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Centrally administered *N*-methyl-D-aspartate evokes the adrenal secretion of noradrenaline and adrenaline by brain thromboxane A_2-mediated mechanisms in rats

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ABSTRACT

Plasma adrenaline mainly originated from adrenaline-containing cells in the adrenal medulla, while plasma noradrenaline reflects the release from sympathetic nerves in addition to the secretion from noradrenaline-containing cells in the adrenal medulla. The present study was undertaken to characterize the source of plasma catecholamines induced by centrally administered *N*-methyl-D-aspartate with regard to the brain prostanoid, using urethane-anesthetized rats. Intracerebroventricularly (i.c.v.) administered *N*-methyl-D-aspartate (1.0, 5.0, 10.0 nmol/animal) dose-dependently elevated plasma levels of noradrenaline and adrenaline. The *N*-methyl-D-aspartate (5.0 nmol/animal, i.c.v.)-induced elevation of both catecholamines was reduced by dizocilpine maleate (5 nmol/animal, i.c.v.), a non-competitive *N*-methyl-D-aspartate receptor antagonist. Indomethacin (0.6 and 1.2 μmol/animal, i.c.v.), an inhibitor of cyclooxygenase, dose-dependently reduced the *N*-methyl-D-aspartate (5.0 nmol/animal, i.c.v.)-induced elevation of both catecholamines. The *N*-methyl-D-aspartate-induced response was dose-dependently attenuated by furegrelate (0.9 and 1.8 μmol/animal, i.c.v.), an inhibitor of thromboxane A_2 synthase. Furthermore, the acute bilateral adrenalectomy abolished the *N*-methyl-D-aspartate-induced responses, indicating that the source of increase in plasma noradrenaline evoked by *N*-methyl-D-aspartate is due to secretion from the adrenal gland and not due to release from sympathetic nerve terminals. These results suggest that centrally administered *N*-methyl-D-aspartate induces the secretion of noradrenaline and adrenaline from adrenal medulla by the brain thromboxane A_2-mediated mechanisms in rats.

1. Introduction

Glutamate plays important roles in functioning as the major excitatory neurotransmitter in the central nervous system (Marmo, 1988). Glutamate interacts with at least three related classes of ligand-gated ionotropic receptor channels, one of which is the *N*-methyl-D-aspartate (NMDA) type receptor (Brann and Mahesh, 1994). The NMDA receptors are abundant, ubiquitously distributed throughout the central nervous system, fundamental to excitatory glutamatergic transmission and critical for normal brain functions (Gardoni and Di Luca, 2006), including central cardiovascular regulation (Soltis and DiMicco, 1991, 1992). Intracerebroventricular administration of NMDA has been shown to increase arterial blood pressure or plasma levels of catecholamines (Maione et al., 1992; Goren et al., 2000b; Yamaguchi and Watanabe, 2005). Furthermore, an immunohistochemical study revealed that NMDA receptors are expressed in all regions of the hypothalamic paraventricular nucleus (Ziegler et al., 2005), which has been recognized as a regulatory center of the central sympatho-adrenomedullary outflow (Sawchenko and Swanson, 1983). NMDA injected into the hypothalamic paraventricular nucleus produced dose-dependent increases in renal sympathetic nerve activity, blood pressure, and heart rate (Goren et al., 2000a; Badoer, 2001; Li et al., 2006). These observations suggest a role for NMDA receptor in regulation of several autonomic responses in the brain (Kenney et al., 2003). However, the central mechanisms underlying these actions of NMDA receptors remain to be completely defined.

Previously, this laboratory reported that intracerebroventricular administration of arachidonic acid-induced elevation of both plasma noradrenaline and adrenaline was abolished by central pretreatment with indomethacin (an inhibitor of cyclooxygenase) (Yokotani et al., 2000). Furthermore, this research group also demonstrated that central pretreatment with furegrelate (an inhibitor of thromboxane A_2 synthase) abolished only the elevation of adrenaline induced by arachidonic acid, but had no effect on the elevation of noradrenaline (Yokotani et al., 2000). These results suggest the involvement of brain prostanoids in the central activation of the sympatho-adrenomedullary outflow in rats.

