Antiplatelet Activity of J78 (2-Chloro-3-[2′-bromo, 4′-fluoro-phenyl]-amino-8-hydroxy-1,4-naphthoquinone), an Antithrombotic Agent, Is Mediated by Thromboxane (TX) A2 Receptor Blockade with TXA2 Synthase Inhibition and Suppression of Cytosolic Ca2+ Mobilization

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ABSTRACT

We previously reported that J78 (2-chloro-3-[2′-bromo, 4′-fluoro-phenyl]-amino-8-hydroxy-1,4-naphthoquinone), a newly synthesized 1,4-naphthoquinone derivative, exhibited a potent antithrombotic effect, which might be due to antiplatelet rather than anticoagulation activity. In the present study, possible antiplatelet mechanism of J78 was investigated. J78 concentration-dependently inhibited rabbit platelet aggregation induced by collagen (10 μg/ml), thrombin (0.05 U/ml), arachidonic acid (100 μM), and U46619 (9,11-dideoxy-9,11-methanoepoxy-prostaglandin F2α; 1 μM), a thromboxane (TX) A2 mimic, with IC50 values of 0.32 ± 0.01, 0.44 ± 0.02, 0.50 ± 0.04, and 0.36 ± 0.02 μM, respectively. J78 also produced a shift to the right of the concentration-response curve of U46619, indicating an antagonistic effect on the TXA2 receptor. J78 concentration-dependently inhibited collagen-induced arachidonic acid liberation. In addition, J78 potently suppressed TXA2 formation by platelets that were exposed to arachidonic acid in a concentration-dependent manner but had no effect on the production of PGD2, indicating an inhibitory effect on TXA2 synthase. This was supported by a TXA2 synthase activity assay that J78 concentration-dependently inhibited TXB2 formation converted from PGH2. Furthermore, J78 was also able to inhibit the [Ca2+]i mobilization induced by collagen or thrombin at such a concentration that completely inhibited platelet aggregation. Taken together, these results suggest that the antiplatelet activity of J78 may be mediated by TXA2 receptor blockade with TXA2 synthase inhibition and suppression of cytosolic Ca2+ mobilization.

Platelet aggregation plays an important role in both physiological hemostatic and pathological thrombotic processes. Once vascular injury occurs, platelets will be activated by endogenous agonists such as ADP, collagen, and thrombin and adhere to the site of injury (Corti et al., 2002, 2003). The formation and release of thromboxane (TX) A2 is a central component in the platelet response to a variety of agonists. TXA2 is an eicosanoid, a metabolite of arachidonic acid formed via the cyclooxygenase (COX)-TXA2 synthase pathway. TXA2 binds to a G protein-coupled receptor to induce phospholipase Cβ activation, which results in an increase of [Ca2+]i, and protein kinase C activation and causes platelets to change shape, extend pseudopods, and adhere to platelets on the damaged surface. It also serves as an agonist of the TX receptors on the vascular smooth muscle cell membranes to cause vasoconstriction and proliferation of smooth muscle cells. In platelets, TXA2 is one of the major COX-1 products of this work was supported by a Chungbuk National University grant in 2004 and by the program of the Research Center for Bioresources and Health, from the Ministry of Science and Technology and Korea Science and Engineering Foundation.

ABBREVIATIONS: TX, thromboxane; COX, cyclooxygenase; J78, 2-chloro-3-[2′-bromo, 4′-fluoro-phenyl]-amino-8-hydroxy-1,4-naphthoquinone; PG, prostaglandin; HETE, 12-hydroxy-eicosatetraenoic acid; BSA, bovine serum albumin; DMSO, dimethyl sulfoxide; U73122, 1-(6-((17β-3-methoxyestra-1,3,5(10)-tri-en-17-yl)(amino)hexy))]-1H-pyrrole-2,5-dione; U46619, 9,11-dideoxy-9,11-methaneoxygen-prostaglandin F2α; PRP, platelet-rich plasma; BW755C, 3-amino-1-((m-(trifluoromethyl)-phenyl)-2-pyrazoline.
arachidonic acid metabolism. Its biosynthesis is also increased in the smooth muscle cells of patients with atherosclerosis (Fitzgerald et al., 1986). TXA$_2$ is considered to be one of the most powerful agonists for platelet activation and a major contributor to the thrombus formation. Therefore, inhibition of the synthesis or the action of TXA$_2$ is a theoretically effective means for treatment of atherothrombotic disorders, which has been demonstrated by the clinical evidences that drugs such as aspirin, picotamide, and ridogrel, are beneficial for the patients with acute coronary syndromes and myocardial infarction (Anonymous, 1994; Jnied et al., 2003).

