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Effects of centrally administered prostaglandin E_3 and thromboxane A_3 on plasma noradrenaline and adrenaline in rats: Comparison with prostaglandin E_2 and thromboxane A_2

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ABSTRACT

Previously, we reported the involvement of brain ω-6 prostanoids, especially prostaglandin E_2 and thromboxane A_2, in the activation of central sympatho-adrenomedullary outflow in rats. ω-3 Prostanoids, including prostaglandin E_3 and thromboxane A_3, are believed to be less bioactive than ω-6 prostanoids, although studies on the functions of ω-3 prostanoids in the central nervous system have not been reported. In the present study, therefore, we compared the effects of centrally administered ω-3 prostanoids, prostaglandin E_3 and thromboxane A_3, with those of ω-6 prostanoids, prostaglandin E_2 and thromboxane A_2, on the plasma catecholamines in anesthetized rats. Intracerebroventricularly (i.c.v.) administered prostaglandin E_2 (0.15, 0.3 and 1.5 nmol/animal) and prostaglandin E_3 (0.3 and 3 nmol/animal) predominantly elevated plasma noradrenaline but not adrenaline, but the latter was less efficient than the former. On the other hand, U-46619 (an analog of thromboxane A_2) (30, 100 and 300 nmol/animal, i.c.v.) and Δ^{17}-U-46619 (an analog of thromboxane A_3) (100 and 300 nmol/animal, i.c.v.) both elevated plasma catecholamines (adrenaline ≫ noradrenaline) to the same degree. These results suggest that centrally administered prostaglandin E_3 is less effective than prostaglandin E_2 to elevate plasma noradrenaline, and that thromboxane A_3 is almost as equipotent as thromboxane A_2 to elevate plasma catecholamines in rats.

1. Introduction

Prostanoids (prostaglandins and thromboxanes) are bioactive lipids derived from membrane polyunsaturated fatty acid (PUFA). Cyclooxygenase is the key enzyme in prostanoids synthesis from arachidonic acid, a common ω-6 PUFA. On the other hand, ω-3 PUFA (eicosapentaenoic acid and docosahexaenoic acid) found primarily in fish oils can function as substrates for cyclooxygenase (Jump, 2002). When the availability of ω-3 PUFA is increased by fish oil ingestion, the formation of ω-3 PUFA-derived prostanoids (ω-3 prostanoids) such as prostaglandin E_3 is increased but the corresponding ω-6 PUFA-derived prostanoids (ω-6 prostanoids) such as prostaglandin E_2 is reduced (Fischer and Weber, 1984; Fischer et al., 1988; Knapp, 1990). Although similar in structure and stability (Hansen, 1983), ω-3 prostanoids have been considered to be less bioactive than ω-6 prostanoids. For instance, prostaglandin E_3, unlike prostaglandin E_2, is not mitogenic to NIH 3T3 fibroblasts and substantially less efficient than prostaglandin E_2 in interleukin-6 synthesis in RAW 264.7 macrophages (Bagga et al., 2003). Prostaglandin F_{3alpha} is less protective than prostaglandin F_{2alpha} against gastric mucosal injury in rats (Faust et al., 1989) and prostaglandin I_3 is less potent than prostaglandin I_2 in inhibition of platelet aggregation in rabbits (Kobzar et al., 2001). However, studies directly comparing the functions of ω-6 versus ω-3 prostanoids in the central nervous system have not been reported, although ω-3 PUFA deficiency has been shown to be associated with memory loss and diminished cognitive function (Salem et al., 2001).

It has been demonstrated that ω-6 prostanoids act as a neurotransmitter and/or neuromodulator in the brain's actions on the cardiovascular function (Wood et al., 1993; Zhang et al., 2003) and regulation of hormone secretion (Bernardini et al., 1989; Reimsnider and Wood, 2006). We previously reported that centrally administered arachidonic acid, a source of ω-6 prostanoids, elevated plasma levels of noradrenaline and adrenaline by a cyclooxygenase-dependent mechanism in rats (Yokotani et al., 2000). Furthermore, centrally administered ω-6 prostanoid prostaglandin E_2 (but not prostaglandin D_2, I_2 and F_{2alpha}) elevated plasma noradrenaline in rats (Yokotani et al., 1995, 2005; Murakami et al., 2002) and thromboxane A_2 mimetic elevated plasma catecholamines (adrenaline ≫ noradrenaline) in rats (Murakami et al., 2002). These lines of evidence suggest that centrally administered ω-6 prostanoids, especially prostaglandin E_2 and thromboxane A_2, activate the central sympatho-adrenomedullary outflow in rats. In the present study, therefore, we compared the effects of centrally administered ω-3 prostanoids (prostaglandin E_3 and thromboxane A_3) and ω-6 prostanoids (prostaglandin E_2 and

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thromboxane A_2) on the plasma catecholamines using urethane-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 papers (Yokotani et al., 1995; Shimizu et al., 2004). The skull was drilled for intracerebroventricular administration of test substances using 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 (Paxinos and Watson, 1986). Three hours was allowed to elapse before the application of reagents.