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In general, plasma noradrenaline reflects the activity of the sympathetic nervous system, while plasma adrenaline reflects the activity of the adrenomedullary system. Various studies provide evidence to indicate a dissociation of the sympathetic nervous system and adrenal medullary responses (Rappaport et al., 1982; Victor et al., 1989; Scheurink and Ritter, 1993). More recently, this laboratory has demonstrated that centrally administered arginine–vasopressin, bombesin, or histamine elicits adrenal secretion of both noradrenaline and adrenaline by brain thromboxane A_2-prostanoid H_2 (TP) receptors, while centrally administered corticotropin releasing factor (CRF) elicits sympathetic noradrenaline release and adrenaline secretion through brain prostanoid EP_3 and TP receptors, respectively, in rats (Okada et al., 2003; Yokotani et al., 2005; Shimizu et al., 2006). In the present study, therefore, we characterized the source of plasma noradrenaline and adrenaline induced by intracerebroventricularly administered NMDA with regard to the brain prostanoids using urethane-anesthetized rats.

2. Materials and methods

2.1. Experimental procedures

Male Wistar rats weighing approximately 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 (1.0 g/kg, intraperitoneally [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, as described previously (Okada et al., 2003). For some animals, acute bilateral adrenalectomy (plus hydrocortisone [5 mg/kg, intramuscularly, (i.m.)] or a sham operation (plus 200 μl saline/animal, i.m.) was carried out just before the experiments by making two dorsal–lateral incisions, and utilizing an aseptic surgical technique (Shimizu et al., 2006).

Next, the animal was placed in a stereotaxic apparatus, as described previously (Okada et al., 2003). A hole was drilled in the skull for intracerebroventricular administration of test substances through a stainless-steel cannula (0.3 mm outer diameter). The stereotaxic coordinates of the tip of the 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 (1997). Three hours were allowed to elapse before the application of NMDA or blocking reagents.

NMDA and other reagents were dissolved in sterile saline and injected slowly into the right cerebral ventricle in a volume of 5 μl, with a 10 μl Hamilton syringe. Dizocilpine maleate (MK-801), a non-competitive NMDA receptor antagonist, water-soluble indomethacin-Na (a cyclooxygenase inhibitor) and furegrelate (a thromboxane A_2 synthase inhibitor) were intracerebroventricularly administered 30 min before NMDA (5 μl/animal). According to our previous reports that the 1.2 μmol (500 μg) dose of indomethacin and the 1.8 μmol (500 μg) dose of furegrelate effectively inhibit cyclooxygenase and thromboxane A_2 synthase (Yokotani et al., 2000; Okada et al., 2003; Yokotani et al., 2005; Shimizu et al., 2006), respectively, we used the doses of these drugs. Referring the results of Laudrup and Klitgaard (1993), we used 5 nmol dose of MK-801. All experiments were conducted in compliance with the guiding principle for the care and use of laboratory animals approved by 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 was 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) (Okada et al., 2003). Briefly, after centrifugation, plasma (100 μl) was transferred to a sample tube containing 30 mg of activated alumina, 1 ng of 3,4-dihydroxybenzylamine as an internal standard and 3 ml of 0.5 M Tris Buffer (pH 8.6) containing 0.1 M disodium EDTA. 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, 750 mg/l 1-octane sulfate sodium (Nacalai Tesque, Kyoto, Japan) and 15% methanol at a flow rate of 0.18 ml/min. The amount of catecholamines in each sample was calculated using the peak height ratio relative to that of 3,4-dihydroxybenzylamine, an internal standard. This assay could determine 0.5 pg of adrenaline and noradrenaline accurately.

2.3. Treatment of data and statistics

Results are expressed as the means±S.E.M. of the net changes above the respective basal values. The data were analyzed by

