomy [plus hydrocortisone (5 mg/kg, i.m.)] or sham-operation (plus 200 μl saline/animal, i.m.) was done just before the experiments by an abdominal midline incision (Yokotani et al., 2005). After these procedures, the animal was placed in a stereotaxic apparatus, as shown in our previous papers (Yokotani et al., 1995; Shimizu et al., 2004). The skull was drilled for intracerebroventricular administration of test substances using stainless-steel cannula (0.3 mm outer diameter). The stereotaxic coordinates of the tip of cannula were as follows (in mm): AP-0.8, L 1.5, V 4.0 (AP, anterior from the bregma; L, lateral from the midline; V, below the surface of the brain), according to the rat brain atlas of Paxinos and Watson (1986). Three hours were allowed to elapse before the application of histamine or the application of blocking reagents.

Histamine dissolved in sterile saline was slowly injected into the right lateral ventricle in a volume of 10 μl/animal using a 25-μl Hamilton syringe. Each animal received only one dose of histamine (or vehicle). Furegrelate dissolved in sterile saline was intracerebroventricularly (i.c.v.) administered in a volume of 5 μl/animal, while ketoprofen and *N*-[2-(cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide (NS-398) dissolved in 2.5 μl of 100% *N*,*N*-dimethylformamide (DMF)/animal were i.c.v. administered using a 10-μl Hamilton syringe. In the case of using blocking reagents, histamine was i.c.v. administered 60 min after application of ketoprofen, NS-398 or furegrelate. Each animal also received only one dose of blocking reagents (or vehicle).

All experiments were conducted in compliance with the guiding principles for the care and use of laboratory animals approved by the Kochi University.

2.2. Measurement of plasma catecholamines

Blood samples (250 μl) were collected through an arterial catheter and were preserved on ice during experiments. Plasma were prepared immediately after the final sampling. Catecholamines in the plasma were extracted by the method of Anton and Sayre (1962) with a slight modification and were assayed electrochemically with high performance liquid chromatography (HPLC) (Shimizu et al., 2004). Briefly, after centrifugation, the plasma (100 μl) was transferred to a centrifuge tube containing 30 mg of activated alumina, 2 ml of double deionized water, 1 ml of 1.5 M Tris Buffer (pH 8.6) containing 0.1 M disodium EDTA and 1 ng of 3,4-dihydroxybenzylamine as an internal standard. The tube was shaken for 10 min and the alumina was washed three times with 4 ml of ice-cold double deionized water. Then, catecholamines adsorbed onto the alumina were eluted with 300 μl of 4% acetic acid containing 0.1 mM disodium EDTA. A pump (EP-300: Eicom, Kyoto, Japan), a sample injector (Model-231XL; Gilson, Villiers-le-Bel, France) and an electrochemical detector (ECD-300: Eicom) equipped with a graphite electrode were used with HPLC. Analytical conditions were as follows: detector, +450 mV potential against a Ag/AgCl reference electrode; column, Eicompack CA-50DS, 2.1×150 mm (Eicom); mobile phase, 0.1 M NaH_2PO_4–Na_2HPO_4 buffer (pH 6.0) containing 50 mg/l EDTA dihydrate, 0.75 g/l sodium 1-octanesulfonate and 15% methanol at a flow of 0.18 ml/min; injection volume, 40 μl. The amount of catecholamines in each sample was calculated using the peak height ratio relative to that of 3,4-dihydroxybenzylamine. By this assay, coefficients of variation for intra- and inter-assay were 3.0% and 3.7%, respectively, and 0.5 pg of noradrenaline and adrenaline were accurately determined.