Prostaglandin E_2 and prostaglandin E_3 were dissolved in 99% ethanol and stored at −20 °C. These stock solutions were diluted with saline whenever we used them and the final concentration of ethanol was adjusted to 0.5%. These diluted solutions were slowly injected into the right lateral ventricle in a volume of 10 µl/animal using a 25-µl Hamilton syringe. U-46619 and Δ^{17}-U-46619 dissolved in 100% *N*,*N*-dimethylformamide (DMF) were intracerebroventricularly (i.c.v.) administered in a volume of 2.5 µl/animal using a 10-µl Hamilton syringe. Each animal received only one dose of these reagents or vehicles.

All experiments were conducted in compliance with the guiding principles 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) (Shimizu et al., 2004). Briefly, after centrifugation (1,500 *g* for 10 min, at 4 °C), the plasma (100 µl) was transferred to a centrifuge tube containing 30 mg of activated alumina, 2 ml of twice 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 twice 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 an 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 disodium EDTA, 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 was accurately determined.

2.3. Treatment of data and statistics

All values are expressed as the means ± S.E.M. of the net changes above the respective basal values. The data were analyzed by repeated-measure analysis of variance (ANOVA), followed by *post-hoc* analysis with the Bonferroni method. *P* values less than 0.05 were taken to indicate statistical significance.

2.4. Compounds

The following drugs were used: prostaglandin E_2 (Sigma Aldrich Fine Chemicals, St. Louis, MO, U.S.A.); prostaglandin E_3, U-46619 (9,11-dideoxy-9α, 11α-methanoepoxy-prosta-5*Z*,13*E*-dien-1-oic acid) and Δ^{17}-U-46619 (9,11-dideoxy-9α, 11α-methanoepoxy-prosta-5*Z*,13*E*,17*Z*-trien-1-oic acid) (Cayman Chemical, Ann Arbor, MI, U.S.A.). All other reagents were of the highest grade available (Nacalai Tesque, Kyoto, Japan).

3. Results

3.1. Effects of centrally administered prostaglandin E_2 and prostaglandin E_3 on the plasma levels of catecholamines

Blood sampling for 5 times during 60 min had no effect on the basal plasma levels of either noradrenaline or adrenaline (Fig. 1A and B). Treatment with vehicle (10 µl of 0.5% ethanol in saline, i.c.v.) also had no effect on the basal plasma levels of catecholamines (Fig. 1A and B). In preliminary studies, we monitored systemic blood pressure in our animal model since a large increase in peripheral noradrenaline is well known to alter systemic blood pressure. The blood pressure was largely unaffected by the blood sampling (data not shown). Ten minutes after administration of prostaglandin E_2 (0.3 nmol/animal, i.c.v.), mean arterial blood pressure was increased from 76 ± 6 to 106 ± 10 mm Hg ($n=4$).

Prostaglandin E_2 [0.15, 0.3 and 1.5 nmol (53, 106 and 529 ng)/animal, i.c.v.] dose-dependently elevated the plasma level of noradrenaline (Fig. 1A). The responses in each dose of prostaglandin E_2 reached a maximum 10 min after administration of the reagent and then declined towards their basal levels (Fig. 1A). On the other hand, prostaglandin E_2 (0.15, 0.3 and 1.5 nmol/animal, i.c.v.) slightly, but not significantly, elevated the plasma level of adrenaline (Fig. 1A).

I.c.v. administered prostaglandin E_3 [0.3 nmol (105 ng)/animal] had little effect on the plasma level of noradrenaline, but a large dose of the reagent [3 nmol (1.1 µg)/animal, i.c.v.] significantly elevated the plasma level of noradrenaline (Fig. 1B). The response also reached a maximum 10 min after administration of the reagent and then declined toward the basal levels (Fig. 1B). On the other hand, prostaglandin E_3 (0.3 and 3 nmol/animal, i.c.v.) slightly elevated the plasma level of adrenaline, but a maximal response was obtained by a dose of 0.3 nmol/animal (Fig. 1B).