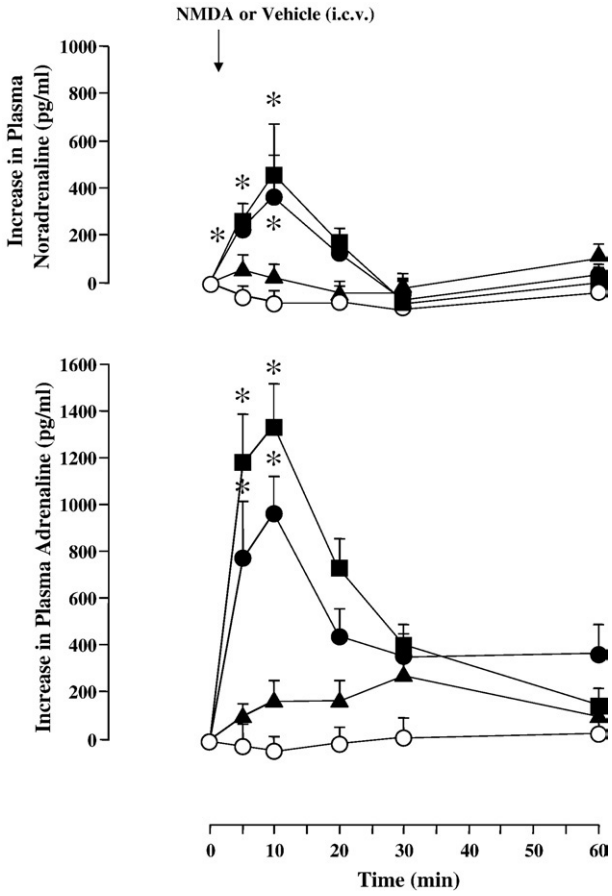

Fig. 1. Effects of NMDA on plasma catecholamine levels. Arrow indicates the time of intracerebroventricular administration of NMDA (1.0, 5.0, 10.0 nmol/animal). ○, vehicle (n=4); ▲, 1.0 nmol (n=5); ●, 5.0 nmol (n=6); ■, 10.0 nmol (n=5). *Significantly different (P<0.05) from vehicle-treated control. Each point represents the mean±S.E.M. The actual values for noradrenaline and adrenaline at 0 min were 375.8±35.1 and 375.4±56.7 pg/ml (n=20), respectively.

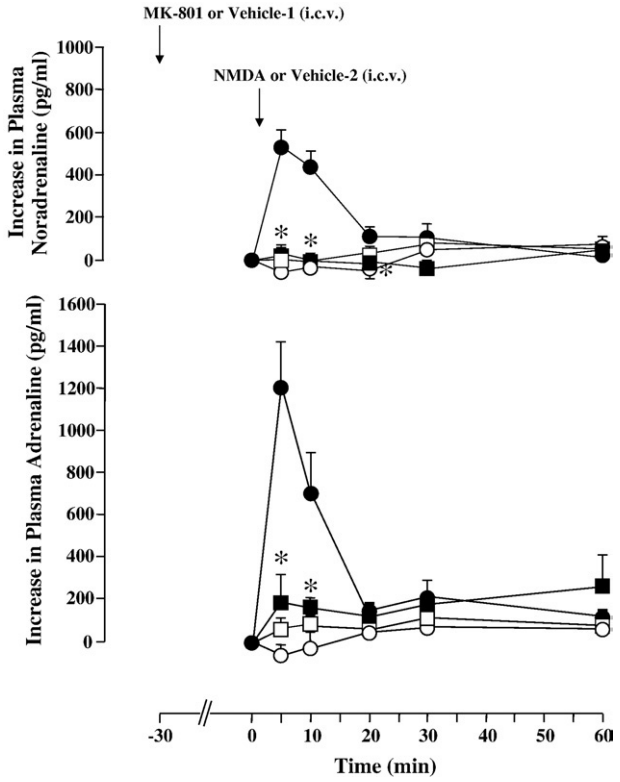

Fig. 2. Effect of MK-801, a NMDA receptor antagonist, on the NMDA-induced elevation of plasma catecholamines. MK-801 (5 nmol/animal, i.c.v.) or vehicle-1 (5 μl saline/animal, i.c.v.) was administered 30 min before NMDA (5 nmol/animal, i.c.v.) or vehicle-2 (5 μl saline/animal, i.c.v.). ●, vehicle-1 plus NMDA (n=6); ■, MK-801 plus NMDA (n=5); □, MK-801 plus vehicle-2 (n=4); ○, vehicle-1 plus vehicle-2 (n=4). * Significantly different (P<0.05) from vehicle-1 plus NMDA. Other conditions were the same as those of Fig. 1. The actual values for noradrenaline and adrenaline at 0 min were 384.2±37.2 and 285.5±49.9 pg/ml in the vehicle-1-pretreated group (n=10) and 238.1±21.4 and 207.0±35.9 pg/ml in the MK-801-pretreated group (n=9), respectively.

repeated-measure analysis of variance (ANOVA), followed by post-hoc analysis with the Bonferroni method (Fig. 1). When only two means were compared, the data were analyzed by unpaired Student's t-test (Figs. 2–5). P values less than 0.05 were taken to indicate statistical significance.