The cytosolic Ca$^{2+}$ mobilization plays a crucial role in platelet activation and aggregation. During platelet activation, the increase of [Ca$^{2+}$], as a result of either Ca$^{2+}$ influx or release from intracellular stores is fundamental to the platelet response to various agonists (Jackson et al., 2003). Accordingly, agents with inhibition of the cytosolic Ca$^{2+}$ mobilization in platelets may suppress the platelet aggregation (Kim et al., 1999; Shah et al., 1999; Kang et al., 2001).

The compounds with backbone of 1,4-naphthoquinone chemical structure have shown a wide variety of pharmacological effects such as antiviral, antifungal, anticancer, and antiplatelet activities (Chen et al., 2002; Lien et al., 2002). In our previous study, we have reported that J78 (2-chloro-3-[2′-bromo, 4′-fluoro-phenyl]-amino-8-hydroxy-1,4-naphthoquinone), a newly synthesized 1,4-naphthoquinone derivative, displayed a potent antithrombotic effect in mice in vivo and antiplatelet activity in vitro as well as in rat ex vivo but had no effect on coagulation system. Available results suggest that antithrombotic effect of J78 may be due to antiplatelet activity (Jin et al., 2004). In the present study, we examined possible antiplatelet mechanism of J78 by measurements of the arachidonic acid liberation and formations of TXB$_2$, prostaglandin (PG) D$_2$, and 12-hydroxy-eicosatetraenoic acid (HETE) from exogenous arachidonic acid in platelets. In addition, the antagonistic effect of J78 on TXA$_2$-mediated platelet aggregation as well as possible inhibitory effects on TXA$_2$ synthase activity and cytosolic Ca$^{2+}$ mobilization were also investigated.

Materials and Methods

Chemicals. J78 was synthesized as previously described (Jin et al., 2004). Briefly, a solution of 1,4-naphthoquinone (0.01 mol) and 2-bromo-4-fluorophenylamine (0.011 mol) in 150 ml of 95% EtOH was refluxed for 5 h. After the reaction mixture was kept overnight at 4°C, precipitate was obtained by filtration. Crystallization of the precipitate from MeOH afforded J78. J78 had color: bright-red crystal, m.p.: 135–137.0°C, IR (KBr, cm$^{-1}$): 3315, 1494, 1240, 733; 1H NMR (DMSO-d$_6$): 6.88 to 7.41 (3H, m, benzene ring), 7.49 to 7.93 (3H, m), 11.48 (1H, s, OH), 9.27 (1H, s, NH), MS (m/z): 397 (M$^+$), 288, 1,4-Naphthoquinone and 2-bromo-4-fluorophenyl amine, bovine serum albumin (BSA), collagen, DMSO, Fura-2 AM, and U73122 [1-(6-((17β-3-methoxyestra-1,3,5(10)-tri-en-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione] were purchased from Aldrich Chemical Co. (Milwaukee, WI). Thrombin and arachidonic acid were obtained from Chrono-Log Co. (Havertown, PA). TXB$_2$, PGD$_2$, 12-HETE, and U46619 was purchased from Cayman Chemical (Ann Arbor, MI). [3H]Arachidonic acid (250 μCi/mmole) was purchased from PerkinElmer Life and Analytical Sciences (Boston, MA). The other chemicals were of analytical grade.

Animals. New Zealand white rabbits were purchased from Sam-Tako Animal Co. (Osan, Korea) and acclimatized for 1 week at 24°C and 55% humidity, with free access to a commercial pellet diet obtained from Samyang Co. (Wonju, Korea) and drinking water before experiments. The animal studies have been carried out in accordance with the Guide for the Care and Use of Laboratory Animals, Chungbuk National University, Korea.

