NMDA receptor blocker ameliorates ischemia-reperfusion-induced renal dysfunction in rat kidneys

Chih-Ching Yang,1,2,3* Chiang-Ting Chien,4* Ming-Hsiou Wu,5 Ming-Chieh Ma,6 and Chau-Fong Chen1

1Department of Physiology, College of Medicine of National Taiwan University; 2School of Medicine, National Yang-Ming University; 3Taipei City Hospital-Heping Branch; Departments of 4Medical Research and 5Internal Medicine, National Taiwan University Hospital and College of Medicine of National Taiwan University; and 6School of Medicine, Fu-Jen Catholic University, Taipei, Taiwan

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Yang C-C, Chien C-T, Wu M-H, Ma M-C, Chen C-F. NMDA receptor blocker ameliorates ischemia-reperfusion-induced renal dysfunction in rat kidneys. Am J Physiol Renal Physiol 294: F1433–F1440, 2008. First published February 13, 2008; doi:10.1152/ajprenal.00481.2007.—N-methyl-D-aspartate (NMDA) receptor activated by glutamate/glycine is located in the kidneys. The NMDA receptor subunit NR1 is increased in damaged renal tissue. This study explored the role of NMDA receptors in ischemia-reperfusion-induced renal dysfunction in rats. With Western blot analysis and renal functional assay, NMDA receptor expression was evaluated, as well as its functional role in female Wistar rat kidneys after 45 min of unilateral ischemia followed by 24 h of reperfusion. The effects of intrarenal NMDA receptor agonist and antagonist on renal blood flow (RBF), glomerular filtration rate (GFR), urine volume, and blood pressure and renal vasodilation in rat kidneys were evaluated. Ischemia-reperfusion-induced renal dysfunction was assessed using tissue and functional methods. The NMDA receptor blocker D-AP-5 completely abolished NMDA-induced renal dysfunction. D-AP-5 treatment significantly ameliorated ischemia-reperfusion-induced glomerular and tubular dysfunction. NMDA antagonists 2-amino-5-phosphonopentanoic acid (D-AP-5) treatment completely abolished NMDA-induced renal dysfunction. D-AP-5 treatment significantly ameliorated ischemia-reperfusion-induced glomerular and tubular dysfunction by restoring decreased GFR, UNaV, and UNaV levels. Ischemia-reperfusion upregulates renal NMDA NR1 receptor expression, leading to reduced glomerular and tubular function in the kidneys. The NMDA antagonist can ameliorate ischemia-reperfusion-induced renal dysfunction.

ischemia-reperfusion; kidney; glutamate; renal function

GLUTAMATE HAS BEEN CHARACTERIZED as an excitatory neurotransmitter in the mammalian central nervous system. It can bind to ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors to mediate synaptic transmission and integrate calcium-dependent type I nitric oxide synthase (NOS-I) (5, 16). Among these functions are the suppression of peripheral sympathetic reflex discharges (28, 37) and cerebral vasodilation (49).

The NMDA receptor is composed of various subunits, including NR1, NR2A, NR2B, NR2C, and NR2D (2, 24, 29). The NR1 subunit is the main subunit of the NMDA receptor (2, 24, 29) and is essential for channel activity, whereas the NR2 subunits confer modulatory properties (50). The AMPA receptor consists of different subunits, GluR1-4 and GluR2/3, which are essential for channel function (37). KA1 and KA2 subunits are thought to participate in the expression of a functional kainate receptor along with other subunits, such as GluR5-7 (37). On the other hand, mGluRs are coupled G protein and group I receptors (mGluR1) acting via Gq/11 to activate the phospholipase C pathway, while groups II (mGluR2/3) and III (mGluR4, 6, 7, and 8) receptors act via Gs to inhibit adenylyl cyclase (7, 12). All three groups are implicated in the modulation of synaptic transmission (15, 19).