2.4. Compounds

The following drugs were used: NMDA and (+)-MK-801 (Tocris Institute, UK,); water-soluble indomethacin sodium trihydrite (a kind gift from Merck, Rahway, NJ, USA); furegrelate sodium (Biomol Research Lab., Plymouth Meeting, PA, USA). All other reagents were the highest grade available (Nacalai Tesque, Kyoto, Japan).

3. Results

3.1. Effects of N-methyl-D-aspartate on the plasma levels of catecholamines

Intracerebroventricularly (i.c.v.) administered vehicle (5 μl of saline/animal) and blood sampling six times over a 60 min period had no effect on the basal plasma levels of either noradrenaline or adrenaline (Fig. 1). NMDA (1.0, 5.0, 10.0 nmol/animal, i.c.v.) dose-dependently elevated plasma levels of noradrenaline and adrenaline (noradrenaline<adrenaline) (Fig. 1). The responses for noradrenaline and adrenaline reached a maximum 10 min after administration of NMDA and then gradually declined toward their basal levels. In the following experiments, 5 nmol NMDA was used for analyses.

3.2. Effect of dizocilpine maleate, a non-competitive N-methyl-D-aspartate receptor antagonist, on the N-methyl-D-aspartate-induced elevation of plasma catecholamines

Administration of MK-801 (5 nmol/animal, i.c.v.) had no effect on the basal plasma levels of catecholamines (Fig. 2). MK-801 abolished the NMDA (5.0 nmol/animal, i.c.v.)-induced elevation of plasma noradrenaline and adrenaline.

3.3. Effect of indomethacin, a cyclooxygenase inhibitor, on the N-methyl-D-aspartate-induced elevation of plasma catecholamines

Administration of indomethacin [1.2 μmol (500 μg)/animal, i.c.v.] had no effect on the basal plasma levels of catecholamines (Fig. 3). Indomethacin dose-dependently attenuated the elevation of both catecholamines induced by NMDA (5.0 nmol/animal, i.c.v.).

3.4. Effect of furegrelate, a thromboxane A_2 synthase inhibitor, on the N-methyl-D-aspartate-induced elevation of plasma catecholamines

Administration of furegrelate [1.8 μmol (500 μg)/animal, i.c.v.] had no effect on the basal plasma levels of catecholamines (Fig. 4). The

