Protein Kinase C β Inhibitor LY333531 Attenuates Intercellular Adhesion Molecule-1 and Monocyte Chemotactic Protein-1 Expression in the Kidney in Diabetic Rats

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Abstract. In vitro studies have shown that activation of protein kinase C (PKC) is a key mediator of intercellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1) in a range of cell types and in response to high glucose, however, its role in the in vivo setting has not been clearly delineated. Streptozotocin-induced diabetic rats were treated with the PKC-β isoform inhibitor LY333531 for 8 weeks. LY333531 treatment significantly attenuated increased urinary albumin excretion rate and glomerular volume and tubulointerstitial injury index as well as elevated PKC activity and PKC-β protein expression in the kidney. Level of malondialdehyde was markedly higher and antioxidant enzyme activity such as superoxide dismutase and catalase as well as glutathione peroxidase were significantly lower in the kidney from diabetic rats than that of the control group. LY333531 administration could remit these changes. Increased macrophages recruitment as well as ICAM-1 and MCP-1 protein expression in the kidney were significantly inhibited by LY333531 in diabetic rats. It is concluded that mechanism of renoprotection of LY333531 may be correlated, at least partly, with suppression of increased macrophages recruitment and overexpression of ICAM-1 and MCP-1 in diabetic rats.

Keywords: LY333531, diabetes mellitus, macrophage, intercellular adhesion molecule-1, monocyte chemotactic protein-1

Introduction

Most of the human and experimental kidney diseases including diabetic nephropathy are characterized by the infiltration of macrophages into the glomerulus and tubulointerstitium in the early stages of the disease, before the development of extracellular matrix expansion and glomerulosclerosis as well as tubulointerstitial fibrosis (1–4). Macrophages could cause structural damage through the release of proteolytic enzymes (5) and oxygen radicals (6), glomerular and tubulointerstitial remodeling by the release of growth factors (7), or glomerular and tubulointerstitial functional alterations via the elaboration of cytokines (8) and eicosanoids (9).

Previous studies have shown that protein kinase C (PKC) β, one of the major isoforms of PKC, was activated by hyperglycemia in the diabetic kidney (10). LY333531 is a selective inhibitor of PKC-β. Oral treatment with LY333531 in streptozotocin (STZ)-induced diabetic rats prevented the onset of early abnormalities in retinal and renal hemodynamics, reduced urinary albumin excretion rate, and mesangial expansion (11, 12). Recent studies have shown evidence that in a model of advanced diabetic nephropathy, inhibition of PKC-β significantly attenuated the structural and functional manifestations of injury despite continued hyperglycemia and hypertension (13).

However, the exact mechanism involved in the renoprotective effects of LY333531 in experimental
diabetes has not been clearly delineated. The infiltration of macrophages is induced by upregulation of cell adhesion molecules and chemokines. Recently, in vivo studies have shown that LY333531 could attenuate osteopontin expression, macrophages recruitment, and tubulointerstitial injury in advanced experimental diabetic nephropathy (14). In vitro studies have demonstrated that PKC activation might induce intercellular adhesion molecule-1 (ICAM-1) and monocyte chemotactic protein-1 (MCP-1) expression in endothelial cells and mesangial cell (15, 16). The purpose of this study was to evaluate quantitatively the effect of LY333531 treatment on ICAM-1 and MCP-1 expression and macrophages recruitment in the kidney in diabetic rats.

Materials and Methods

Animals

Adult male Munich-Wistar rats, with initial weights of 180 to 200 g (Grade II, Certificate No 01), were obtained from Experimental Animal Center of Anhui Medical University. The research protocol was in accordance with the principles approved by the animal ethics committee of Anhui Medical University. Animals were housed at a temperature of 23 ± 1°C and humidity of 65%–70%, submitted to a 12 h light/dark cycle, and allowed free access to standard laboratory chow and tap water.

