Angiotensin II Type 1 Receptor-Dependent Nuclear Factor-κB Activation-Mediated Proinflammatory Actions in a Rat Model of Obstructive Acute Pancreatitis

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Received April 29, 2007; accepted July 3, 2007

ABSTRACT

Angiotensin II is a key mediator of inflammation, and nuclear factor-κB (NF-κB) plays a critical role in various inflammatory diseases, including acute pancreatitis (AP). This study sought to elucidate the mechanism mediating angiotensin II involvement in angiotensin II type 1 (AT1) receptor-mediated NF-κB activation, and ultimately in proinflammatory actions of AP pathogenesis. A rat model of obstructive pancreatitis was induced by ligation of the common biliopancreatic duct. Pancreatic injury was determined by assessing pancreatic histology, myeloperoxidase activity, and serum interleukin-6. Losartan treatment also reduced AP-associated depletion of IκBα and elevation of phospho-NF-κB p65 protein expression as well as the enhanced nuclear κB binding activity and elevated levels of κB-related proteins. In addition, losartan treatment suppressed pancreatic glutathione and nitrotyrosine levels, which were consistent with decreased NADPH oxidase expression. These data provide substantial evidence that angiotensin II is involved in AT1 receptor-mediated NADPH oxidase-dependent NF-κB activation; thus, it might ultimately promote proinflammatory actions during AP pathogenesis.

Acute pancreatitis (AP) is a pathological state with various degrees of severity, ranging from edematous AP to hemorrhagic necrotic AP. The mortality rate, which approaches 20%, is closely associated with systemic complications, manifesting as acute respiratory distress syndrome and multiple organ dysfunction syndrome. An approximate 80% of cases can be etiologically determined, whereas 20% are considered idiopathic (UK Working Party on Acute Pancreatitis, 2005). Accumulating data suggest that the renin-angiotensin system (RAS) plays an important role in AP pathogenesis. During caerulein-induced pancreatitis, major components of a local pancreatic RAS were markedly up-regulated (Tsang et al., 2004a). Treatment with RAS blockers could ameliorate pancreatic oxidative stress and histological deterioration observed in experimental AP (Ip et al., 2003; Tsang et al., 2003). A specific antagonist for the AT1 receptor, 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt (C22H23ClN6O) (losartan), has been shown to protect against AP and its associated pulmonary injury (Tsang et al., 2004b; Chan and Leung, 2006). Of great interest in this context is the evidence that AT1 receptor antagonism decreases oxidative stress by reducing NADPH oxidase (Tsang et al., 2004b), which is a major source of reactive oxygen species (ROS). Notwithstanding the evidence of this beneficial effect, the mechanisms of the RAS blockade involvement in AP remain undefined. In addition, previous data were heavily derived from a caerulein-induced model of experimental AP, and they did not use more clinically relevant settings.

ABBREVIATIONS: AP, acute pancreatitis; RAS, renin-angiotensin system; AT, receptor, angiotensin II type 1 receptor; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; IκBα, inhibitory subunit α of NF-κB; IκBβ, inhibitory subunit β of NF-κB; CBPD, common biliopancreatic duct; ICAM, intercellular adhesion molecule; COX, cyclooxygenase; EMSA, electrophoretic mobility shift assay; MPO, myeloperoxidase; GSH, glutathione; IL, interleukin-1; EXP 3179, 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxaldehyde (C22H21ClN6O).
vant animal models such as obstruction-induced AP, which mimics clinical gallstone-obstruction AP (Chan and Leung, 2007).

Nuclear factor-κB (NF-κB) is a well-established transcription factor for an array of proinflammatory genes. It is a heterodimer of proteins belonging to the Rel family, including p50/p65 (NFκB1), p65 (RelA), p52 (NFκB2), and Rel B (Thompson et al., 1995). Inactive NF-κB is coupled to its inhibitory subunit (IκB), and it remains in the cytoplasm. Upon activation, IκB is phosphorylated, ubiquitinated, and subsequently degraded. Activated NF-κB can translocate into the nucleus and induce transcription of κB-related genes (Thompson et al., 1995; Flohé et al., 1997). Previous studies demonstrated that angiotensin II elicits proinflammatory actions via generation of ROS and thereby activates NF-κB in cells, such as fibroblasts, leukocytes, and adipocytes (Dandonu et al., 2003; El Bekay et al., 2003; Chen et al., 2004; Skurk et al., 2004; Brotzatki et al., 2005). Moreover, NF-κB has been shown to be activated in different animal models of AP, including caerulein-induced AP (Gukovsky et al., 1998) and taurocholate-induced AP (Vaquero et al., 2001).