Washed Platelet Preparation. Blood was withdrawn from the ear aorta of male New Zealand white rabbits and collected directly into 0.15 (v/v) of anticoagulant citrate dextrose solution that contained 0.8% citric acid, 2.2% trisodium citrate, and 2% dextrose (w/v). Washed platelet was prepared as previously described (Son et al., 2004). Briefly, platelet-rich plasma (PRP) was centrifuged at 10,000 g for 10 min. Platelets were sedimented by centrifugation of the PRP at 800 g for 15 min and washed with Hepes buffer (137 mM NaCl, 2.7 mM KCl, 1 mM MgCl$_2$, 5.6 mM glucose, and 3.8 mM Hepes, pH 6.5) containing 0.35% BSA and 0.4 mM EGTA. The washed platelets were resuspended in Hepes buffer (pH 7.4) and adjusted to 4 $\times$ 10$^8$ cells/ml.

Measurement of Platelet Aggregation in Vitro. Platelet aggregation was measured by using an aggregometer (Chrono-Log Co.) according to the turbidimetry method of Born and Cross (1963). Briefly, washed platelet suspension of rabbits was incubated at 37°C for 4 min in the aggregometer with stirring at 1000 rpm before aggregation was challenged by the addition of collagen (10 μg/ml), thrombin (0.05 U/ml), arachidonic acid (100 μM), and U46619 (1 μM), respectively. The resulting aggregation, measured as the change in light transmission, was recorded for 10 min. To investigate the antagonism of J78 on U46619-induced rabbit platelet aggregation, concentration-response relationships were determined in the absence or presence of a range of concentrations of J78; for these experiments, indomethacin-treated washed rabbit platelets (50 μM for 3 min) were used to prevent any possible contribution of endogenous arachidonic acid metabolites to platelet aggregation. The extent of inhibition of platelet aggregation is expressed as percentage of inhibition (X) using the following equation: X (percent) = (1 – B/A) $\times$ 100%, where A is the maximum aggregation rate of vehicle-treated platelets, and B is the maximum aggregation rate of sample-treated platelets.

Measurement of TXB$_2$, PGD$_2$, and 12-HETE Generation. The TXB$_2$, PGD$_2$, and 12-HETE generations were measured as previously described (Son et al., 2004). Briefly, washed platelets (4 $\times$ 10$^8$ cells/ml) for 3 min, and then further incubated with a mixture of [3H]arachidonic acid and unlabeled arachidonic acid (2 μM, 1 μCi/ml) for 5 min. The reaction was terminated by the addition of stop solution containing 2.6 mM EGTA and 130 μM BW755C 3-amin-1-(m-trifluoromethyl)-phenyl)-2-pyrazoline, a COX and lipoygenase inhibitor. Lipids were extracted and separated by thin-layer chromatography on Silica Gel G plates (Analtach, Newark, DE) with the following development system: ethyl acetate/isooctane/acetic acid/1,3,5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione was redissolved immediately in ethanol. Platelet suspension (10$^8$ cells/ml) for 5 min. The reaction was terminated by the addition of stop solution containing 2.6 mM EGTA and 130 μM BW755C 3-amin-1-(m-trifluoromethyl)-phenyl)-2-pyrazoline, a COX and lipoygenase inhibitor. Lipids were extracted and separated by thin-layer chromatography on Silica Gel G plates (Analtech, Newark, DE) with the following development system: ethyl acetate/isooctane/acetic acid/H$_2$O (9:5:2:10, v/v/v/v). The area corresponding to each lipid was scraped off, and the radioactivity was determined by liquid scintillation counting (model LS 8801; Beckman Coulter, Fullerton, CA).

TXA$_2$ Synthase Activity Assay. The TXA$_2$ synthase activity was assayed as previously described (Son et al., 2004). Briefly, aliquots of PGH$_2$ in anhydrous acetone, were pipetted into glass tubes, and then the acetone was evaporated under a gentle stream of nitrogen, and PGH$_2$ was redissolved immediately in ethanol. Platelet suspensions were incubated with the test compounds at 37°C for 3 min prior to the addition of 5 μM PGH$_2$. The final concentration of ethanol was 0.1% (v/v). At 5 min after the addition of PGH$_2$, the incubations were terminated by the addition of cooling EGTA (2 mM) and centrifuged at 12,000 g at 4°C for 4 min. The amount of TXB$_2$ in the supernatants was assayed by a commercial enzyme immunoassay kit according to the manufacturer’s instructions (Amersham Biosciences UK, Ltd., Little Chalfont, Buckinghamshire, UK). TXA$_2$ synthase activity is reflected by the production of TXB$_2$.
Results