Experimental protocol

All rats were initially subjected to removal of the right kidney under anesthesia with sodium pentobarbital (50 mg/kg, i.p.) to hasten the development of diabetic nephropathy as described previously (17), and then they were rendered diabetic two weeks later by a single injection of STZ (Sigma Chemical Co., St. Louis, MO, USA) at a dose of 65 mg/kg, i.p., diluted in citrate buffer 0.1 M (pH 4.0). Two days later, the diabetic state was confirmed by measurement of tail blood glucose (BG) levels using a glucometer (one touch II Glucometer; LifeScan, Milpitas, CA, USA). Three experimental groups were studied: non-diabetic uninephrectomized rats (group C, n = 10), uninephrectomized rats made diabetic (group DM, n = 10), diabetes treated with LY333531 (10 mg/kg per day by gastric gavage, group DM + LY333531, n = 10). LY333531 (Eli-Lilly, Indianapolis, IN, USA) was dissolved in the drinking water.

Metabolic parameters and tissue collection

After eight weeks, body weight was measured at the conclusion of the experiment. Rats were then anesthetized with sodium pentobarbital (50 mg/kg, i.p.), placed on a temperature-regulated table, and the right jugular artery was catheterized; this arterial catheter was used for blood sampling. BG level was determined with a glucose analyzer. The kidneys were perfused in vivo via the abdominal aorta with 100 ml of normal saline at 4°C, while the left renal vein was punctured to permit the perfusate to drain; the kidneys were removed immediately and then fixed in 10% formalin and processed in paraffin for subsequent histologic assessment and immunohistochemical studies. The remaining kidney was stored at −80°C for evaluation of oxidative stress parameter and PKC activity as well as Western blotting analysis.

Urinary albumin measurements

On the last two day of the experiment, rats were individually housed in metabolic cages. After 24 h in metabolic cages, an aliquot of urine (5 ml) was collected from 24 h urine sample and stored at −80°C for subsequent analysis of albumin. Albuminuria levels were measured by the one-step sandwich enzyme immunoassay (EIA) technique using a commercial kit (Nephrat; Exocell, Inc., Philadelphia, PA, USA) according to the manufacturer’s instructions. The 24 h urinary albumin excretion rate (AER) was calculated by multiplying the urinary protein excretion by 24 h urine volume.

Renal pathology

Formalin-fixed kidney sections (2 μm) were stained with Periodic acid-Schiff (PAS) reagent to identify kidney structure and hematoxylin to distinguish cell nuclei. Digital images of glomeruli and interstitial areas were obtained from microscopy (magnification, ×400). The glomerular cross-sectional area (A_G) was measured in 50 glomerular profiles per rat by using computerized image analysis system (Beijing Aeronautic and Aerospace University, Beijing, China). The glomerular volume (V_G) was then calculated as: \( V_G = \beta/K[A_G]^{1/2} \), where \( \beta = 1.38 \) is the size distribution coefficient and \( K = 1.1 \) is the shape coefficient for glomeruli idealized as a sphere (18). Tubulointerstitial area in the cortex was evaluated and graded as: 0, normal; 1, the area of interstitial inflammation and fibrosis, tubular atrophy, and dilation with cast formation involving <25% of the field; 2, lesion area between 25% and 50% of the field; and 3, lesions involving >50% of the field. The indices for tubulointerstitial injury (TI) were calculated by averaging the grades assigned to all tubule fields (19). All measurements and scoring were performed on blinded slides.
**Oxidative stress**

Oxidative stress was evaluated by determination of renal level of malondialdehyde (MDA) as well as activity of an antioxidant enzyme (AOE) such as superoxide diamutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-PX). MDA, SOD, CAT, and GSH-PX were measured by using commercially available kits according to the manufacturer’s protocol (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). The data on urinary MDA level was expressed as nmol of MDA in 24 h, those for renal MDA level was expressed as nmol MDA per milligram protein (nmol/mg prot), and those for antioxidant activities was expressed as U/mg prot. The protein content was estimated by the dye binding assay of Bradford (20), with bovine serum albumin used as a standard.

