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Vasopressin V_1 receptor-mediated activation of central sympatho-adrenomedullary outflow in rats

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Abstract

The present study was designed to characterize the vasopressin receptor subtype involved in the vasopressin-induced activation of the central sympatho-adrenomedullary outflow using urethane-anesthetized rats. Intracerebroventricularly (i.c.v.) administered vasopressin (0.1, 0.2 and 0.5 nmol/animal) dose-dependently elevated plasma levels of adrenaline and noradrenaline (adrenaline>noradrenaline). The vasopressin (0.2 nmol/animal)-induced elevation of both catecholamines was significantly attenuated by [d(CH_2)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin, a selective vasopressin V_1 receptor antagonist, in a dose-dependent manner (0.1 and 0.2 nmol/animal, i.c.v.). The same doses (0.1 and 0.2 nmol/animal, i.c.v.) of [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6, Arg^{8,9}]-vasopressin, a potent vasopressin V_2 receptor antagonist, had no effect; however, a large dose of this antagonist (1.6 nmol/animal, i.c.v.) effectively reduced the vasopressin-induced elevation of catecholamines. On the other hand, [5-dimethylamino-1-{4-(2-methylbenzoylamino)benzoyl}-2,3,4,5-tetrahydro-1*H*-benzazepine], a selective vasopressin V_2 receptor antagonist (5 and 10 nmol/animal, i.c.v.), had no effect on the vasopressin-induced elevation of catecholamines. The vasopressin-induced elevation of catecholamines was abolished by indomethacin, an inhibitor of cyclooxygenase (1.2 μmol/animal, i.c.v.). These results suggest that the vasopressin activates the central sympatho-adrenomedullary outflow by brain vasopressin V_1 receptor- and cyclooxygenase-dependent mechanisms in rats.

Keywords: Vasopressin; Cyclooxygenase, brain; Vasopressin V_1 receptor, brain; Adrenaline plasma; Noradrenaline, plasma; Sympatho-adrenomedullary outflow

1. Introduction

Vasopressin is one of the first neuropeptides that were isolated, sequenced and synthesized (Du Vigneaud et al., 1954). Vasopressin is commonly recognized as a hypothalamic neurohypophyseal peptide to function as a circulating pressor agent and antidiuretic hormone (Acher, 1993). The peptide has also been recognized as a neurotransmitter or neuromodulator to modulate diverse brain functions such as memory and behavior (De Wied et al., 1991; Drago et al., 1997), fever (Wilkinson and Kasting, 1987) and central cardiovascular regulation. Specific vasopressin binding sites have also been demonstrated in many areas of the rat brain (Ostrowski et al., 1992). Although the peptide has been originally proposed to cause vasoconstriction and renal water absorption through V_1 and V_2 receptor subtypes, respectively (Michell et al., 1979), pharmacological and binding properties of vasopressin in the brain are similar to those of peripheral V_1 receptor (Tribollet et al., 1998).

According to the central regulation of the cardiovascular system, peripherally administered vasopressin has been shown to enhance the baroreflex by stimulating the vagal center as well as inhibiting central vasosympathetic outflow (Courtice et al., 1984; Cowley et al., 1984). On the other hand, the intracerebroventricularly administered peptide paradoxically evokes increases in blood pressure and sympathetic nerve activity (Pittman et al., 1982; Zerbe et al., 1983; Feuerstein et al., 1984). However, the stimulating central mechanisms are largely undefined.

Previously we reported that the brain arachidonic acid cascade can be involved in the central activation of the sympatho-adrenomedullary outflow (Yokotani et al., 1988, 1995a,b, 2000, 2001). The present study, therefore, was designed to characterize the mechanisms involved in the vasopressin-induced activation of the central sympatho-adrenomedullary outflow in regard to the vasopressin recep-

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tor subtype and the brain arachidonic acid cascade 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. After these procedures, the animal was placed in a stereotaxic apparatus, as shown in our previous paper (Murakami et al., 1996).