The presence of NMDA receptors has been found in extraneuronal tissues, including pancreatic β cells, the male lower urogenital tract, kidneys, lymphocytes, megakaryocytes, and cerebral microvasculature (10, 11, 21, 22, 26, 27, 34, 51, 57). Although NMDA receptor activation can stimulate NO release from aortic rings (23), there is scant evidence regarding its physiological function in extraneuronal tissues, especially in the kidneys, where systemic infusion of L-glycine causes NO-dependent renal vasodilation (54). NOS-I colocalizes with NMDA receptor in the brain and is prominently expressed in renal macula densa cells (14), where it exerts a tonic vasodilatory effect on glomerular microvasculature by modulating tubuloglomerular feedback (25, 57).

In gentamicin nephrotoxicity, a high expression of NMDA receptors has been demonstrated in the renal proximal tubules (6). The application of an NMDA receptor antagonist efficiently ameliorates gentamicin nephrotoxicity (6) and paraquat- or xanthine oxidase-induced lung injury (45), suggesting a detrimental response caused by NMDA receptor activation in extraneuronal tissues. Overstimulation of NMDA receptors can modulate glomerular postsynaptic neurotransmission by generating Ca2+ channel openings, and by overloading (3, 36, 38) and excessive reactive oxygen species generation (8, 9). Ischemia, followed by reperfusion, impairs kidneys and contributes to renal dysfunction (1–4). Ischemia-reperfusion or hypoxia-
reoxxygenation injury also evokes burst amounts of reactive oxygen species and Ca\(^{2+}\) overload in damaged renal tubules, triggering the entry of these tubular cells into apoptotic and necrotic cell death, and subsequently, to renal dysfunction (1, 4, 13). We speculate that ischemia-reperfusion injury may lead to NMDA receptor activation or upregulation in damaged kidneys.

In this study, we aimed to determine the expression of several types of iGluRs and mGluRs in the kidneys and explore whether ischemia-reperfusion affected NMDA NR1 and other types of iGluR and mGluR expression in rat kidneys. We also examined the possible functional role of NMDA and glutamate receptors by the application of the NMDA receptor agonist and antagonist D-2-amino-5-phosphonopentanoic acid (D-AP-5) on renal hemodynamic and excretory responses to ischemia-reperfusion injury.

MATERIALS AND METHODS

Surgery. Female Wistar rats, weighing 200–250 g, were housed at the Experimental Animal Center, National Taiwan University, at a constant temperature and with consistent light cycle (light from 0700 to 1800 h). The animal care and experimental protocols adhered to the guidelines of the National Science Council of Republic of China (NSC 1997) and were approved by the Laboratory Animal Care Committee of the National Taiwan University College of Medicine.

Induction of unilateral renal ischemia. Under temporary anesthesia, the left renal artery was clamped with a small vascular clamp for induction of total ischemia in the kidneys (8). Briefly, all of the rats were anesthetized with a combination of intraperitoneal (ip) ketamine (50 mg/kg body wt) and pentobarbital sodium (15 mg/kg body wt), and a midline abdominal incision was made. The rats were randomly divided into two groups: 45-min unilateral renal ischemia (RAO) and sham-operated (control; animals underwent similar operative procedures without occlusion of the renal artery). Reperfusion was initiated by removal of the clamp for 24 h. Following ischemia, the rats were allowed to recover for 24 h reperfusion in an individual metabolic cage.

On the day of the experiments (after 24-h reperfusion), the rats were anesthetized and underwent a tracheotomy. Catheters were placed in the left carotid artery for blood sampling and for continuous measurement of the systemic arterial blood pressure (ABP), which was recorded on a Gould polygraph (RS 4300, Valley View, OH) with a transducer (P23 ID; Gould-Statham, Oxnard, CA). Another PE-50 catheter was inserted into the left femoral vein for anesthetic supplement and blood administration. The rat was then placed on its right side, and the left kidney was exposed via a flank incision and dissection from the surrounding tissue (35). For intrarenal arterial infusion, the left renal artery was cannulated with PE-10 tubing from the left femoral artery via the aorta. The left ureter was cannulated with PE-10 tubing for urine collection from the left kidney.

Assessment of renal function. For assessment of glomerular filtration rate (GFR), a sustained infusion of saline (1.2 ml/h in total), which contained Inutest (Laevosan-Gesellschaft), was given simultaneously from the femoral vein (0.72 ml/h) and renal artery (0.48 ml/h) with a transducer (P23 ID; Gould-Statham, Oxnard, CA). Another PE-50 catheter was inserted into the left femoral vein for anesthetic supplement and blood administration. The rat was then placed on its right side, and the left kidney was exposed via a flank incision and dissection from the surrounding tissue (35). For intrarenal arterial infusion, the left renal artery was cannulated with PE-10 tubing from the left femoral artery via the aorta. The left ureter was cannulated with PE-10 tubing for urine collection from the left kidney.