In light of these prior findings, we hypothesized that up-regulation of a pancreatic RAS by means of enhancing the local generation of angiotensin II contributes to the AT1 receptor-dependent NF-κB activation-mediated proinflammatory actions during the course of AP. We tested this hypothesis by examining and comparing the effects of losartan, an AT1 receptor antagonist, on changes in NF-κB and its related proteins in a rat model of obstructive AP.

Materials and Methods

Animal and Experimental AP Model. Male Wistar rats (250–300 g) were obtained from the Laboratory Services Centre of The Chinese University of Hong Kong (Hong Kong, China). The experimental procedures were approved by the Animal Experimentation Ethics Committee of the Chinese University of Hong Kong (Ref. 04/036/ERG). They had free access to water and standardized rat chow, but they were fasted for 24 to 28 h before being subjected to the experiments. Obstruction pancreatitis was induced as described previously (Nathan et al., 2002; Barlas et al., 2004; Chan and Leung, 2007). In brief, the animals were anesthetized by injection (i.p.) with 2.5% sodium pentobarbital. The abdomens were opened via midline laparotomy, and the common biliopancreatic duct (CBPD) was doubly ligated at a site near the duodenal wall. We first performed a time course effects (3, 6, and 24 h) of ligation on protein expression of RAS components. From this study, and in accordance with previous reports, the animals were euthanized 6 h after the surgery (Nathan et al., 2002; Barlas et al., 2004). The animals in the control group received similar surgical manipulation with the exception of duct ligation. Animals in the losartan treatment group were subjected to intra gastric administration of losartan (0.3, 3, or 30 mg/kg) 1 h before surgery. Isovolumetric distilled water was given to animals in the nonligated control and no-drug AP groups. Blood was obtained by cardiac puncture, whereas pancreatic tissues were isolated and snap-frozen in liquid nitrogen for further analysis. Tissues for immunohistochemistry processing were isolated, fixed in 4% paraformaldehyde in phosphate-buffered saline, and embedded in paraffin for sectioning.

Western Blot Analysis. Pancreatic protein was extracted using CytoBuster Protein Extraction Reagent (Novagen, San Diego, CA). In brief, the sample was homogenized in CytoBuster Protein Extraction Reagent and centrifuged at 15,000 g for 15 min at 4°C. The supernatant was collected, and the protein concentration was quantified using commercially available Bradford reagent (Bio-Rad, Hercules, CA). Samples (40 g protein/lane) were subjected to SDS-polyacrylamide gel electrophoresis, and then they were transferred to polyvinylidene difluoride membrane for Western blot analysis. Antibodies against angiotensinogen as described previously (Leung et al., 1999), AT1 receptor (1:500; Santa Cruz Biotechnology, Inc., Santa Cruz, CA), IκBα (1:500; Santa Cruz Biotechnology, Inc.), IκBβ (1:500; Santa Cruz Biotechnology, Inc.), phospho-NF-κB p65 (1:500; Cell Signaling Technology Inc., Danvers, MA), NADPH oxidase p67 (1:500; Santa Cruz Biotechnology, Inc.), NADPH oxidase p22 (1:250; Santa Cruz Biotechnology, Inc.), intercellular adhesion molecule (ICAM)-1 (1:500; Seikagaku America, Rockville, MD), or cyclooxygenase (COX)-2 (1:500; Santa Cruz Biotechnology, Inc.), were incubated with the membrane overnight at 4°C. Bands were visualized with the appropriate horseradish peroxidase-linked secondary antibodies, and they were visualized by enhanced chemiluminescence with ECL kit (GE Healthcare, Little Chalfont, Buckinghamshire, UK). The intensity of the band was quantified using the FlouroChem8000 (Alpha Innotech, San Leandro, CA).