Three hours after the animal was placed in a stereotaxic apparatus, a stainless-steel cannula (0.35 mm outer diameter) or a double lumens cannula (0.50 mm outer diameter) was inserted into the right lateral ventricle according to the rat brain atlas of Paxinos and Watson (1986). The stereotaxic coordinates of the tip of cannula was as follows (in mm): AP − 0.8, L 1.5, H 4.0 (AP, anterior from the bregma; L, lateral from the midline; H, below the surface of the brain). Vasopressin was dissolved in sterile saline and slowly injected into the right lateral ventricle in a volume of 10 μl using a 50-μl Hamilton syringe. Antagonists of vasopressin V_1 and V_2 receptors and water-soluble indomethacin-Na dissolved in sterile saline were also administered into the right lateral ventricle in a volume of 10 μl before the application of vasopressin. Correct placement of the cannula was confirmed at the end of each experiment by verifying that a blue dye, injected through the cannula, had spread throughout the entire ventricular system. In some experiments, vasopressin was slowly injected into the femoral vein.

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

2.2. Measurement of plasma catecholamines

Blood samples (250 μl) were collected through an arterial catheter. Catecholamines in the plasma were extracted by the method of Anton and Sayre (1962) with a slight modification and were assayed electrochemically by high performance liquid chromatography (Okada et al., 2000). 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 ng of 3,4-dihydroxybenzylamine as an internal standard and 1 ml of 1.5 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 high performance liquid chromatography. 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 of 0.22 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 were expressed as the mean ± S.E.M. of the net changes above the respective basal values, because of individual variations. The data were analyzed by repeated-measure analysis of variance (ANOVA), followed by post hoc analysis with the Bonferroni method for comparing a

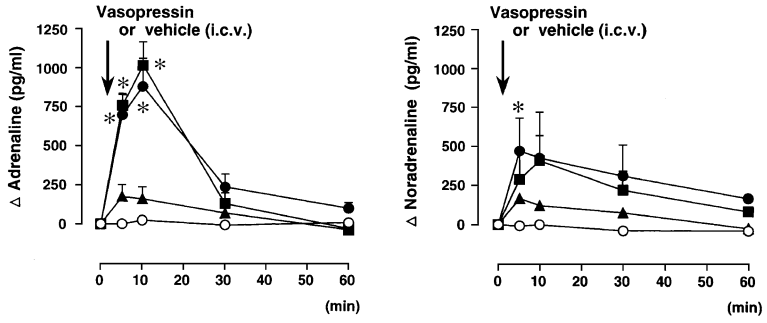

Fig. 1. Effect of vasopressin on plasma levels of adrenaline and noradrenaline. ΔAdrenaline and Δnoradrenaline: increase of adrenaline and noradrenaline above the basal. Arrow indicates intracerebroventricular (i.c.v.) administration of vehicle (saline 10 μl/animal) or vasopressin (0.1, 0.2 and 0.5 nmol/animal). ○, vehicle ($n=5$); ▲, vasopressin (0.1 nmol/animal) ($n=3$); ●, vasopressin (0.2 nmol/animal) ($n=5$); ■, vasopressin (0.5 nmol/animal) ($n=7$). Each point represents the mean ± S.E.M. *Significantly different ($P<0.05$) from vehicle-treated control. The actual values for adrenaline and noradrenaline at 0 min were 344 ± 37 and 388 ± 38 pg/ml ($n=20$), respectively.

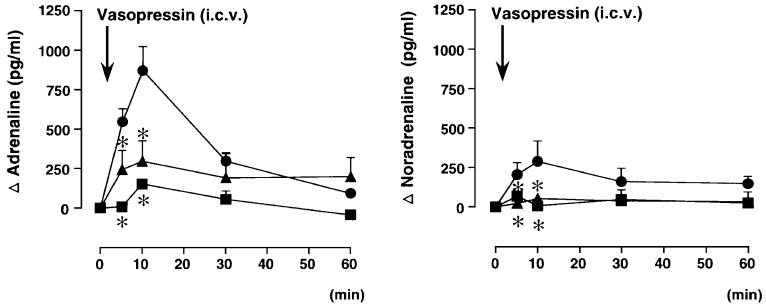

Fig. 2. Effect of [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin, a highly selective vasopressin V$_1$ receptor antagonist, on the vasopressin-induced elevation of plasma catecholamines. [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (0.1 and 0.2 nmol/animal) or vehicle (saline 10 μl/animal) was i.c.v. administered 15 min before administration of vasopressin (0.2 nmol/animal, i.c.v.). ●, vehicle plus vasopressin; ▲, [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (0.1 nmol/animal) plus vasopressin; ■, [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (0.2 nmol/animal) plus vasopressin. *Significantly different ($P<0.05$) from the group treated with vehicle plus vasopressin. Other conditions were the same as those in Fig. 1. The actual values for adrenaline and noradrenaline at 0 min were 372 ± 71 and 452 ± 69 pg/ml in the group treated with vehicle plus vasopressin ($n=4$); 296 ± 32 and 394 ± 61 pg/ml in the group treated with [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (0.1 nmol/animal) plus vasopressin ($n=5$); 267 ± 44 and 442 ± 60 pg/ml in the group treated with [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (0.2 nmol/animal) plus vasopressin ($n=5$), respectively.