3.2. Effects of centrally administered U-46619 (an analog of thromboxane A_2) and Δ^{17}-U-46619 (an analog of thromboxane A_3) on the plasma levels of catecholamines

Treatment with vehicle (2.5 µl of DMF, i.c.v.) also had no effect on the basal plasma levels of catecholamines (Fig. 2A and B). U-46619 [30, 100 and 300 nmol (11, 35 and 105 µg)/animal, i.c.v.] significantly elevated the plasma levels of noradrenaline and adrenaline (adrenaline ≫ noradrenaline); maximal noradrenaline responses were obtained by a dose of 100 nmol/animal (i.c.v.) and maximal adrenaline responses were obtained by a dose of 300 nmol/animal (i.c.v.), respectively (Fig. 2A). The noradrenaline and adrenaline responses reached a maximum at 5 and 10 min after administration of U-46619, respectively, and then declined towards basal levels (Fig. 2A).

I.c.v. administered Δ^{17}-U-46619 [100 nmol (35 µg)/animal] had little effect on the plasma levels of noradrenaline and adrenaline, but

the reagent significantly elevated the plasma levels of both catecholamines (adrenaline ≫ noradrenaline) with a large dose [300 nmol (105 μg)/animal, i.c.v.] (Fig. 2B). These responses reached a maximum 10 min after administration of the reagent and then declined towards basal levels (Fig. 2B).

4. Discussion

So far four types of prostanoid receptors (EP_1, EP_2, EP_3 and EP_4) have been identified to couple with prostaglandin E_2 (Breyer et al., 2001). Prostanoid EP_3 receptor mRNA is highly expressed in brain regions such as the hippocampus, preoptic area and hypothalamus (Sugimoto et al., 1994; Vasilache et al., 2007). Previously, we reported the involvement of brain prostanoid EP_3 receptors in the centrally administered prostaglandin E_2-induced elevation of plasma noradrenaline in rats (Yokotani et al., 1995). Recently, prostanoid EP_3 receptors have been shown to bind with less affinity and lower efficiency to prostaglandin E_3 than prostaglandin E_2 (Wada et al., 2007). In the present experiment, centrally administered prostaglandin E_2 (0.15, 0.3 and 1.5 nmol/animal) effectively elevated plasma noradrenaline in a dose-dependent manner, while prostaglandin E_3 effectively elevated plasma noradrenaline only at a larger dose (3 nmol/animal). Both prostaglandin E_2 and E_3 had little effect on plasma adrenaline. These results suggest that centrally administered prostaglandin E_3 is less effective than prostaglandin E_2 to elevate plasma noradrenaline in rats.

Messenger RNA of thromboxane receptors (prostanoid TP receptors) has been reported to be present in the brain (Namba et al., 1992; Gao et al., 1997). Previously, we reported that centrally administered thromboxane A_2 mimetic induced the elevation of plasma catecholamines (adrenaline ≫ noradrenaline) by activation of the brain prostanoid TP receptors in rats (Murakami et al., 2002). In the present experiment, we used two analogs of thromboxane A_2 and A_3, U-46619 and Δ^{17}-U-46619 (Abramovitz et al., 2000), because of the instability of thromboxanes ($t_{1/2}$ for thromboxane A_2, ~30 s). Centrally administered U-46619 (100 and 300 nmol/animal) effectively elevated plasma levels of both catecholamines (adrenaline ≫ noradrenaline) in rats. On the other hand, centrally administered Δ^{17}-U-46619 significantly elevated plasma levels of both catecholamines (adrenaline ≫ noradrenaline) only at a larger dose (300 nmol/animal), at this dose Δ^{17}-U-46619-induced responses were almost the same as those induced by U-46619. Recently, it has been shown that both U-46619 and Δ^{17}-U-46619 activate human platelet aggregation via TP receptors and the EC_{50} values for them are similar (650 and 850 nM, respectively) (Wada et al., 2007). These lines of evidence suggest that centrally administered thromboxane A_3 is almost equipotent for thromboxane A_2 to elevate plasma catecholamines in rats.