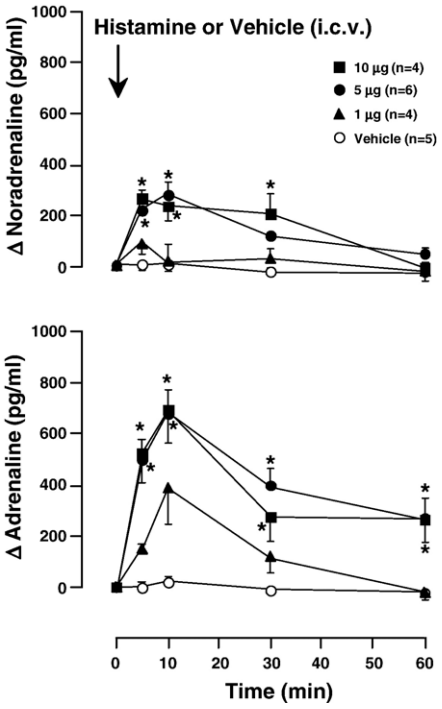

Fig. 1. Effect of histamine on plasma levels of noradrenaline and adrenaline. Δ Noradrenaline and Δ adrenaline: increments of noradrenaline and adrenaline above the basal. Arrow indicates the intracerebroventricular (i.c.v.) administration of vehicle (saline 10 μl/animal) or histamine [1, 5 and 10 μg (5.4, 27 and 54 nmol)/animal]. Each point represents the mean±S.E.M. *$p<0.05$, significantly different from vehicle-treated group with the Bonferroni method. The actual values for noradrenaline and adrenaline at 0 min were 349.6±56.2 and 349.5±38.0 pg/ml ($n=19$), respectively.

2.3. Treatment of data and statistics

All values are expressed as the means ± S.E.M. The data were analyzed by repeated-measure analysis of variance (ANOVA), followed by post-hoc analysis with the Bonferroni method (Figs. 1–3). When only two means were compared, an unpaired Student's *t*-test was used (Fig. 4). *P* values less than 0.05 were taken to indicate statistical significance.

2.4. Compounds

The following drugs were used: ketoprofen (Wako, Osaka, Japan); NS-398 (Cayman Chemical, Ann Arbor, MI, U.S.A.); furegrelate sodium (Biomol Research Lab., Plymouth Meeting, PA, U.S.A.); hydrocortisone (Sigma Aldorich Fine Chemicals, St. Louis, MO, U.S.A.). Histamine dihydrochloride and all other reagents were the highest grade available (Nacalai Tesque, Kyoto, Japan).

3. Results

3.1. Effect of histamine on plasma catecholamines

I.c.v. administered vehicle (10 μl saline/animal) and blood sampling for 5 times over 60 min had no effect on the basal plasma levels of either noradrenaline and adrenaline (Fig. 1).

Histamine [1, 5 and 10 μg (5.4, 27 and 54 nmol)/animal, i.c.v.] dose-dependently elevated plasma levels of noradrenaline and adrenaline, and the maximal effect was obtained at 5 μg/animal (i.c.v.) (Fig. 1). These responses reached a maximum 5–10 min after the administration of histamine and then declined toward their basal levels. Intravenous administration of histamine (5 μg/animal), however, had no effect on plasma levels of catecholamines (data not shown).

3.2. Effects of ketoprofen and NS-398, inhibitors of cyclooxygenase-1 and -2, on the histamine-induced elevation of plasma catecholamines

Treatments with vehicle-1 (2.5 μl DMF/animal, i.c.v.) and vehicle-2 (10 μl saline/animal, i.c.v.) had no effect on the basal plasma levels of catecholamines (Fig. 2A and B). Pretreatment with ketoprofen [100, 250 and 500 μg (0.4, 1.0 and 2.0 μmol)/animal, i.c.v.] and NS-398 [250 and 500 μg (0.8 and 1.6 μmol)/animal, i.c.v.] also had no effect on the basal plasma levels of catecholamines (Fig. 2A and B).