control to all other means (Figs. 1–4). When only two means were compared, an unpaired Student's *t*-test was used (Fig. 5). *P* values less than 0.05 were taken to indicate statistical significance.

2.4. Compounds

The following drugs were used: water-soluble indomethacin sodium trihydrate (a kind gift from Merck, Rahway, NJ, USA); [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin, [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (Sigma-RBI, St. Louis, MO, USA); arginine-vasopressin (vasopressin) (Peptide Institute, Osaka, Japan); 5-dimethylamino-1-{4-(2-methylbenzoylamino)benzoyl}-2,3,4,5-tetrahydro-1*H*-benzazepine (OPC-31260) (a kind gift from Otsuka Pharmaceutical Company, Tokushima, Japan). All other reagents were of the highest grade available (Nacalai Tesque).

3. Results

3.1. Effect of vasopressin on plasma catecholamines

Intracerebroventricularly (i.c.v.) administered vehicle (10 μl saline/animal) and blood sampling for 5 times over a 60-min period did not affect the basal plasma levels of either adrenaline or noradrenaline (Fig. 1).

Administration of vasopressin (0.1, 0.2 and 0.5 nmol/animal, i.c.v.) dose-dependently elevated plasma levels of adrenaline (Fig. 1, left panel), but the maximal effect of the peptide on plasma noradrenaline levels was obtained at 0.2

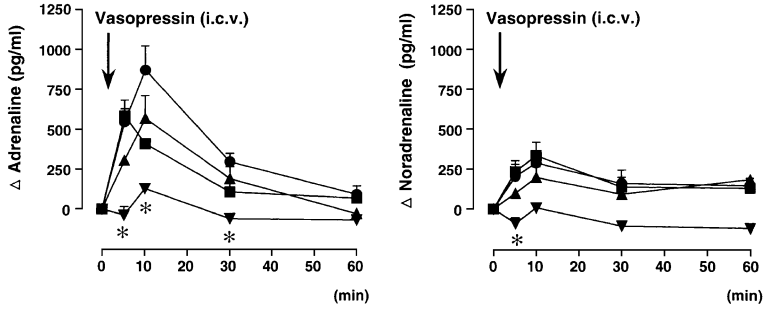

Fig. 3. Effect of [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin, a relatively selective vasopressin V$_2$ receptor antagonist, on the vasopressin-induced elevation of plasma catecholamines. [1-Adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.1, 0.2 and 1.6 nmol/ animal) or vehicle (saline 10 μl/animal) was i.c.v. administered 15 min before administration of vasopressin (0.2 nmol/animal, i.c.v.). ●, vehicle plus vasopressin (cited from Fig. 2); ▲, [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.1 nmol/animal) plus vasopressin; ■, [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.2 nmol/animal) plus vasopressin; ▼, [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (1.6 nmol/animal) plus vasopressin. *Significantly different ($P<0.05$) from the group treated with vehicle plus vasopressin. Other conditions were the same as those in Figs. 1 and 2. The actual values for adrenaline and noradrenaline at 0 min were 298 ± 33 and 343 ± 54 pg/ml in the group pretreated with [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.1 nmol/animal) plus vasopressin ($n=4$); 234 ± 31 and 413 ± 44 pg/ml in the group pretreated with [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.2 nmol/animal) plus vasopressin ($n=4$); 285 ± 35 and 409 ± 44 pg/ml in the group pretreated with [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (1.6 nmol/animal) plus vasopressin ($n=5$), respectively.