Preparation of Nuclear Extracts. Pancreatic nuclear protein for gel shift assay was extracted using methods described previously (Gukovsky et al., 1998; Vaquero et al., 2001) with minor modifications. In brief, the pancreatic tissue was homogenized in a hypotonic buffer, pH 7.9, containing 10 mM HEPES, 10 mM KCl, and 10 mM EDTA. Just before homogenization, the buffer was supplemented with phenylmethylsulfonyl fluoride and dithiothreitol to a final concentration of 1 mM each and with the protease-inhibitor cocktail from Sigma-Aldrich (St. Louis, MO). The homogenate was incubated on ice for 15 to 20 min. Igepal CA-630 (10%; Sigma-Aldrich) was added to a final concentration of 0.3% (v/v), and then the solution was briefly vortexed and allowed to sit on ice for 1 to 2 min. The nuclei were then collected by 30-s microcentrifugation. Nuclear protein was extracted from the pellet using hypertonc buffer, pH 7.9 (20 mM HEPES, 0.4 M NaCl, 1 mM EDTA, and 10% glycerol) supplemented with 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol, and the protease inhibitor cocktail (Sigma-Aldrich) for 1 h at 4°C on a rocking platform. The nuclear protein was obtained by microcentrifugation for 10 min at 4°C, and the clear supernatant (nuclear extract) was separated into aliquots and stored at −80°C. The protein content of the nuclear extract was determined using a protein assay (Bio-Rad).

Electrophoretic Mobility Shift Assay. Electrophoretic mobility shift assay (EMSA) was performed using a commercially available Gel Shift Assay System (Promega, Madison, WI). In brief, the nuclear extract (5 μg) or HeLa cell extract (positive control) was incubated with [32P]-labeled oligonucleotide probe (5'-AGT TGA GGC GAC TTT CCC AGG C-3') in the presence of binding buffer [4% glycerol, 1 mM MgCl2, 0.5 mM EDTA, 0.5 mM dithiothreitol, 50 mM NaCl, 10 mM Tris-HCl, pH 7.5, and 50 μg/ml poly(dI-dC)-poly(dI-dC)] at room temperature for 20 min. After the incubation, the DNA-protein complex was resolved by 4% nondenaturing polyacrylamide gel at 150 V. The gel was dried and exposed to X-ray film overnight at −80°C. The phosphorimaging was analyzed and quantified by FlouroChem8000 (Alpha Innotech).

Histology and Immunohistochemistry. Five micrometer-thick sections were collected from paraffin-embedded tissue, de-waxed, and rehydrated. For morphological study, the sections were stained with hematoxylin and eosin, and they were evaluated by observers who were blind to the identity of the sections. The degree of pancreatic injury is related to the enlargement of interlobular space (i.e., the degree of edema) and destruction of the histarchitecture of all or part of acini as described previously in our laboratory (Chan and Leung, 2006). For immunofluorescent staining, the slides were incubated with mouse anti-nitrotyrosine (1:100; Zymax, South San Francisco, CA), rabbit anti-p22 or anti-p67 (1:100; Santa Cruz Biotechnology, Inc.), together with goat...
anti-α-amylase (1:100; Santa Cruz Biotechnology, Inc.) antibodies overnight at 4°C, and then they were incubated with Cy3-anti-mouse or rhodamine-anti-rabbit and aminomethylcoumarin-antigoat secondary antibodies (Zymax). Images were then captured with a Leica digital camera (Leica, Wetzlar, Germany) mounted on a fluorescent microscope attached to a PC running Leica 50 software.

Biochemical and Other Assays. Plasma α-amylase, pancreatic myeloperoxidase (MPO) activity, and glutathione (GSH) levels were assessed using a previously described method (Tsang et al., 2003; Chan and Leung, 2006). Serum interleukin (IL)-6 and IL-1 were determined using commercially available enzyme-linked immunosorbent assay kits (BioSource International, Camarillo, CA). Pancreatic edema was expressed in terms of pancreatic-to-body mass ratio as described previously (Chan and Leung, 2006).

Statistical Analysis. All results are expressed as the means ± S.E.M. The vertical bars represent S.E.M. The absence of this vertical bar indicates that the S.E.M. is too small to be illustrated. Student’s t test and one-way analysis of variance were used to detect significant differences between two groups and three (or more) groups, respectively. p values less than 0.05 were considered significant in all cases.