Effect of J78 on Rabbit Platelet Aggregation in Vitro. As shown in Fig. 1, J78 concentration-dependently inhibited collagen (10 μg/mL), U46619 (1 μM), thrombin (0.05 U/mL), and arachidonic acid (100 μM)-challenged washed rabbit platelet aggregation, with IC₅₀ values of 0.32 ± 0.01, 0.36 ± 0.02, 0.44 ± 0.02, and 0.50 ± 0.04 μM, respectively.

Effects of J78 on Conversions of Arachidonic Acid to TXB₂, PGD₂, and 12-HETE in Rabbit Platelet. As shown in Fig. 2, J78 concentration-dependently suppressed TXB₂ generation, which reflected the formation of TXA₂, induced by the addition of [³H]arachidonic acid in intact rabbit platelets. The TXB₂ formations were inhibited by 21.8, 35.4, 53.7, and 76.3% at the concentrations of 0.2, 0.4, 0.6, and 0.8 μM, respectively. J78, however, has no effect on PGD₂ generation. These results suggest that J78 may selectively inhibit activity of TXA₂ synthase rather than that of COX because TXA₂ and PGD₂ are simultaneously produced from arachidonic acid through the COX pathway. In addition, J78 has no effect on 12-HETE production (data not shown), suggesting that lipoxygenase pathway was not involved in the antiplatelet effect of J78.

Effect of J78 on TXA₂ Synthase Activity in Rabbit Platelet. The conversion of arachidonic acid to TXA₂ in platelets requires the action of two enzymes, COX and TXA₂ synthase. TXA₂ synthase catalyzes the conversion of PGH₂ to TXA₂ in platelets. By utilizing PGH₂, it is possible to circumvent the COX step during arachidonic acid metabolism. The addition of increasing concentrations of PGH₂ to washed rabbit platelet suspensions produced a concentration-dependent decrease of TXB₂ (data not shown). Thus, washed rabbit platelet suspensions containing PGH₂ are adequate for the direct evaluation of the TXA₂ synthase inhibitor. In washed rabbit platelet suspensions, the level of TXB₂ in unstimulated platelets was about 15 ng/4 × 10⁸ platelets. After incubation of washed platelet suspensions with PGH₂ (5 μM) at
37°C for 5 min, TXB₂ formation was increased to 88.8 ng/4 × 10⁶ platelets. As shown in Fig. 3, J78 inhibited the conversion of PGH₂ into TXB₂ by 9.8, 20.3, 45.3, and 63.1% at concentrations of 0.2, 0.4, 0.6, and 0.8 μM in washed rabbit platelet suspensions, respectively. Imidazole, a typical TXA₂ synthase inhibitor, also markedly inhibited the conversion of PGH₂ into TXB₂.

**Effect of J78 on U46619-Induced Rabbit Platelet Aggregation.** When J78 was preincubated with washed rabbit platelets for 3 min, it reduced platelet aggregation elicited by various concentrations of U46619 under COX blockade with indomethacin in a concentration-dependent manner. At concentrations of 0.36 and 0.80 μM, J78 produced a shift to the right of the concentration-response curve of U46619, suggesting an antagonism on the TXA₂ receptor (Fig. 4).

**Effect of J78 on [Ca²⁺]ᵢ in Rabbit Platelet.** The representative traces in which two different agonists were added to induce [Ca²⁺]ᵢ mobilization were shown in Fig. 5. The effect of J78 on [Ca²⁺]ᵢ mobilization was observed after 3 min of incubation with platelet before adding the respective inducers. Collagen induced a slow but stable increase of [Ca²⁺]ᵢ, which reached the peak level of 300 μM after 5 min, whereas thrombin caused a rapid but transient increase in [Ca²⁺]ᵢ. Treatment of the platelet suspension with J78 (0.8 μM) almost completely inhibited the elevation of the [Ca²⁺]ᵢ in response to collagen and thrombin, respectively. The right panels in A and B (Fig. 5) are the average of three times separated experiments, similar to that shown in left panels in A and B.