**Assay for PKC activity**

Membrane and cytosolic fractions in renal tissue were obtained by the method described by Kikkawa et al. (21). PKC activity was determined by the method described by Heasley and Johnson (22). Briefly, membrane and cytosolic fractions were preincubated with the salt solution for 10 min at 37°C, incubated for another 15 min in the presence or absence of 100 µM PKC-specific peptide substrate, and subsequently with another 15 min in the presence or absence of 100 µM [γ-32P]ATP (<1,500 cpm/pmol). The reaction was terminated with 5% TCA (final concentration). Aliquots of the reaction mixture were spotted on 3 × 3 cm phosphocellulose papers and washed with three changes of 75 mM phosphoric acid and one change of 75 mM sodium phosphate (pH 7.5). The radioactivities of phosphorylated substrate was determined by liquid scintillation counting. PKC activity was expressed as pmol/mg·min. The protein content was estimated by the dye binding assay of Bradford (20), with bovine serum albumin used as a standard.

**Western blotting analysis**

Kidney samples were homogenized in RIPA buffer (PBS, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, 100 µg/ml aprotinin, 100 µg/ml phenylmethylsulfonyl fluoride, sodium orthovanadate) at 4°C throughout all procedures. The protein concentration was measured by the dye binding assay of Bradford and separated by 10% – 15% SDS-PAGE. After transferring onto nitrocellulose membrane, the membranes were hybridized with Anti-PKC-β (diluted 1:500; Zymed, San Francisco, CA, USA) and Anti-MCP-1 (diluted 1:1000; Santa Cruz Biotechnology, CA, USA) antibody and then incubated with a horseradish peroxidase-conjugated secondary antibody (diluted 1:1000; Amersham Life Science, Little Chalfont, UK). Immunoreactive bands were visualized using the ECL detection system (Amersham Life Science). Housekeeping protein β-actin was used as a loading control. Positive immunoreactive bands were quantified densitometrically (Leica Q500IW image analysis system; Leica, Cambridge, UK) and expressed as an intensity ratio.

**Immunohistochemistry**

Immunostaining of ED-1 (macrophages marker) and ICAM-1 in renal tissue sections was conducted using the streptavidin-biotin-peroxidase complex (SABC) method. The primary antibodies that were used included a monoclonal mouse anti-rat ED-1 antibody (diluted 1:50; Serotec, Oxford, UK) and a polyclonal rabbit anti-ICAM-1 antibody (diluted 1:200, Santa Cruz Biotechnology). Three-micrometer paraffin sections of kidneys were microwave-treated at 800 w for 12 min in 10 mM sodium citrate (pH 6.0) and incubated for 20 min with 0.6% H2O2 followed by avidin and biotin block and 20% normal sheep serum to prevent nonspecific detection. Sections were then incubated overnight at 4°C with primary antibody in 1% bovine serum albumin. After washing in PBS, sections were incubated with biotinylated goat antibodies (1:200) for 1 h followed by SABC solution and developed with 3,3-diaminobenzidine to produce a brown color. Normal IgG was used as a negative control in the staining. Sections were then counterstained with Mayer’s hematoxylin and stained area of the sections under the same light intensity. Quantitative analysis of ED-1-positive cells in glomeruli was performed under ×400 magnification and expressed as cells/glomerular cross section (gcs); for each section, 50 sequential glomerular profiles were examined. ED-1-positive cells in tubulointerstitium were counted in 25 consecutive high power (×400) interstitial fields by means of a 0.02 mm2 graticule fitted in the eyepiece of the microscopy and expressed as cells/mm2 (23). Immunostaining of ICAM-1 in glomeruli was evaluated using the following semiquantitative scale: 0 = diffuse, very weak or absent staining; 1 = staining involving less than 25%; 2 = staining involving 25% to 50%; 3 = staining involving 50% to 75%; and 4 = staining involving 75% to 100% (24). Immunostaining of ICAM-1 in tubulointerstitium was quantified using a computerized image analysis system (Beijing Aeronautic and Aerospace University) by evaluating the positively stained area of the sections under the same light intensity for microscopy (25). All scoring was performed on blinded slides.
Statistics
Data are expressed as the mean ± S.E.M. unless otherwise stated. Statistical significance was determined by a two-way ANOVA with a Fisher’s post hoc comparison. Albuminuria was analyzed using log-transformed data and represented as geometric means ×/÷tolerance factors. Differences were considered statistically significant when the probability value was less than 0.05.