Results

Effects of Obstructive AP on Protein Expression of RAS Components. We examined the expression of two key RAS components at protein levels in time course study: angiotensinogen (an indispensable element for a local RAS) and the AT1 receptor (by which most, if not all, of the actions of angiotensin II are mediated). Western blot analysis showed that CBPD ligation led to 2.7-, 3-, and 5-fold up-regulation of angiotensinogen protein levels at 3, 6, and 24 h, respectively (Fig. 1A). However, AT1 receptor levels did not differ between control and AP groups at any of these time points (Fig. 1B).

Determination of Effective Losartan Dose in Ameliorating Obstructive AP. The effects of three concentrations of losartan (0.3, 3, and 30 mg/kg) on pancreatic-to-body mass ratio, serum amylase, pancreatic MPO, and IL-6 were studied after 6-h CBPD ligation. These four parameters were markedly enhanced in animals with AP (Fig. 2). However, only pancreatic MPO and serum IL-6 exhibited a dose-dependent decrease after losartan treatment, with a significantly
effective dose at 30 mg/kg (Fig. 2, c and d). In contrast, histological evaluation showed that there is an enlargement in interlobular space and inflammatory cell infiltration in the pancreatic sections from AP group compared with that from control (Fig. 3); these observations indicate that CBPD ligation led to edema and inflammation, respectively. Interestingly, pancreatic tissues from the 30 mg/kg losartan treatment partially reversed the deleterious effects on histological assessment compared with the untreated AP group (Fig. 3). However, treatment of losartan at 30 mg/kg alone in control pancreas did not affect these parameters (data not shown).

**Effects of Losartan on IκBα, IκBβ, and Phospho-NF-κB Expression and Binding Activity.** To determine whether NF-κB is involved in proinflammatory actions, the inhibitory units IκBα and IκBβ and the activated form phospho-NF-κB p65 after 6-h CBPD ligation were examined by Western blot analysis. Neither AP induction nor losartan treatment affected IκBα protein levels (Fig. 4A). On the contrary, AP was associated with a marked depletion of IκBβ (i.e., approximately 27% of the control), which was significantly restored after losartan treatment (Fig. 4B). Phospho-NF-κB p65 protein levels were up-regulated by 16-fold in the untreated AP group, but they remained almost at control levels in losartan-treated AP animals (Fig. 4C). Our EMSA data further showed that AP resulted in enhanced DNA binding activity of nuclear extract, compared with nonligated controls, and this enhancement in DNA binding activity was attenuated by losartan treatment (Fig. 5).

**Effects of Losartan on GSH, Nitrotyrosine, and NADPH Oxidase.** The GSH assay results revealed that AP induction resulted in depletion of the protective cellular antioxidant GSH in pancreas. This deleterious effect was reversed by losartan treatment (Fig. 6). In keeping with the GSH data, nitrotyrosine expression (an oxidative stress marker) was significantly elevated in acinar cells from AP animals relative to controls, as demonstrated by double immunostaining (Fig. 7). On the other hand, enhanced immunoreactivity of nitrotyrosine by AP in pancreatic acinar cells was significantly decreased by losartan treatment (Fig. 7, C, F, and I).

To test whether this enhanced oxidative stress during AP might be due to up-regulation of NADPH oxidase, a major source of ROS, the expression levels of two NADPH oxidase

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**Fig. 2.** Dose-dependent effects of losartan on pancreatic-to-body mass ratio (a), serum amylase (b), pancreatic MPO activity (c), and plasma IL-6 level (d) 6 h after CBPD ligation. 0.3 mg/kg Los and 0.3 mg/kg losartan; 3 mg/kg Los and 3 mg/kg losartan; and 30 mg/kg Los and 30 mg/kg losartan. Results are expressed as means ± S.E.M. ***, p < 0.001 versus nonligated control. †, p < 0.05 versus no-drug AP. **, p < 0.01 versus no-drug AP.

**Fig. 3.** Representative diagram showing histological changes of pancreatic section from two microscopic fields (magnification, 200×) from control (A and B), 6-h CBPD ligation-induced AP (C and D), and 30 mg/kg losartan treatment + AP (E and F) groups.
isoforms, p67 and p22, were studied by Western blot analysis. We found that the protein levels of NADPH oxidase p67 and p22 were elevated during obstructive AP, reaching up to 7.2- and 3.9-fold of control levels, respectively. Losartan treatment greatly suppressed these NADPH oxidase p67 and p22 increases, by \( \frac{67}{100} \) and \( \frac{63}{100} \)%, respectively (Fig. 8).