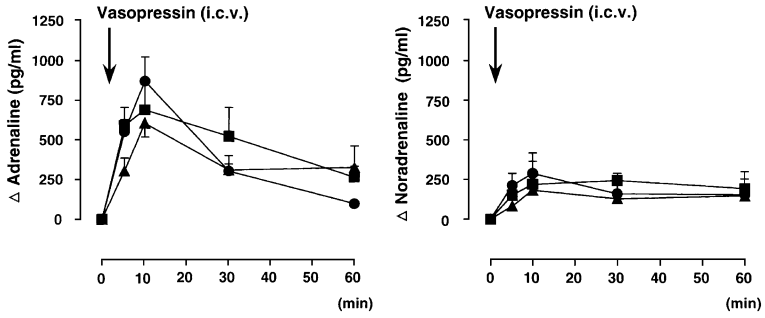

Fig. 4. Effect of OPC-31260, a highly selective vasopressin V_2 receptor antagonist, on the vasopressin-induced elevation of plasma catecholamines. OPC-31260 (5 and 10 nmol/ animal) or vehicle (saline 10 μl/animal) was i.c.v. administered 15 min before administration of vasopressin (0.2 nmol/animal, i.c.v.). ●, vehicle plus vasopressin (cited from Fig. 2); ▲, OPC-31260 (5 nmol/animal) plus vasopressin; ■, OPC-31260 (10 nmol/animal) plus vasopressin. Other conditions were the same as those in Figs. 1–3. The actual values for adrenaline and noradrenaline at 0 min were 248 ± 86 and 393 ± 22 pg/ml in the group treated with OPC-31260 (5 nmol/animal) plus vasopressin ($n = 7$); 255 ± 107 and 362 ± 34 pg/ml in the group treated with OPC-31260 (10 nmol/animal) plus vasopressin ($n = 5$), respectively.

nmol/animal (i.c.v.) (Fig. 1, right panel). These responses reached a maximum 5–10 min after the administration of vasopressin and then declined toward their basal levels. Intravenous administration of vasopressin (0.2 nmol/animal), however, had no effect on plasma levels of catecholamines.

3.2. Effects of [d(CH2)5[1],Tyr(Me)[2],Arg[8]]-vasopressin, [1-adamantaneacetyl[1],D-Tyr(Et)[2],Val[4],Abu[6],Arg[8,9]]-vasopressin, and OPC-31260 on the vasopressin-induced elevation of plasma catecholamines

The pretreatments with [d(CH_2)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (0.1 and 0.2 nmol/animal, i.c.v.), [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.1, 0.2 and 1.6 nmol/animal, i.c.v.), OPC-31260 (5 and 10 nmol/animal, i.c.v.) or vehicle (10 μl saline/animal, i.c.v.) had no effect on the basal plasma levels of catecholamine.

[d(CH_2)$^1_5$,Tyr(Me)^2,Arg^8]-Vasopressin, a highly selective vasopressin V_1 receptor antagonist, reduced the vasopressin (0.2 nmol/animal, i.c.v.)-induced elevation of plasma levels of adrenaline and noradrenaline in a dose-dependent manner (0.1 and 0.2 nmol/animal, i.c.v.) (Fig. 2, left and right panels).

The same doses of [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (0.1 and 0.2 nmol/animal, i.c.v.), a potent vasopressin V_2 receptor antagonist, had no effect on the vasopressin (0.2 nmol/animal, i.c.v.)-induced elevation of plasma adrenaline and noradrenaline levels. At a higher dose (1.6 nmol/animal, i.c.v.), however, this analog significantly attenuated the vasopressin-induced elevation of plasma catecholamine levels (Fig. 3, left and right panels).

On the other hand, OPC-31260 (5 and 10 nmol/animal, i.c.v.), a highly selective vasopressin V_2 receptor antagonist, had no effect on the vasopressin (0.2 nmol/animal, i.c.v.)-induced elevation of plasma catecholamine levels (Fig. 4, left and right panels).

3.3. Effect of indomethacin on the vasopressin-induced elevation of plasma catecholamines

Administration of indomethacin [1.2 μmol (500 μg)/animal, i.c.v.], an inhibitor of cyclooxygenase, had no effect