Results

Clinical and metabolic parameter
In comparison with control animals, diabetic rats had reduced body weight, which was unaffected by treatment with LY333531. Blood glucose level was elevated to a similar extent in treated and untreated diabetic rats. Diabetes was associated with an increase in ratio of kidney weight to body weight (relative kidney weight) and AER when compared with controls. Treatment with LY333531 reduced relative kidney weight and AER in diabetic rats (Table 1).

Renal histology
Diabetic rats had an increase in the glomerular volume when compared with the values in control animals. LY333531 treatment ameliorated the increase of the glomerular volume (Figs. 1 and 2A). Diabetic rats had an increase in the tubulointerstitial injury index when compared to control animals, LY333531 treatment was associated with a reduction in tubulointerstitial injury index as compared with diabetic rats (Figs. 1 and 2B).

Oxidative stress
Renal MDA level was increased in diabetic rats when compared to control rats. LY333531 treatment caused significantly lowering of renal MDA level compared to the diabetic state alone (Table 2). In diabetic rats, activity of AOE such as SOD, CAT, and GSH-PX had all decreased compared with control rats, LY333531 treatment was associated with a significant increase in SOD, CAT, and GSH-PX activity (Table 2).

Table 1. Clinical and metabolic parameters in three groups of rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Numbers of rats</th>
<th>Blood glucose (mg/dl)</th>
<th>Body weight (g)</th>
<th>Relative kidney weight (×10⁻³)</th>
<th>AER (mg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>10</td>
<td>107.33 ± 7.48</td>
<td>358.75 ± 22.02</td>
<td>4.20 ± 0.42</td>
<td>0.48 ×/÷ 1.3</td>
</tr>
<tr>
<td>DM</td>
<td>10</td>
<td>401.96 ± 22.43**</td>
<td>261.11 ± 22.81*</td>
<td>9.38 ± 0.84**</td>
<td>1.26 ×/÷ 1.1**</td>
</tr>
<tr>
<td>DM + LY333531</td>
<td>10</td>
<td>356.87 ± 24.59</td>
<td>300.87 ± 15.39</td>
<td>7.19 ± 0.34</td>
<td>0.84 ×/÷ 1.1*</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, compared with C group; *P<0.05, compared with DM group. Data are presented as the mean ± S.E.M. ×/÷ tolerence factor. AER, albumin excretion rate.

Table 2. Oxidative stress parameters in three groups of rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Numbers of rats</th>
<th>MDA (nmol/mg prot)</th>
<th>SOD (U/mg prot)</th>
<th>CAT (U/mg prot)</th>
<th>GSH-PX (U/mg prot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>10</td>
<td>1.74 ± 0.07</td>
<td>441.02 ± 3.57</td>
<td>12.18 ± 0.32</td>
<td>8.24 ± 0.19</td>
</tr>
<tr>
<td>DM</td>
<td>10</td>
<td>3.60 ± 0.08**</td>
<td>377.70 ± 2.25*</td>
<td>7.63 ± 0.24**</td>
<td>3.63 ± 0.19**</td>
</tr>
<tr>
<td>DM + LY333531</td>
<td>10</td>
<td>2.93 ± 0.05*</td>
<td>454.68 ± 7.01*</td>
<td>9.57 ± 0.48*</td>
<td>6.44 ± 0.35*</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, compared with C group; *P<0.05, compared with DM group. Data are presented as the mean ± S.E.M.