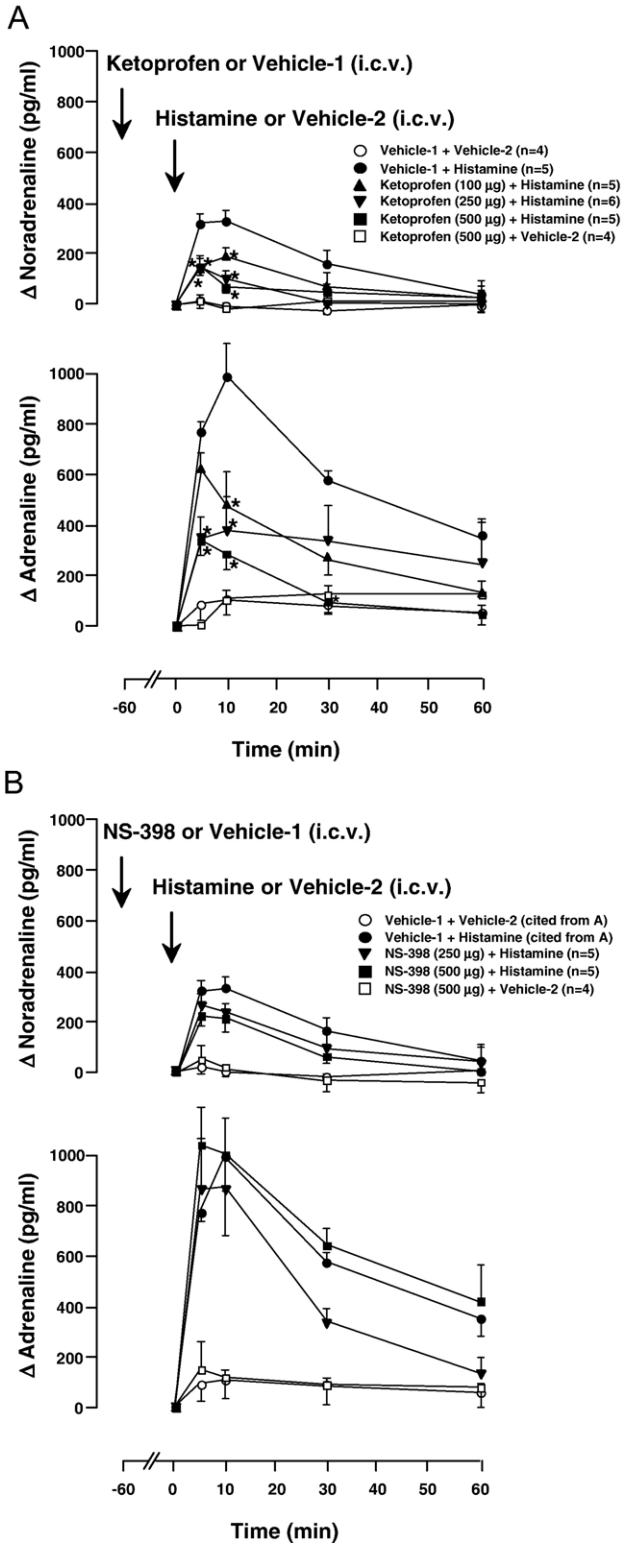

Fig. 2. Effects of ketoprofen (a highly selective inhibitor of cyclooxygenase-1) and NS-398 (a highly selective inhibitor of cyclooxygenase-2) on the histamine-induced elevation of plasma noradrenaline and adrenaline. Ketoprofen [100, 250 and 500 μg (0.4, 1.0 and 2.0 μmol)/animal, i.c.v.], NS-398 [250 and 500 μg (0.8 and 1.6 μmol)/animal, i.c.v.] or vehicle-1 (2.5 μl DMF/animal) was i.c.v. administered 60 min before the administration of histamine (5 μg/animal, i.c.v.) or vehicle-2 (10 μl saline/animal, i.c.v.). Arrows indicate the i.c.v. administrations of ketoprofen/NS-398/vehicle-1 and histamine/vehicle-2. $*p<0.05$, significantly different from vehicle-1- and histamine-treated group with the Bonferroni method. Other conditions were the same as those of Fig. 1. The actual values for noradrenaline and adrenaline at 0 min were 320.2±48.5 and 229.3±48.1 pg/ml in the vehicle-1 (DMF)-pretreated group ($n=9$); 330.9±89.3 and 374.3±103.1 pg/ml in the ketoprofen (100 μg/animal)-pretreated group ($n=5$); 352.4±91.2 and 367.3±124.2 pg/ml in the ketoprofen (250 μg/animal)-pretreated group ($n=6$); 290.1±30.2 and 313.7±93.4 pg/ml in the ketoprofen (500 μg/animal)-pretreated group ($n=9$); 484.8±105.7 and 405.4±104.8 pg/ml in the NS-398 (250 μg/animal)-pretreated group ($n=5$); 342.6±49.9 and 315.1±135.8 pg/ml in the NS-398 (500 μg/animal)-pretreated group ($n=9$), respectively.