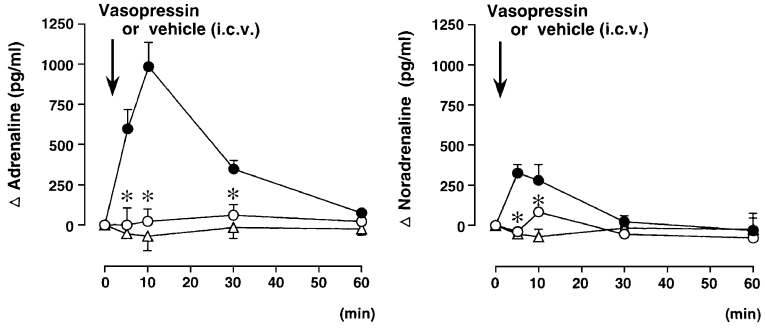

Fig. 5. Effect of indomethacin on the vasopressin-induced elevation of plasma catecholamines. Indomethacin [1.2 μmol (500 μg)/animal] or vehicle (saline 10 μl/animal) was i.c.v. administered 60 min before administration of vasopressin (0.2 nmol/animal, i.c.v.) or vehicle (saline 10 μl/animal, i.c.v.). ●, vehicle plus vasopressin ($n = 5$); ○, indomethacin plus vasopressin ($n = 6$); △, indomethacin plus vehicle ($n = 4$). *Significantly different ($P < 0.05$) from the group treated with vehicle plus vasopressin. Other conditions were the same as those in Figs. 1–4. The actual values for adrenaline and noradrenaline at 0 min were 433 ± 68 and 539 ± 43 pg/ml in the group pretreated with indomethacin ($n = 10$) and 418 ± 63 and 544 ± 85 pg/ml in the group pretreated with vehicle ($n = 5$), respectively.

on the basal plasma levels of both adrenaline and noradrenaline. Indomethacin abolished the elevation of both catecholamines induced by vasopressin (0.2 nmol/animal, i.c.v.) (Fig. 5, left and right panels).

4. Discussion

Vasopressin receptors have been divided into two broad subtypes, vasopressin V_1 and V_2 receptors (Lolait et al., 1995). Stimulation of the vasopressin V_1 receptors results in the hydrolysis of phosphatidylinositol and an increase in cytosolic calcium: the vasopressin V_{1a} receptors mediate the vasoconstrictor and hepatic glycogenolytic actions of vasopressin (Michell et al., 1979); the vasopressin V_{1b} receptor is a novel type in the adenohypophysis (Antoni, 1984; Baertschi and Friedli, 1985). The vasopressin V_2 receptors are coupled to adenylate cyclase and are found in the kidney where they mediate the antidiuretic effect of vasopressin (Ausiello et al., 1980). Many of the central effects of vasopressin have been attributed to the vasopressin V_{1a} receptors (Dorsa et al., 1983; De Wied et al., 1993); however, the vasopressin V_{1b} receptors have recently been shown to be also localized in the brain (Vaccari et al., 1998; Hernando et al., 2001).

Central administration of vasopressin to experimental animals has been shown to raise blood pressure (Berecek, 1986) and elevate plasma catecholamines (King et al., 1985; Martin et al., 1988). The vasopressin-induced central cardiovascular effects such as increasing blood pressure and heart rate have been shown to be mediated by vasopressin V_1 receptor in dogs (Noszczyk et al., 1993). In the present experiment, centrally administered vasopressin also effectively elevated plasma catecholamine levels (adrenaline>noradrenaline) in rats. Therefore, we attempted to characterize the brain vasopressin receptor subtype involved in the centrally administered vasopressin-induced elevation of plasma catecholamines using selective antagonists of vasopressin V_1 and V_2 receptor subtypes.

[^{3}H]-[d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin has dissociation constants of 0.3 and 218 nM for binding to vasopressin V_1 receptors (rat liver) and V_2 receptors (rat kidney), while [^{3}H]-vasopressin has dissociation constants of 3 and 0.4 nM for binding to vasopressin V_1 receptors and V_2 receptors (Tribollet et al., 1998). This analog has also antivasopressor effect with pA_2 value of 8.62 against vasopressin-induced vasopressor effect and antidiuretic activity with 0.3 U/mg (antidiuretic activity of vasopressin is 1745 U/mg) in rats (Kruszynski et al., 1980). These results suggest that [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin is a highly selective antagonist of vasopressin V_1 receptors (Drago et al., 1997). [1-Adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin has antiantidiuretic effect with 0.53 nmol/kg against the intravenously administered vasopressin-induced antidiuretic effect in water-loaded rats and antivasopressor effect with 1.2 nmol/kg against the intravenously administered vasopressin-induced vasopressor effect in phenoxybenzamine-treated rats, suggesting a potent vasopressin V_2 receptor antagonist (Manning et al., 1987). OPC-31260 has IC_{50} values of 1.4 and 0.012 μM for [^{3}H]-vasopressin binding to vasopressin V_1 receptors (rat liver) and V_2 receptors (rat kidney), respectively, suggesting a highly selective vasopressin V_2 receptor antagonist (Yamamura et al., 1992; Kondo et al., 1999).