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transferred to nitrocellulose membranes (Amersham-Phar-macia, Buck-
tingham, UK) as described previously (8, 18). After blocking, the
membranes were incubated overnight at 4°C with rabbit anti-NR1
receptor (1:500, Novus Biologicals, Littleton, CO), anti-NR2C recep-
tor (also known as NMDAe3; H-80, 1:400, Santa Cruz Biotechnology,
Santa Cruz, CA), rabbit polyclonal anti-Glu2/3 receptor antiserum
(1:500, Chemicon, Temecula, CA), goat polyclonal anti-KA1 anti-
sерum (1:500, Santa Cruz Biotechnology), rabbit polyclonal anti-
mGluR1 (1:1,000, Upstate Biotechnology, Milan, Italy), and mono-
clonal mouse antimouse β-actin (Sigma, St. Louis, MO).

After washing, the membranes were incubated for 1 h at room
temperature with either horseradish peroxidase (HRP)-conjugated
goat anti-rabbit IgG (Vector, Burlingame, CA) or HRP-conjugated
goat anti-mouse IgG (Lenico, St. Louis, MO) as appropriate. These
were washed, and the bound antibody was visualized by using a
commercial 3,3′-diaminobenzidine peroxidase substrate kit (Vector).

The densities of the bands with appropriate molecular masses were
determined semiquantitatively by densitometer using an image-anal-
ysis system (Alpha Innotech, San Leandro, CA).

Data analysis. The data are expressed as means ± SE. Statistical
analysis was performed using the Newman-Keuls test of analysis of
variance for multiple comparisons. A significance level of 5% was
adapted.

RESULTS

NR1 and AMPA GluR2/3 are abundant in normal kidneys.

To assess the role of the NMDA receptor in sham control and
postischemic kidneys, NMDA subunit NR1 protein expression in
kidneys of sham control (n = 5) was first measured, followed by ischemia-reperfusion (n = 5) by Western blot
analysis. NR1 protein abundance was significantly higher in
the renal outer medulla of the sham control kidneys compared
with the cortex and inner medulla (Fig. 1). NR1 receptor
protein was expressed in the membrane protein fraction of
brush border and glomeruli (Fig. 1A). NR1 receptor protein
was homogenously distributed in the cortex, inner medulla, and
outer medulla (n = 3), but non-NMDA kainate receptor KA1
and mGluR1 expression was only sparsely detected (n = 3)
(Fig. 1D).

Ischemia-reperfusion enhanced NR1 in the cortex and inner
and outer medulla. Because histological changes and glomer-
ular tubularization at the glomerulotubular junction have been
described in ischemia-reperfusion-induced acute kidney injury
(24), these changes might have affected the integrity of the
isolated glomeruli and brush-border membrane. Therefore,
NR1, NR2C, and GluR2/3 expression in the cortex, medulla,
and pelvis was evaluated in postischemic kidney followed by
24 h of reperfusion. In response to ischemia-reperfusion, NR1
protein abundance was significantly increased in postischemic
kidneys within the renal cortex, medulla, and pelvis (Fig. 2).
However, NR2C and GluR2/3 protein expression in these areas
was not significantly affected by ischemia-reperfusion.

We also found that ischemia-reperfusion significantly in-
creased NMDA NR1 receptor expression as indicated by den-
sity units in the cortex (0.57 ± 0.15), inner medulla (0.78 ±
0.11), and outer medulla (1.39 ± 0.19) of postischemic kidneys
compared with the respective areas (0.04 ± 0.01, 0.06 ± 0.01,
and 0.8 ± 0.08 in the cortex, inner medulla, and outer medulla,
respectively) of sham control kidneys (Fig. 3).