Table 3. Change of PKC activity in the kidney in three groups of rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Numbers of rats</th>
<th>PKCt (pmol/min · mg)</th>
<th>PKCc (pmol/min · mg)</th>
<th>PKCm (pmol/min · mg)</th>
<th>PKCm/PK Ct</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>10</td>
<td>9.83 ± 0.97</td>
<td>7.57 ± 0.95</td>
<td>2.26 ± 0.33</td>
<td>0.23 ± 0.03</td>
</tr>
<tr>
<td>DM</td>
<td>10</td>
<td>34.34 ± 4.75**</td>
<td>16.70 ± 2.44**</td>
<td>17.65 ± 2.25**</td>
<td>0.51 ± 0.02*</td>
</tr>
<tr>
<td>DM + LY333531</td>
<td>10</td>
<td>12.38 ± 0.55*</td>
<td>8.31 ± 0.65*</td>
<td>4.07 ± 0.44*</td>
<td>0.32 ± 0.05*</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, compared with C group; *P<0.05, compared with DM group. Data are presented as the mean ± S.E.M.
Compared with control animals, PKC activity in the total cell (PKCt), the cytosolic fraction (PKCc), the membrane fraction (PKCm), and the ratio of the PKC activity in the membrane fraction to cytosolic fraction (PKCm/PKCt) were significantly elevated in renal tissue from diabetic rats, suggesting that the diabetic state induced renal PKC activation. Increased PKC activity was effectively inhibited by LY333531 administration (Table 3).
Renal PKC-β expression

Western blot analysis noted that an increase in the amount of immunoreactive peptide was seen in the kidney of diabetic rats compared to that from control animals. Densitometric analysis of the Western blot showed a 2.45 fold increase in the amount of PKC-β from diabetic rats with respect to control animals; LY333531 treatment reduced PKC-β protein expression by approximately 53% (Fig. 3: A and B).

Renal macrophages infiltration

ED-1-positive cells (representing macrophages) infiltrated the glomeruli of diabetic rats at eight weeks. ED1-positive cells infiltrated into the periglomerular and tubulointerstitial areas were also observed in diabetic rats. ED-1-positive cell infiltration into the glomeruli and tubulointerstitial areas was significantly suppressed by treatment with LY333531 (Figs. 4 and 5A and B).

Fig. 3. Western blot analysis of PKC-β protein (A) and densitometric analysis (B) in renal tissue in C, DM, and DM + LY333531 rats. Lane 1 shows the control, lane 2 shows DM, and lane 3 shows DM + LY333531. Values are the mean ± S.E.M. **P<0.01 vs C, *P<0.05 vs DM.

Fig. 5. The number of ED-1 positive cells in glomerulus (A) and tubulointerstitium (B) in C, DM, and DM + LY333531 rats. Values are the mean ± S.E.M. **P<0.01 vs C, *P<0.05 vs DM.

Fig. 7. The score of ICAM-1 (A) in glomerulus and immunostaining area of ICAM-1 (B) in tubulointerstitium in C, DM, and DM + LY333531 rats. Values are the mean ± S.E.M. **P<0.01 vs C, *P<0.05 vs DM.
ICAM-1 protein immunostaining was observed in the glomerulus and, to a lesser degree, the tubulointerstitium in control animals. Immunostaining for ICAM-1 was increased in diabetic rats in glomeruli and tubulointerstitium and markedly reduced by treatment with LY333531 (Figs. 6: A – C and 7: A and B). Western blot analysis noted that an increase in the amount of immunoreactive peptide was seen in kidney for diabetic rats compared to that from control animals. Densitometric analysis of the Western blot showed a 5.29 fold increase in the amount of MCP-1 from diabetic rats with respect to control animals, LY333531 treatment reduced MCP-1 protein expression by approximately 52% (Fig. 8: A and B).

**Discussion**

The present study demonstrated that despite the presence of continuing hyperglycemia, inhibition of PKC-β with LY333531 reduced the development of structural and functional manifestations of renal injury in this model. Increased macrophages infiltration in glomeruli and tubulointerstitium were found to correlate with glomeruli hypertrophy and tubulointerstitial injury that were substantially reduced by LY333531 in diabetic animals. To our knowledge, this is the first in vivo study to demonstrate that inhibition of PKC activity reduces glomerular macrophages recruitment in diabetic rats. The effect of LY333531 on tubulointerstitial macrophages infiltration was in accordance with the findings of Kelly et al. (14).