Dietary supplements of fish oils rich in ω-3 PUFA have been reported to increase the levels of ω-3 PUFA (docosahexaenoic acid) in the hippocampus and forebrain of aged rats (Puskás et al., 2003; Dyall et al., 2007). Interestingly, these supplements have been shown to drastically reduce the levels of arachidonic acid in the hippocampus (Puskás et al., 2003). Recently, we reported the possibility that brain phosphatidylinositol-derived arachidonic acid is involved in the centrally administered histamine-induced elevation of plasma catecholamines (Shimizu et al., 2007). Dietary ω-3 PUFA has been shown

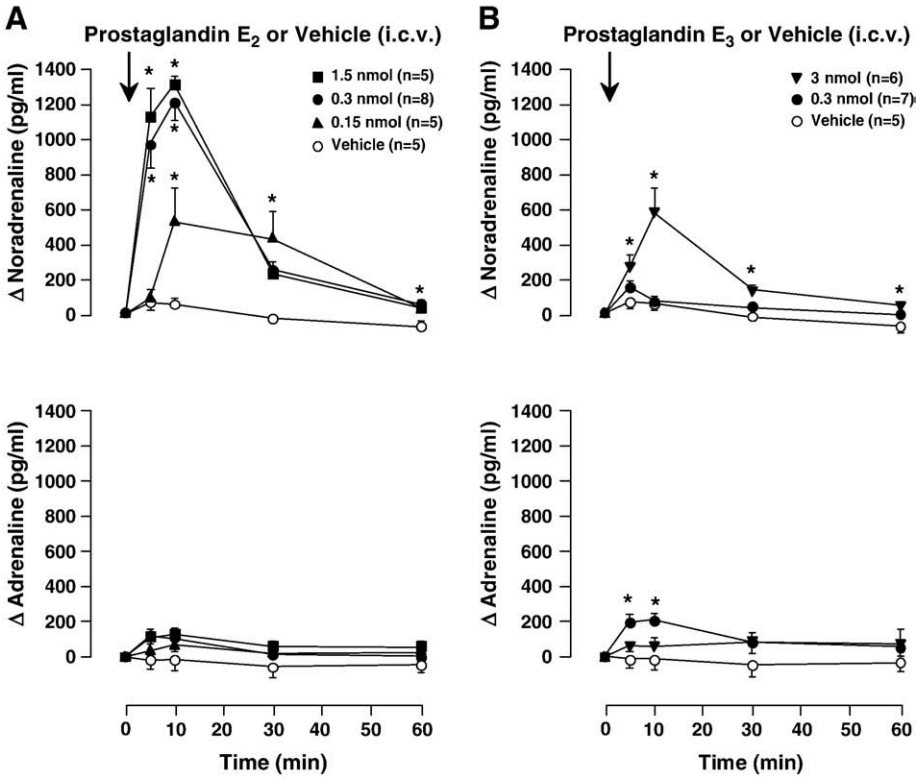

Fig. 1. Effects of centrally administered prostaglandin E_2 and prostaglandin E_3 on the plasma levels of catecholamines. ΔNoradrenaline and ΔAdrenaline: increments of noradrenaline and adrenaline above the basal level. Each point represents the mean ± S.E.M. (A) Arrow indicates the administration of vehicle (0.5% ethanol in saline 10 μl/animal, i.c.v.) or prostaglandin E_2 (0.15, 0.3 and 1.5 nmol/animal, i.c.v.). *Significantly different from the vehicle-treated group with the Bonferroni method [noradrenaline; at 5 min, $F(3,19) = 13.12$, $P<0.017$; at 10 min, $F(3,19) = 26.39$, $P<0.017$; at 30 min, $F(3,16) = 5.09$, $P<0.017$; at 60 min, $F(3,19) = 3.48$, $P<0.017$]. (B) Arrow indicates the administration of vehicle or prostaglandin E_3 (0.3 and 3 nmol/animal, i.c.v.). The vehicle-treated group is the same as that in (A). *Significantly different from the vehicle-treated group with the Bonferroni method [noradrenaline; at 5 min, $F(2,14) = 3.38$, $P<0.025$; at 10 min, $F(2,15) = 6.43$, $P<0.025$; at 30 min, $F(2,15) = 10.77$, $P<0.025$; at 60 min, $F(2,14) = 8.02$, $P<0.025$: adrenaline; at 5 min, $F(2,15) = 5.17$, $P<0.025$; at 10 min, $F(2,15) = 5.27$, $P<0.025$]. The actual values for noradrenaline and adrenaline at 0 min were 261 ± 18 and 288 ± 27 pg/ml ($n = 36$), respectively.