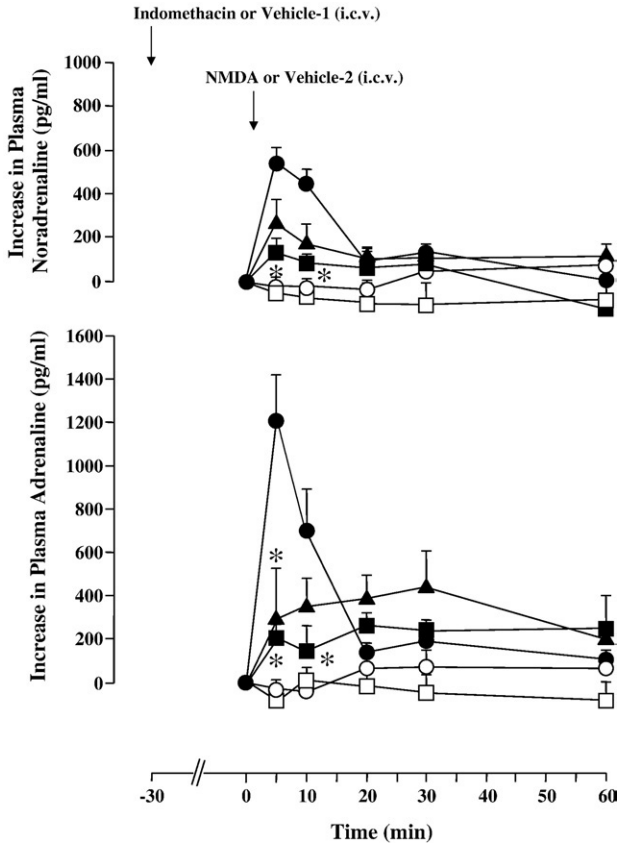

Fig. 3. Effect of indomethacin, a cyclooxygenase inhibitor, on the NMDA-induced elevation of plasma catecholamines. Indomethacin (0.6 and 1.2 μmol/animal, i.c.v.) or vehicle-1 (5 μl saline/animal, i.c.v.) was administered 30 min before NMDA (5 nmol/animal, i.c.v.) or vehicle-2 (5 μl saline/animal, i.c.v.). ●, vehicle-1 plus NMDA (cited from Fig. 2.) (n=6); ▲, indomethacin (0.6 μmol/animal, i.c.v.) plus NMDA (n=5); ■, indomethacin (1.2 μmol/animal, i.c.v.) plus NMDA (n=6); □, indomethacin plus vehicle-2 (n=4); ○, vehicle-1 plus vehicle-2 (cited from Fig. 2.) (n=4). *Significantly different (P<0.05) from vehicle-1 plus NMDA. Other conditions were the same as those of Figs. 1 and 2. The actual values for noradrenaline and adrenaline at 0 min were 384.2±37.2 and 285.5±49.9 pg/ml in the vehicle-1-pretreated group (n=10); 337.8±48.8 and 472.7±87.3 pg/ml in the indomethacin (0.6 μmol/animal)-pretreated group (n=5); 423.2±38.4 and 474.5±94.4 pg/ml in the indomethacin (1.2 μmol/animal)-pretreated group (n=10), respectively.

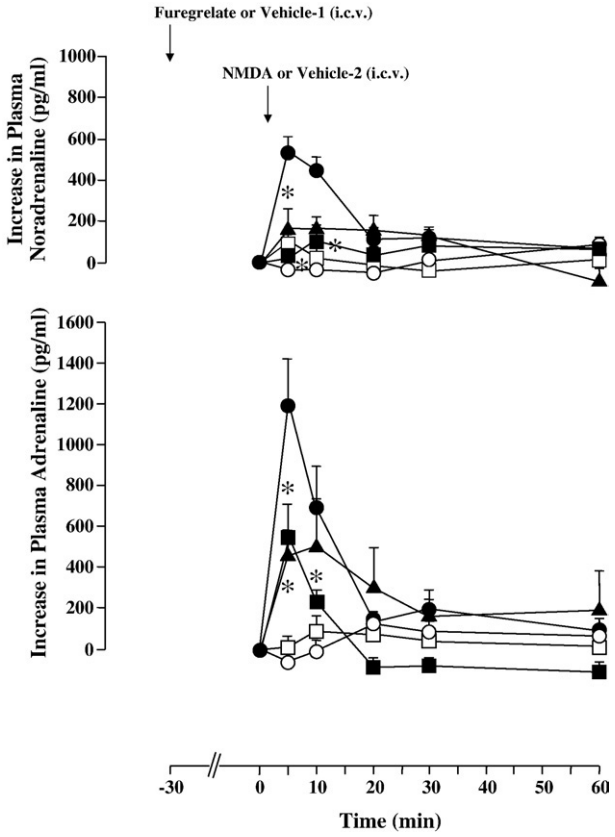

Fig. 4. Effect of furegrelate, a thromboxane A_2 synthase inhibitor, on the NMDA-induced elevation of plasma catecholamines. Furegrelate (0.9 and 1.8 μmol/animal, i.c.v.) or vehicle-1 (5 μl saline/animal, i.c.v.) was administered 30 min before NMDA (5 nmol/animal, i.c.v.) or vehicle-2 (5 μl saline/animal, i.c.v.). ●, vehicle-1 plus NMDA (cited from Fig. 2.) (n=6); ▲, furegrelate (0.9 μmol/animal, i.c.v.) plus NMDA (n=5); ■, furegrelate (1.8 μmol/animal, i.c.v.) plus NMDA (n=6); □, furegrelate plus vehicle-2 (n=4); ○, vehicle-1 plus vehicle-2 (cited from Fig. 2.) (n=4). * Significantly different (P<0.05) from vehicle-1 plus NMDA. Other conditions were the same as those of Figs. 1–3. The actual values for noradrenaline and adrenaline at 0 min were 384.2±37.2 and 285.5±49.9 pg/ml in the vehicle-1-pretreated group (n=10); 524.2±32.9 and 394.8±81.0 pg/ml in the furegrelate (0.9 μmol/animal)-pretreated group (n=5); 339.9±25.6 and 429.9±24 pg/ml in the furegrelate (1.8 μmol/animal)-pretreated group (n=10), respectively.