Ketoprofen [100, 250 and 500 μg (0.4, 1.0 and 2.0 μmol)/animal, i.c.v.], a highly selective inhibitor of cyclooxygenase-1, dose-dependently reduced the histamine (5 μg/animal, i.c.v.)-induced elevation of plasma noradrenaline and adrenaline (Fig. 2A). On the other hand, the histamine-induced response was not influenced by NS-398 (a highly selective inhibitor of cyclooxygenase-2) [250 and 500 μg (0.8 and 1.6 μmol)/animal, i.c.v.] (Fig. 2B).

3.3. Effect of furegrelate, an inhibitor of thromboxane A_2 synthase, on the histamine-induced elevation of plasma catecholamines

Treatments with vehicle-1 (5 μl saline/animal, i.c.v.) and vehicle-2 (10 μl saline/animal, i.c.v.) had no effect on the basal plasma levels of catecholamines (Fig. 3). Pretreatment with furegrelate [250 and 500 μg (0.9 and 1.8 μmol)/animal, i.c.v.] also had no effect on the basal plasma levels of catecholamines (Fig. 3).

The histamine (5 μg/animal, i.c.v.)-induced elevation of plasma catecholamines was attenuated by furegrelate in a dose-dependent manner [250 and 500 μg (0.9 and 1.8 μmol)/animal, i.c.v.] (Fig. 3).

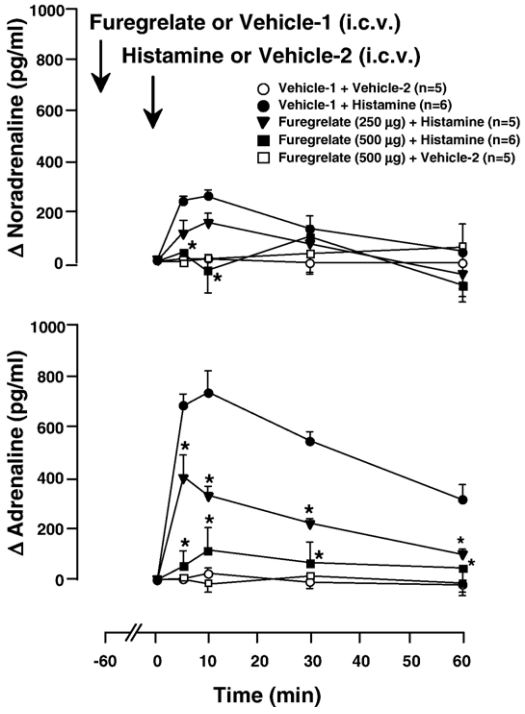

Fig. 3. Effect of furegrelate, an inhibitor of thromboxane A_2 synthase, on the histamine-induced elevation of plasma noradrenaline and adrenaline. Furegrelate [250 and 500 μg (0.9 and 1.8 μmol)/animal, i.c.v.] or vehicle-1 (5 μl saline/animal) was i.c.v. administered 60 min before the administration of histamine (5 μg/animal, i.c.v.) or vehicle-2 (10 μl saline/animal, i.c.v.). *$p<0.05$, significantly different from vehicle-1- and histamine-treated group with the Bonferroni method. Other conditions were the same as those of Figs. 1 and 2. The actual values for noradrenaline and adrenaline at 0 min were 346.1±49.6 and 325.5±51.3 pg/ml in the vehicle-1 (saline)-pretreated group ($n=11$); 482.1±60.7 and 294.5±19.5 pg/ml in the furegrelate (250 μg/animal)-pretreated group ($n=5$); 304.7±108.1 and 304.2±123.2 pg/ml in the furegrelate (500 μg/animal)-pretreated group ($n=11$), respectively.