To examine the potential source of NADPH oxidase, immunohistochemistry was performed to determine its precise cellular localization in the pancreas. In keeping with the results of Western blot (Fig. 8), immunoreactivity of p67 and p22 was more intense in obstruction-induced AP, reaching up to 7.2- and 3.9-fold of control levels, respectively. Losartan treatment greatly suppressed these NADPH oxidase p67 and p22 increases, by \( \sim 67 \) and \( \sim 63\% \), respectively (Fig. 8).

**Effects of Losartan on NADPH Oxidase Activity.**

Fig. 4. Effects of 30 mg/kg losartan on protein expression of IkBα (A), IkBβ (B), and phospho-NF-κB p65 (C) 6 h after CPBD ligation. Results are expressed as means ± S.E.M. *p < 0.05 versus nonligated control. **p < 0.001 versus nonligated control. ***p < 0.05 versus no-drug AP group. ****p < 0.001 versus no-drug AP group.

**Discussion**

Although previous investigations have demonstrated a protective effect of AT₁ receptor antagonism on caerulein-induced AP and its associated pulmonary injury, this is the first mechanistic study to report that angiotensin II may be involved in AT₁ receptor-dependent NADPH oxidase-dependent NF-κB activation and thus that this interaction may mediate proinflammatory actions during the course of AP. Previous studies have also shown the close linkage between angiotensin II and NF-κB in vitro (El Bekay et al., 2003; Skurk et al., 2004; Browatzki et al., 2005) as well as in vivo systems (Mori and Cowley, 2004; Bataller et al., 2005; Johar et al., 2006). Moreover, pharmacological inhibition or genetic deletion of the AT₁ receptor attenuates NF-κB activation during inflammatory disorders (Suzuki et al., 2001; Dandona et al., 2003; Liu et al., 2006). Thus, there is now a convergence of evidence consistent with our hypothesis that NF-κB may serve as the central executor in angiotensin II and/or AT₁ receptor-mediated inflammation during AP.

**Effects of Losartan on xB-Related Genes.**

The effects of losartan on xB-related genes, i.e., protein levels of ICAM-1 and COX-2 were assessed by Western blot analysis (Fig. 10). Ligation of the CPBD induced up-regulation of protein expression of ICAM-1 and COX-2 by 7- and 22-fold, respectively, and this up-regulation was attenuated by losartan treatment (Fig. 10, A and B). In contrast, AP induction also resulted in augmentation of serum IL-1, which was similarly attenuated by losartan treatment (Fig. 10C).

**Fig. 5.** Representative image showing the results from EMSA. Lane 1, nonligation control; lane 2, 30 mg/kg losartan treatment + AP group; lane 3, 6-h ligation CBPD-induced AP; lane 4, distilled water (negative control); and lane 5, HeLa cell extract from EMSA kit (positive control). Similar results were obtained from three independent experiments with different rats.

**Fig. 6.** Effect of 30 mg/kg losartan on pancreatic GSH levels 6 h after CPBD ligation. ***, p < 0.001 versus nonligated control. ***, p < 0.001 versus no-drug AP group.
Several proposed mediators could contribute to NF-κB activation, including tumor necrosis factor, phorbol myristic acetate, and oxidative stress. Among these, ROS, which can function as second messengers, were closely associated with NF-κB-mediated inflammation during AP pathogenesis. Oxidative stress-induced NF-κB activation has been demonstrated in a number of animal models of AP, including caerulein-induced AP (Gukovsky et al., 1998; Altavilla et al., 2003), taurocholate-induced AP (Vaquero et al., 2001), and obstruction-induced AP (Ramudo et al., 2005). In the present study, it was clear by the reduced levels of GSH and nitrotyrosine that the pancreatic tissues afflicted with AP were under oxidative stress; these changes could be reversed by losartan treatment. It is possible that AT1 receptor-induced ROS may facilitate degradation of NF-κB inhibitory subunits and thereby lead to activation of NF-κB.