ICAM-1, a cell surface glycoprotein, is one of the major molecules involved in promoting leukocyte firm attachment to the endothelium and transmigration through its expression on the vascular endothelium and binding to β2 leukocyte integrins (26). ICAM-1 is produced in many cell types, including mesangial cell, vascular endothelial cells, tubular and interstitial cells; and it is upregulated at sites of inflammation. Increased expression of ICAM-1 has been reported in various renal diseases and may participate in inflammatory cell recruitment into the injured kidneys (27, 28). Previous studies have demonstrated the accumulation of macrophages and increased expression of cell adhesion molecules, such as ICAM-1 and selections, in the kidneys of patients with diabetic nephropathy (29). Furthermore, Sugimoto et al. reported that the upregulation of ICAM-1 associated with macrophages infiltration occurred in very early stages, soon after the induction of diabetes, and was maintained throughout the observation period in STZ-induced diabetic rats (30); their studies suggested that administration of monoclonal antibodies against ICAM-1 prevented the infiltration of macrophages in glomeruli in diabetic rats. In addition, Okada et al. reported knockout mice lacking the gene for ICAM-1 were resistant against renal injury after induction of diabetes (31). MCP-1, a member of the β-chemokine family, is a potent chemoattractant for monocyte/macrophage (32). Numerous cell types, including tubular epithelial cells and mesangial cells, are known to be capable of expressing MCP-1. Recent investigations have described the increased expression of MCP-1 in renal diseases with macrophages infiltration. As reported previously, secondary to renal macrophages infiltration in diabetic rats, MCP-1 expression was up-regulated (33, 34). The mechanisms leading to the up-regulation of MCP-1 in various types of renal injury, including diabetic nephropathy, have yet to be fully understood. However, human and rodent mesangial cells can synthesize MCP-1 in response to several factors that are thought to be involved in glomerular injury, such as interleukin-1, TNF-α, and low-density lipoprotein (35). In the case of human mesangial cells, high concentration of glucose as well as glycated albumin has been reported to promote MCP-1 production (36). An additional influence that may induce synthesis of MCP-1 is the generation of reactive oxygen species (ROS) (37).

In this study, the administration of LY333531 to the diabetic rats significantly decreased the expression of ICAM-1 and MCP-1 in the kidney. The decreased expression of ICAM-1 presented by LY333531-treated rats might be explained by inhibition of PKC activation.
because high glucose-induced ICAM-1 expression through an osmotic effect in rat mesangial cells was PKC-NF-κB-dependent (15). The mechanism by which LY333531 ameliorates up-regulation of MCP-1 expression in diabetes is not well understood. Previous reports have demonstrated that NF-κB was involved in the induction of MCP-1 in mesangial cells cultured under high glucose (38). MCP-1 promoter and enhancer regions contain NF-κB binding sequences (39). A recent study demonstrated that high glucose rapidly activated NF-κB in mesangial cells through PKC and ROS (38). An in vitro study has shown that a PKC inhibitor and PKC depletion could significantly suppress high glucose-induced ROS generation as well as NF-κB activation, suggesting that PKC plays a role in HG-induced ROS generation, leading to NF-κB activation (40). Another report demonstrated PKC-dependent ROS generation in vascular cells cultured under high glucose (41). On the other hand, ROS could regulate the activation of PKC through redox changes in sulfhydryl groups of cysteine-rich regions of PKC or through activation of phospholipase D, leading to production of diacylglycerol. Studer et al. have shown that antioxidants effectively inhibited PKC activation in MC cultured under high glucose (42). More recently, a study by Nishikawa et al. also suggested the role of ROS in PKC activation in endothelial cells cultured under high glucose (43). To examine the role of PKC-β in the in vivo setting, we used the specific PKC-β isoform inhibitor LY333531, showing a reduction in MDA level and an increase in AOE as SOD, CAT, and GSH-PX activity in renal tissue and consequent MCP-1 expression in diabetic rats. The activity of PKC and expression of PKC-β were higher in diabetic rats compared with the control rats, which were substantially attenuated in diabetic animals that had received LY333531.

In summary, our data demonstrate that inhibition of PKC-β exerts anti-inflammatory effects by preventing upregulation of ICAM-1 and MCP-1 in the kidneys in diabetic rats. Our study describes a novel mechanism by which inhibition of PKC-β confers a renoprotective effect.

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