**Effect of J78 on Collagen-Induced Arachidonic Acid Liberation in Rabbit Platelet.** As shown in Fig. 6, pretreatment of J78 concentration-dependently inhibited collagen-induced arachidonic acid liberation in [³H]arachidonic acid-prelabeled rabbit platelets by 2.6, 16.8, 33.7, and 55.6% at concentrations of 0.2, 0.4, 0.6, and 0.8 μM, respectively. U73122, a phospholipase C inhibitor that was used as a positive control, completely blocked arachidonic acid liberation at a concentration of 50 μM.

**Discussion**

Platelet aggregation is a complex process, and it is generally considered that platelet activation is mainly mediated through adhesiveness of platelets to the site of injury and through the action of endogenous agonists such as ADP, collagen, and thrombin, followed by the release of TXA₂, which acts as an amplifying factor in the platelet aggregation (Jackson et al., 2003; Farndale et al., 2004). The important role of TXA₂ has been demonstrated by the clinical effectiveness of aspirin in the prevention of cardiovascular diseases such as acute coronary syndromes (Awtry and Loscalzo, 2000; Catella-Lawson et al., 2001; Jneid et al., 2003). In the present study, we demonstrate that the antiplatelet activity of J78, an antithrombotic agent, may be mediated by TXA₂ receptor blockade with TXA₂ synthase inhibition and suppression of [Ca²⁺]ᵢ mobilization.

It is well known that U46619, which is a TXA₂ mimic, acts directly on the TXA₂ receptor to induce G protein-coupled phospholipase Cβ activation, resulting in an increase of [Ca²⁺]ᵢ, and protein kinase C activation (Jackson et al., 2003). Similarly, arachidonic acid, which acts directly on membrane COX enzyme pathway to produce TXA₂, mediates platelet activation in the same way as U46619 (Parise et al., 1984). From the platelet aggregation study (Fig. 1), J78 inhibited TXA₂-mediated platelet aggregation such as arachidonic acid- and U46619-induced aggregation in a concentration-dependent manner, suggesting that J78 may interfere with the TXA₂ synthesis or its action directly. Therefore, the effect of J78 on the generation of TXA₂ was first determined by using [³H]arachidonic acid in intact rabbit platelet. As shown in Fig. 2, J78 concentration-dependently inhibited [³H]TXA₂ formation, whereas it had no effect on the production of [³H]PGD₂. These results indicate that J78 may selectively inhibit the activity of TXA₂ synthase rather than that of COX because TXA₂ and PGD₂ are simultaneously produced from arachidonic acid through COX pathway in platelets. It was also confirmed by TXA₂ synthase activity assay that J78 potently reduced PGH₁₂, a precursor of the PGs and TXA₂, mediated TXB₂ formation (Fig. 3). Although the inhibition of
**Fig. 5.** Effects of J78 on \([Ca^{2+}]_i\) in collagen- and thrombin-stimulated rabbit platelet. Calcium (1 mM) was added to the platelet suspension 10 s before data collection started (zero time). J78 solution was added to yield a final concentration of 0.8 \(\mu M\) in the platelet suspension. Collagen (10 \(\mu g/ml\)) or thrombin (0.05 U/ml) was added 3 min later. The traces shown are from a representative experiment; similar results were obtained from separate experiments conducted in triplicate, and average data are presented in right panels in A and B. *P < 0.01 versus corresponding stimulus control.

TXA$_2$ synthesis by TXA$_2$ synthase inhibition is theoretically rational to inhibit platelet aggregation, considering that accumulated PGH$_2$, the precursor of TXA$_2$, can interact with the same receptor (TXA$_2$/PGH$_2$ receptor) as TXA$_2$ to induce platelet activation, it seems that J78 may also have any inhibitory effect on the TXA$_2$/PGH$_2$ receptor directly. Therefore, the possible inhibitory effect of J78 on TXA$_2$/PGH$_2$ receptor was investigated. Indeed, it completely inhibited platelet aggregation induced by the stable TXA$_2$ mimic, U46619, in rabbit platelets by shifting, in a parallel way, the concentration-response curve to U46619 to the right (Fig. 4), suggesting that J78 may specifically block platelet TXA$_2$/PGH$_2$ receptor, possibly in a competitive manner. It has also been reported that other drugs possessing the dual property of TXA$_2$/PGH$_2$ receptor antagonistic and TXA$_2$ synthase inhibitory effects act also as competitive antagonists of U46619-induced aggregation (Chang et al., 1997; Rolin et al., 2001; Miyamoto et al., 2003). These results correlated well with the in vivo antithrombotic effect of J78 on the murine pulmonary thrombosis (Jin et al., 2004), the lethal effect of collagen plus epinephrine on which is caused by massive occlusion of microcirculation of lung by platelet thrombomobilisom or by vasoconstriction due to the release of TXA$_2$ and PGF$_{2\alpha}$ from activated platelets.