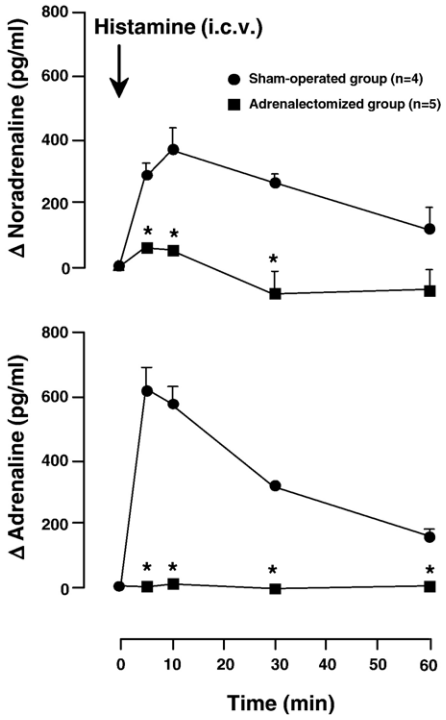

Fig. 4. Effect of acute bilateral adrenalectomy on the histamine-induced elevation of plasma noradrenaline and adrenaline. Hydrocortisone (5 mg/kg) or 200 μl saline was intramuscularly administered in adrenalectomized or sham-operated group, respectively. Arrow indicates the administration of histamine (5 μg/animal, i.c.v.). *$p<0.05$, significantly different from sham-operated group with the Student's t-test. Other conditions were the same as those in Figs. 1–3. The actual values for noradrenaline and adrenaline at 0 min were 344.3±35.0 and 303.2±20.4 pg/ml in sham-operated group ($n=4$) and 498.0±87.5 and 44.1±8.5 pg/ml in bilateral adrenalectomized group ($n=5$), respectively.

3.4. Effect of bilateral adrenalectomy on the histamine-induced elevation of plasma catecholamines

The basal plasma levels of noradrenaline and adrenaline were not influenced by sham-operation. The basal plasma levels of noradrenaline were not influenced by bilateral adrenalectomy, while the basal plasma adrenaline was greatly low in bilaterally adrenalectomized group (Fig. 4).

The histamine (5 μg/animal, i.c.v.)-induced elevation of plasma levels of both catecholamines was abolished by bilateral adrenalectomy (Fig. 4).

4. Discussion

We previously reported the involvement of central cyclooxygenase in the bombesin-, CRF- and vasopressin-induced elevation of plasma catecholamines using indomethacin, a non-selective inhibitor of cyclooxygenase, in rats (Okuma et al., 1996; Yokotani et al., 2001; Okada et al., 2002). Cyclooxygenase is divided into two isoforms, cyclooxygenase-1 and cyclooxygenase-2. Cyclooxygenase-1 is constitutively expressed in the majority of tissues, while cyclooxygenase-2 is generally undetectable or present at low levels in resting state but is induced by various stimuli such as inflammatory cytokines (Smith et al., 1996). However, cyclooxygenase-2 has also been found to be

constitutively expressed in some tissues including brain (Breder et al., 1995; Hetu and Riendeau, 2005). In the first experiment, therefore, we attempted to clarify whether brain cyclooxygenase is involved in the histamine-induced elevation of plasma catecholamines in according to cyclooxygenase isoforms.

We used two kinds of cyclooxygenase inhibitors, ketoprofen and NS-398. Ketoprofen has IC_{50} values of 0.02 and 1.08 μM for cyclooxygenase-1 and cyclooxygenase-2 activity in human whole blood (Brideau et al., 1996). On the other hand, NS-398 has IC_{50} values of 75 μM and 1.77 μM for human recombinant cyclooxygenase-1 and cyclooxygenase-2 (Barnett et al., 1994). These results indicate that ketoprofen and NS-398 are highly selective inhibitors of cyclooxygenase-1 and cyclooxygenase-2, respectively. In the present experiment, central pretreatment with ketoprofen reduced the histamine-induced elevation of plasma noradrenaline and adrenaline in a dose-dependent manner, while this response was not influenced by a large dose of NS-398. These results suggest that brain cyclooxygenase-1 is involved in the histamine-induced elevation of plasma catecholamines in rats.