furegrelate dose-dependently attenuated the elevation of noradrenaline and adrenaline induced by NMDA (5.0 nmol/animal, i.c.v.).

3.5. Effect of bilateral adrenalectomy on the N-methyl-D-aspartate-induced elevation of plasma catecholamines

The basal plasma levels of noradrenaline and adrenaline were reduced slightly by sham operation. The basal plasma level of noradrenaline was reduced slightly, but not significantly, by bilateral adrenalectomy, while the basal plasma level of adrenaline was reduced significantly by the procedure (Fig. 5).

The NMDA (5.0 nmol/animal, i.c.v.)-induced elevation of plasma noradrenaline and adrenaline was abolished by bilateral adrenalectomy (Fig. 5).

4. Discussion

Centrally administered NMDA effectively elevated plasma levels of catecholamines (adrenaline>noradrenaline). These elevations were suppressed by MK-801, a non-competitive NMDA receptor antagonist (Wong et al., 1986). Several studies suggest centrally administered NMDA induces a dose-dependent increase in blood pressure and heart rate and that these effects are antagonized by intracerebroventricular administration of NMDA receptor antagonists, MK801 and 2-amino-5-phosphono valerate (Maione et al., 1992; Goren et al., 2000b; Yamaguchi and Watanabe, 2005). In addition, Jezova et al. (1995) showed that MK-801 inhibited the elevation of noradrenaline and adrenaline induced by immobilization stress. These studies suggest that centrally administered NMDA induces sympatho-adrenomedullary outflow via an activation of brain NMDA receptors in rats.

Previously, this laboratory reported that the brain cyclooxygenase is involved in centrally administered CRF-, arginine–vasopressin-, bombesin-induced elevation of plasma noradrenaline and adrenaline using indomethacin in rats (Okuma et al., 1996; Yokotani et al., 2001; Okada et al., 2002). Indomethacin has been established as a potent inhibitor of the prostaglandin-forming cyclooxygenase (Insel, 1996). In further experiments, this laboratory examined the effect of centrally administered indomethacin on the NMDA-induced elevation of plasma catecholamines. Indomethacin does not penetrate the blood-brain barrier easily after peripheral administration, requiring administration of this reagent directly into the lateral ventricle of the rat brain (Okuma et al., 1996). The elevation of plasma catecholamines induced by NMDA was reduced by central pretreatment with indomethacin, suggesting a role of