The immediate question to be addressed is this: what is the link between AT1 receptor and oxidative stress? In this context, the membrane-bound enzyme NADPH oxidase accounts for angiotensin II-induced oxidative stress. Indeed, angioten-
sin II could activate the NADPH oxidase system via AT₂ receptors (Griendling et al., 1994; Rajagopalan et al., 1996). Once activated, NADPH oxidase enhances the rate of conversion of molecular oxygen (O₂) to superoxide free radical (O₂⁻), which leads to oxidative stress (Griendling et al., 2000). Our Western blot results revealed that the expression of NADPH oxidase p67 and p22 was elevated during obstructive AP and that these effects were antagonized by losartan treatment. These results indicate that up-regulation of NADPH oxidase depends on AT₂ receptor activation during obstructive pancreatitis. In keeping with our findings, expression and activity of NADPH oxidase subunits were augmented in pancreatic acinar cells of cerulein-stimulated pancreatitis model (Yu et al., 2005). Interestingly, our results from immunohistochemistry coupled with double staining indicate that one of the potential sources of NADPH oxidase during obstructive AP was due, at least partly, to the pancreatic acinar cells. However, we cannot rule out the other cellular sources of NADPH oxidase such as the neutrophil (Babior, 1999). In this respect, infiltrated neutrophils may play a crucial role in AP pathophysiology. Future investigations need to be performed so as to determine the proportion of NADPH oxidase activation in acinar cell and neutrophil during pancreatic inflammation.

In the present study, the actual proinflammatory actions of NF-κB were reflected to some extent by changes in critical κB-related proteins: serum IL-1 and pancreatic ICAM-1 as well as COX-2 protein expression. Both ICAM-1 and COX-2 have been shown to be up-regulated during experimental AP; and blockade of ICAM-1 or genetic deletion of COX-2 resulted in attenuation of pancreatitis (Zaninovic et al., 2000; Song et al., 2002). The suppressive effect of losartan on these κB-related mediators prompted us to speculate that AT₂ receptor blockade in an early stage of AP could inhibit NF-κB activation-dependent proinflammatory actions observed in AP.

It is worthwhile to note that a disparity between protein
expression levels of inhibitory subunits IκBα and IκBβ was observed during the course of AP in the present study. A similar observation was reported previously with caerulein-induced AP (Gukovsky et al., 1998). This disparity might be due to a difference in the kinetics of the two inhibitory units. The IκBα gene is under the control of a κB binding region, whereas the IκBβ gene does not contain any κB motif; thus, it is not controlled by NF-κB (Thompson et al., 1995; Han and Brasier, 1997; Gukovsky et al., 1998). Upon activation and nuclear translocation, NF-κB transcribes an array of κB-related genes, including IκBα. Thus, IκBα can be resynthesized so quickly that its levels remain unchanged throughout the induction period. Thus, the disproportionate depletion of IκBβ protein observed during AP and the discrete pattern of the two inhibitory subunits observed in the present study may be due to the direct induction of IκBα, but not IκBβ, by NF-κB.

One of the limitations of the present investigation is to use a single agent, the AT1 receptor antagonist losartan, to inhibit the RAS. The beneficial effects observed might be due to the off-target actions of losartan alone or to its metabolites. Actually, the active metabolite of losartan, EXP 3179, could have AT1 receptor-independent effects, including COX-2 inhibition and ROS scavenging ability (Sadoshima, 2002). Moreover, EXP 3179 itself was shown to suppress the prostaglandin-released ICAM-1 and COX-2 expression (Krämer et al., 2002). Losartan and EXP 3179 were also shown to serve as an agonist of peroxisome proliferator-activated receptor γ, which negatively regulates the inflammatory responses (Marshall et al., 2006; Schupp et al., 2006). Taken together, losartan might exert anti-inflammatory responses on the obstruction AP in an AT1 receptor-independent manner. Further investigation should be carried out to investigate the AT1-independent pathway. In this regard, it would be worth studying the effects of other RAS blockers, such as angiotensin-converting enzyme and renin inhibitor, on the experimental AP to strengthen the role of RAS in AP pathophysiology.

In conclusion, the present study provides proof of principle that endogenous angiotensin II could be involved in AT1 receptor-dependent NF-κB activation and that it affects proinflammatory processes in an animal model of obstructive AP. Our findings further suggest that AT1 receptor blockade, which is AP model nonspecific, could serve as a potential therapeutic approach to clinical AP.

Acknowledgments
Losartan was generously provided by Merck (Whitehouse Station, NJ).

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