NMDA agonist dose dependently decreased renal parameters
in sham control kidneys. As shown in Fig. 4, intrarenal
arterial infusion of an NMDA agonist (10, 100, 1,000
µg·min⁻¹·h⁻¹) dose dependently decreased GFR and UV, as
well as UNaV and UKV, in normal (control) kidneys. Analysis by
one-way ANOVA revealed that even though the mean ABP and
RBF were not changed in sham control kidneys after they re-
ceived the intrarenal NMDA agonist vs. sham controls without
NMDA treatment, the GFR decreased from 1.1 ± 0.1 to 0.42 ±
0.04 ml·min⁻¹·g⁻¹ after receipt of the intrarenal NMDA agonist
and returned to the original level after NMDA infusion was
stopped. UV (from 7.1 ± 0.6 to 5.2 ± 0.5 µL·min⁻¹·g⁻¹), UNaV
(from 7.4 ± 1.0 to 4.1 ± 0.7 µL·min⁻¹·g⁻¹), and UKV (from
30 ± 2 to 20 ± 4 µL·min⁻¹·g⁻¹) decreased during infusion of the
intrarenal NMDA agonist in a dose-dependent manner.

Fig. 1. Western blot analysis displays the differential expression of NMDA receptors (functional subunit NR1) in various renal tissues. A: concentration-
dependent protein expression of NR1 NMDA receptors was illustrated in different areas of the rat kidneys. NR1 protein is primarily expressed in the outer
medulla (OM), but is little expressed in the cortex (C) and inner medulla (IM). B: NR1 receptor expressed in membrane protein fraction of brush border (BBM)
of the proximal tubules, glomeruli (Glo), and brain cortex (BC). The expression of other components of glutamate receptors in the rat kidney is shown. C: GluR2/3 protein belonging to AMPA receptors is expressed in the C, IM, and OM compared with positive control of brain cortex (BC). mGluR1 is not detected in C, IM, and
OM in the rat kidney.
NMDA antagonist D-AP-5 ameliorated ischemia-reperfusion-induced renal dysfunction. The results of GFR, renal excretory response, and renal hemodynamic analyses are presented in Figs. 4 and 5. Rats with acute renal failure induced by temporary unilateral renal ischemia for 45 min showed significantly decreased GFR (0.71 ± 0.06 in postischemic kidneys vs. 1.10 ± 0.11 ml·min⁻¹·g⁻¹ in controls) and RBF (1.2 ± 0.3 in postischemic kidneys vs. 2.5 ± 0.4 ml·min⁻¹·g⁻¹ in controls), indicating acute renal insufficiency. The values of UV (12.1 ± 1.1 in the postischemic kidney vs. 7.1 ± 0.6 µl·min⁻¹·g⁻¹ in controls) and UNaV (14.1 ± 2.4 in the postischemic kidney vs. 7.4 ± 1.0 µl·min⁻¹·g⁻¹ in the control kidney) were significantly increased 24 h after renal ischemia.

The effects of an NMDA receptor antagonist on intrarenal NMDA receptor expression in the postischemic kidney subjected to 45-min renal ischemia followed by 24-h reperfusion were evaluated. Injured kidneys were treated by continuous intrarenal arterial infusion of D-AP-5 (n = 6), an effective NMDA receptor antagonist, or an inactive NMDA receptor antagonist of L-AP-5 (n = 6). In the ischemia-reperfusion kidney, treatment with intrarenal NMDA antagonists D-AP-5 and L-AP-5 did not affect mean ABP and RBF. Pretreatment with D-AP-5 completely abolished intrarenal NMDA-decreased GFR, UV, UNaV, and UKV, but inactive controls, indicating acute renal insufficiency. The values of UV (12.1 ± 1.1 in the postischemic kidney vs. 7.1 ± 0.6 µl·min⁻¹·g⁻¹ in the control kidney) and UNaV (14.1 ± 2.4 in the postischemic kidney vs. 7.4 ± 1.0 µl·min⁻¹·g⁻¹ in the control kidney) were significantly increased 24 h after renal ischemia.
Fig. 5. Intrarenal arterial infusion of d-2-amino-5-phosphonopentanoic acid (D-AP-5) blocks the NMDA-mediated renal functional changes in the post-ischemic kidney. Intrarenal arterial administration of ineffective enantiomer [2 mg l-2-amino-5-phosphonopentanoic acid (L-AP-5); in 50 ml] before infusion is ischemic kidney. Intrarenal arterial administration of ineffective enantiomer [2 (D-AP-5) blocks the NMDA-mediated renal functional changes in the post-ischemia-reperfusion significantly (*P < 0.05) reduced GFR, UV, UNaV, and UKV to the control level of both Sham and IR kidneys. These meant that NMDA receptor inhibition blocked the upregulation in NMDA NR1 expression-mediated functional changes in the postischemic kidney. After D-AP-5 infusion was stopped, the increased GFR, UV, UNaV, and UKV levels returned to their respective control levels.