The i.c.v. administered vasopressin-induced elevation of plasma catecholamines (adrenaline>noradrenaline) was abolished by [d(CH$_2$)$^1_5$,Tyr(Me)^2,Arg^8]-vasopressin (a highly selective vasopressin V_1 receptor antagonist), while a large dose of [1-adamantaneacetyl^1,D-Tyr(Et)^2,Val^4,Abu^6,Arg^{8,9}]-vasopressin (a potent vasopressin V_2 receptor antagonist) had only a weak blocking effect on the vasopressin-induced elevation of plasma catecholamines. On the other hand, these response was not influenced by a large doses of OPC-31260 (a highly selective vasopressin V_2 receptor antagonist). These results suggest the involvement of brain vasopressin V_1 receptors in the vasopressin-induced activation of the central sympatho-adrenomedullary outflow in rats.

The brain phospholipase A_2 hydrolyzes the *sn*-2 ester bond of membrane phospholipids with the release of arachidonic acid (Flower and Blackwell, 1976; Irvine, 1982; Axelrod, 1990). Phospholipase C also cleaves the phosphodiester bond, resulting in the formation of a 1,2-diglyceride; arachidonic acid is then released from the diglyceride by the sequential actions of diglyceride lipase (Bell et al., 1979). A portion of the released arachidonic acid is metabolized rapidly to oxygenated products by several distinct enzyme systems including cyclooxygenase, and the products of arachidonic acid cascade may act as intracellular or intramembrane signaling molecules.

Recently, we reported that the elevation of plasma adrenaline and noradrenaline induced by centrally administered corticotropin-releasing factor (Yokotani et al., 2001) and arachidonic acid (Yokotani et al., 2000) was abolished by the central pretreatment with indomethacin, an inhibitor of the prostaglandin-forming cyclooxygenase (Insel, 1996). The elevation of plasma noradrenaline induced by centrally administered interleukin-1β was also abolished by the central pretreatment with indomethacin (Murakami et al., 1996). Centrally administered prostaglandin E_2 elevates plasma noradrenaline by activation of the brain prostanoid EP_3 receptors (Yokotani et al., 1988, 1995a). Furthermore, the brain thromboxane A_2 is involved in the centrally mediated elevation of plasma adrenaline (Murakami et al., 1998, 2002; Okada et al., 2000; Yokotani et al., 2001). These results suggest the involvement of brain arachidonic acid cascade in the central activation of the sympatho-adrenomedullary outflow in rats.

In the present experiment, therefore, we examined the effect of centrally administered indomethacin on the vasopressin-induced elevation of plasma catecholamines. The elevation of plasma catecholamines induced by vasopressin

was also abolished by central pretreatment with indomethacin. Vasopressin has been shown to release arachidonic acid from Chinese hamster ovary cells expressed with vasopressin V_{1a} receptor (Briley et al., 1994). These results also suggest the involvement of brain arachidonic acid cascade in the vasopressin-induced activation of the central sympatho-adrenomedullary outflow in rats.

The hypothalamus, especially the paraventricular nucleus, has been considered to be the control center of the sympatho-adrenomedullary outflow (Swanson and Sawchenko, 1980). A retrograde tracer study suggests a possible connection between the sympatho-adrenomedullary system and the paraventricular nucleus through the splanchnic nerve and spinal cord (Jansen et al., 1995). Several studies have now suggested that the parvocellular neurons located in the paraventricular nucleus are a source of the vasopressin fibers that are seen at brainstem and spinal levels (Sawchenko and Swanson, 1982). Vasopressin also activates preganglionic sympathetic neurons in the spinal lateral column by activation of the vasopressin V_1 receptor (Gilbey et al., 1982; Kolaj and Renaud, 1998). However, the acting site of centrally administered vasopressin to facilitate the central sympatho-adrenomedullary outflow remains to be elucidated.

In summary, we demonstrated here that the activation of the central sympatho-adrenomedullary outflow induced by centrally administered vasopressin is mediated by the brain vasopressin V_1 receptor- and cyclooxygenase-dependent mechanisms in rats.

Acknowledgements

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