In addition, it seems that J78 may also have an inhibitory effect on cytosolic Ca$^{2+}$ mobilization because J78 inhibited calcium ionophore, A23187-induced platelet aggregation concentration-dependently (Jin et al., 2004). Concomitant with aggregation data, in the platelets loaded with Fura-2 AM, J78 completely blocked the cytosolic Ca$^{2+}$ mobilization induced by collagen and thrombin at a concentration of 0.8 \(\mu M\), which is sufficient to inhibit platelet aggregation completely (Fig. 5). Thrombin and collagen, both of which are strong agonists, have different platelet aggregation mechanisms (Colman et al., 1994). Thrombin interacts with platelet through a specific receptor belonging to the superfamily of receptors that are coupled to G proteins and phospholipase C/\(\beta\), producing diacylglycerol, which stimulates protein kinase C closely linked to secretion. Inositol trisphosphate is also produced and plays a role in increasing \([Ca^{2+}]_i\) (Lapetina, 1990), whereas collagen induces platelet activation through a tyrosine kinase-based signaling pathway that involves the kinase Syk and phospholipase C/\(\gamma2\), which results in \([Ca^{2+}]_i\) increase, shape change, and granule release; adhesion is partly and aggregation is largely dependent on ADP and TXA$_2$/PGH$_2$ release (Farndale et al., 2004). Considering that inhibition of TXA$_2$ synthesis was only partly effective to inhibit the collagen- or thrombin-mediated platelet aggregation, and several compounds with the same 1,4-naphthoquinone backbone as J78 have been reported to inhibit the rise of \([Ca^{2+}]_i\), by suppression of phosphoinositide breakdown in various cell types including platelet (Chang et al., 1993; Wang and Kuo, 1997; Chen et al., 2002), it is reasonable to speculate that antiplatelet activity of J78 was not only mediated by the TXA$_2$/PGH$_2$ receptor antagonism and TXA$_2$ synthase inhibition but also by the inhibition of cytosolic Ca$^{2+}$ mobilization, possibly by interfering with the phosphoinositide breakdown. This was indirectly supported by the arachidonic acid liberation assay that J78 inhibited collagen-mediated arachidonic acid liberation from \([3H]\)arachidonic acid-prelabeled rabbit platelets in a concentration-dependent manner (Fig. 6). In fact, in lower concentrations (1–20 \(\mu g/ml\)) of collagen-mediated platelet activation, inhibition of phosphoinositide breakdown was able to block the arachidonic acid liberation completely (Balsinde et al., 2002).

Recent studies have demonstrated that injury-induced vascular proliferation and platelet activation are depressed in mice genetically deficient in the TXA$_2$ receptor or treated with a TXA$_2$ antagonist (Cheng et al., 2002). Thus, it is conceivable that J78 might be particularly effective for the improvement of atherothrombotic conditions associated with platelet activation. Drugs such as picotamide and ridogrel...
that act both as TXA2 synthase inhibitors and as TXA2/PGH2 receptor antagonists have been developed. Picotamide may be an effective drug in patients with peripheral occlusive arterial disease of the lower limbs and cerebral infarction (Coto et al., 1989, 1998). Ridogrel seems to have efficacy in patients with peripheral occlusive arterial disease and acute myocardial infarction (Hoet et al., 1990; Neirotti et al., 1994).

In summary, our results demonstrate that antiplatelet activity of J78 may, at least partly, result from a combination of TXA2 synthase inhibition and TXA2 synthase inhibition and a suppression of [Ca2+] mobilization.

References


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