Prostanoids, prostaglandins and thromboxane A_2, have been demonstrated to act as neuromediator and/or neuromodulator in the brain actions including cardiovascular function (Chiu and Richardson, 1983; Wood et al., 1993) and regulation of hormone secretion (Brooks et al., 1986; Bernardini et al., 1989). Previously, we reported that centrally administered prostaglandin E_2 (but not prostaglandin D_2, prostaglandin I_2 and prostaglandin $F_{2\alpha}$) elevates plasma noradrenaline from sympathetic nerves by activation of brain prostanoid EP_3 receptors (Yokotani et al., 1995, 2005; Murakami et al., 2002). Microinjection of thromboxane A_2 mimetic into the hypothalamic paraventricular nucleus, which has been considered to be the control center of the sympatho-adrenomedullary outflow (Swanson and Sawchenko, 1980; Jansen et al., 1995), predominantly elevates plasma adrenaline (Murakami et al., 2002). Furthermore, centrally administered CRF elicits sympathetic noradrenaline release by brain prostaglandin E_2-mediated mechanisms and adrenal adrenaline secretion by brain thromboxane A_2-mediated mechanisms, while bombesin and vasopressin elicit adrenal secretion of both noradrenaline and adrenaline by brain thromboxane A_2-mediated mechanisms in rats (Okada et al., 2003; Yokotani et al., 2005).

In the next experiment, we examined which types of prostanoids are involved in the histamine-induced elevation of plasma noradrenaline and adrenaline using furegrelate, a selective inhibitor of thromboxane A_2 synthase (Gorman et al., 1983). Central pretreatment with furegrelate effectively reduced the histamine-induced elevation of plasma noradrenaline and adrenaline, suggesting the involvement of brain thromboxane A_2 in the centrally administered histamine-induced elevation of plasma noradrenaline and adrenaline, as shown in the bombesin- and vasopressin-induced secretion of both catecholamines from adrenal medulla (Okada et al., 2003; Yokotani et al., 2005). These results suggest that centrally administered histamine elicits adrenal secretion of both noradrenaline and adrenaline by brain thromboxane A_2-mediated mechanisms in rats.

To further explore the source of noradrenaline and adrenaline evoked by centrally administered histamine, we examined the effect of acute bilateral adrenalectomy [plus hydrocortisone (5 mg/kg, i.m.)] on the histamine-induced elevation of plasma catecholamines. In preliminary studies, we measured plasma concentration of corticosterone and cortisol. Three hours after sham-operation or adrenalectomy (plus hydrocortisone), corticosterone and cortisol were 358.0±21.6 ng/ml and 23.3± 4.1 ng/ml in sham-operated rats (n=3) and 28.1±3.1 ng/ml and 484.0± 151.5 ng/ml in adrenalectomized rats with hydrocortisone (n=3), respectively. These results suggest that cortisol (hydrocortisone) supplementation in adrenalectomized rats resulted in similar concentrations compared to corticosterone in sham-operated rats. In the last experiment, bilateral adrenalectomy abolished the centrally administered histamine-induced elevation of plasma noradrenaline and adrenaline. Previously, we reported that bilateral adrenalectomy abolishes the centrally administered bombesin- and vasopressin-induced elevation of plasma noradrenaline and adrenaline, while the procedure only abolished the CRF-induced elevation of plasma adrenaline alone (Okada et al., 2003; Yokotani et al., 2005). These results suggest that centrally administered histamine evokes the secretion of both noradrenaline and adrenaline from adrenal medulla in rats.

Histaminergic neurons are exclusively localized in the tuberomammillary nucleus of the posterior hypothalamic region, while their varicose fibers are found in almost all regions of the brain (Panula et al., 1984, 1989; Watanabe et al., 1984; Inagaki et al., 1988). The highest density of histamine-containing fibers in the brain is found in the hypothalamus, which has been shown to be a control center of the autonomic and neuroendocrine functions (Panula et al., 1989; Sakata et al., 1997; Brown et al., 2001). This evidence further suggests a role of brain histaminergic neurons in the central activation of adrenomedullary outflow in rats.

In summary, we demonstrated here that centrally administered histamine evokes the secretion of both noradrenaline and adrenaline from the adrenal medulla via brain cyclooxygenase-1- and thromboxane A_2-mediated mechanisms in rats.

Acknowledgments

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