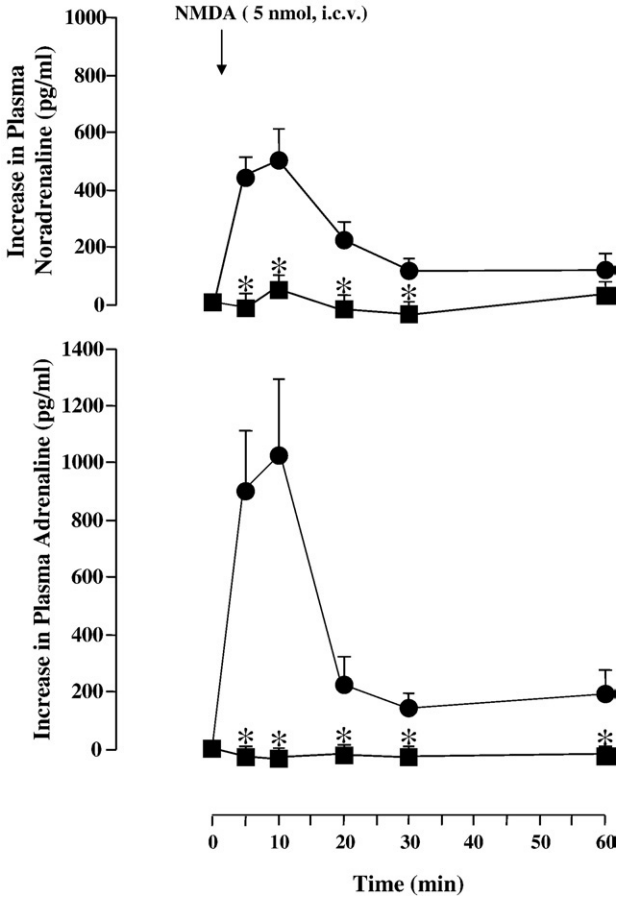

Fig. 5. Effect of acute bilateral adrenalectomy on the NMDA-induced elevation of catecholamines. Hydrocortisone (5 mg/kg) or 200 μl saline was administered intramuscularly in the adrenalectomized group (■) or sham-operated group (●), respectively. Arrow indicates the administration of NMDA (5.0 nmol/animal, i.c.v.). *Significantly different (P<0.05) from the sham-operated group with the Student's t-test. Other conditions were the same as those in Figs. 1–4. The actual values for noradrenaline and adrenaline at 0 min were 302.0±50.7 and 218.3±49.8 pg/ml in the sham-operated group (n=5) and 224.6±41.1 and 26.8±11.9 pg/ml in the bilateral adrenalectomized group (n=5), respectively.

the brain arachidonic acid cascade in the NMDA-induced activation of central sympatho-adrenomedullary outflow in rats.

Previously, this research group reported that furegrelate, a selective thromboxane A_2 synthase inhibitor (Gorman et al., 1983), abolished the elevation of plasma adrenaline induced by centrally administered CRF, arginine–vasopressin, or bombesin (Yokotani et al., 2001; Okada et al., 2002; Yokotani et al., 2005). Furthermore, injection of thromboxane A_2 mimetics into the hypothalamic paraventricular nucleus predominantly elevates plasma adrenaline (Murakami et al., 2002). These results suggest the involvement of brain thromboxane A_2 in the activation of central adrenomedullary outflow.

In the present study, therefore, the effect of furegrelate on the NMDA-induced elevation of plasma catecholamines was examined. The NMDA-induced elevation of plasma noradrenaline and adrenaline was reduced by centrally administered furegrelate. The present results are also consistent with our previous report that the reagent abolished the elevation of both catecholamines induced by NMDA applied into the paraventricular nucleus of the hypothalamus (Okada et al., 2000). Taking these observations into account, it would be reasonable to assume that brain thromboxane A_2 is involved in the NMDA-induced adrenal secretion of noradrenaline and adrenaline in rats.

Anatomical studies have provided histochemical differentiation that the noradrenaline-containing cells and adrenaline-containing cells are innervated by separate groups of preganglionic neurons in the spinal cord (Grynszpan-Winograd, 1974; Edwards et al., 1996). In addition, several lines of evidence have suggested the existence of a functionally distinct preganglionic innervation of adrenaline- and noradrenaline-releasing adrenal chromaffin cells (Vollmer et al., 1992; Morrison and Cao, 2000). More recently, a study demonstrated that adrenal adrenaline- and noradrenaline-containing cells and celiac sympathetic ganglia are differentially controlled by centrally administered CRF and arginine–vasopressin in brain prostanoids dependent manner in rats (Yamaguchi-Shima et al., 2007). In an effort to determine the origin of plasma catecholamines induced by centrally administered NMDA, an acute bilateral adrenalectomy was performed. Bilateral adrenalectomy abolished the centrally administered NMDA-induced elevation of both plasma catecholamines. The results clearly demonstrate that centrally administered NMDA evokes the secretion of noradrenaline and adrenaline from the adrenal gland.

In summary, we have demonstrated that brain thromboxane A_2 is involved in the centrally administered NMDA-induced increase in plasma noradrenaline and adrenaline in rats. Furthermore, the present results suggest that the source of increase in plasma noradrenaline evoked by NMDA is due to secretion from the adrenal gland and not due to release from sympathetic nerve terminals.

Acknowledgment

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