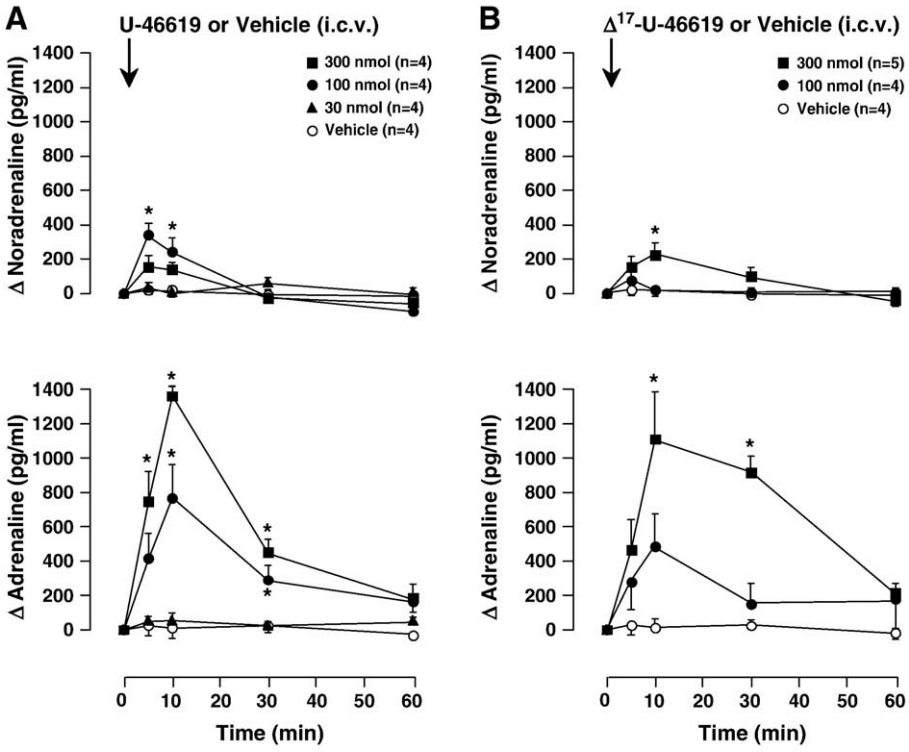

Fig. 2. Effects of centrally administered U-46619 (an analog of thromboxane A_2) and Δ^{17}-U-46619 (an analog of thromboxane A_3) on the plasma levels of catecholamines. Each point represents the mean ± S.E.M. Other conditions are the same as those of Fig. 1. (A) Arrow indicates the administration of vehicle (100% DMF 2.5 μl/animal, i.c.v.) or U-46619 (30, 100 and 300 nmol/animal, i.c.v.). *Significantly different from the vehicle-treated group with the Bonferroni method [noradrenaline; at 5 min, $F(3,12)=7.20$, $P<0.017$; at 10 min, $F(3,12)=5.04$, $P<0.017$: adrenaline; at 5 min, $F(3,12)=8.67$, $P<0.017$; at 10 min, $F(3,12)=9.88$, $P<0.017$; at 30 min, $F(3,12)=10.41$, $P<0.017$]. (B) Arrow indicates the administration of vehicle or Δ^{17}-U-46619 (100 and 300 nmol/animal, i.c.v.). The vehicle-treated group is the same as that in (A). *Significantly different from the vehicle-treated group with the Bonferroni method [noradrenaline; at 10 min, $F(2,10)=7.31$, $P<0.025$: adrenaline; at 10 min, $F(2,10)=6.43$, $P<0.025$; at 30 min, $F(2,10)=14.17$, $P<0.025$]. The actual values for noradrenaline and adrenaline at 0 min were 263 ± 21 and 231 ± 29 pg/ml ($n=25$), respectively.

to increase the incorporation of ω-3 PUFA (docosahexaenoic acid) in the brain structural phosphatidylinositol and to reduce blood pressure in hypertensive rats (de Wilde et al., 2003). These observations suggest a possibility that supplemented ω-3 PUFA competes with arachidonic acid at the level of incorporation into membrane phospholipids and at the level of substrate for cyclooxygenase, thereby increasing the synthesis of ω-3 prostanoids in the brain. Additionally, it has been reported that sympathetic outflow is reduced by ω-3 PUFA as suggested by decreased plasma level of noradrenaline after increased dietary intake of fish or fish oils in humans or rats, respectively (Singer et al., 1983; Hashimoto et al., 1999). Taken together with the results of the present study, ω-3 PUFA supplementation may attenuate the activation of central sympatho-adrenomedullary outflow by increasing the synthesis of ω-3 prostanoids such as prostaglandin E_3 in the brain.

In summary, we demonstrated here that (1) centrally administered prostaglandin E_3 is less effective than prostaglandin E_2 on elevation of plasma noradrenaline, and (2) centrally administered thromboxane A_3 is almost as effective as thromboxane A_2 on elevation of plasma catecholamines (adrenaline ≫ noradrenaline) in rats.

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