DISCUSSION

The present study demonstrates the distribution and function of the NMDA NR1 subunit in kidneys subjected to ischemia-

Fig. 6. Renal functional and excretory responses to NMDA receptor blocker D-AP-5 between sham (Sham) and IR kidneys. IR significantly reduced GFR and increased UV and UNaV. Intrarenal arterial infusion of D-AP-5 significantly increased GFR, UV, UNaV, and UKV in the Sham and IR kidneys compared with the respective control value. The increments in UV and UNaV due to D-AP-5 infusion (NMDA receptor inhibition) in the IR kidneys were significant higher than those of Sham kidneys except GFR and UKV. In the recovery stage, stopped D-AP-5 infusion returned the increments of GFR, UV, UNaV, and UKV to the control level of both Sham and IR kidneys. *P < 0.05 Sham vs. IR group. †P < 0.05 compared with respective control value of the Sham or IR kidney.
reperfusion injury. The results show that NMDA receptor NR1 protein is primarily detectable in the outer medulla of the kidneys and more specified in the cortical brush-border membrane and glomeruli. NR2C protein, on the other hand, is sparsely detected in the cortex, medulla, and pelvis. GluR2/3 protein is homogenously displayed in the cortex and inner and outer medulla, while KA1 and mGluR1 were sparsely detected in these areas. Ischemia-reperfusion injury significantly enhances renal NMDA receptor NR1, but not NR2C and GluR2/3, expression. Intrarenal arterial NMDA infusion gradually decreases GFR and UV, as well as \( \text{UNaV} \) and \( \text{UKV} \), in the control and ischemia-reperfusion kidneys. Pretreatment with the NMDA antagonist D-AP-5 completely abolishes the intrarenal NMDA-induced renal dysfunction in control and ischemia-reperfusion kidneys. Intrarenal arterial infusion of D-AP-5 significantly increased GFR and renal excretion in both sham control and ischemia-reperfusion kidneys. However, the increments due to D-AP-5 in the ischemia-reperfusion kidneys were significantly higher than those of the controls, except \( \text{UKV} \).

During the stage of prolonged ischemia during surgery or organ harvest for renal transplantation, hypoxia and the subsequent reperfusion can initiate \( \text{Ca}^{2+} \) overload and burst amounts of reactive oxygen species, triggering a cascade of apoptosis and necrosis (1, 4, 13, 44, 46, 53). The spectrum of biochemical and physiological renal abnormalities includes reduced GFR due to glomerular damage and impaired tubular reabsorption function, such as increased urine \( \text{H}_{2}\text{O} \) and sodium fractions (55). These altered parameters are consistent with our present findings. In most animal models of ischemia-reperfusion, it is the S3 segment of the proximal tubule in the outer strip of the outer medulla, and not the medullary thick ascending limb that is most susceptible to ischemic injury (20, 40, 48). The severity of damage in the proximal tubule and collecting duct in posts ischemic kidneys plays a critical role in the impairment of urinary concentration encountered in oliguric, maintenance, and polyuric phases of experimental ischemia-induced acute renal failure. This is likely due to ischemic-related reductions in microvascular blood flow and oxygen delivery to the outer medulla at a time when cortical blood flow is returned to near-normal levels. In addition, S3 segments have a limited ability to undergo anaerobic metabolism (i.e., glycolysis).

In the present study, NMDA receptor activation may also provide a death pathway in ischemia-reperfusion kidneys because an upregulation in NMDA NR1 receptor expression is noted in the outer medulla, brush-border membrane, and glomeruli. Previous results illustrate that glutamate-gated NMDA and non-NMDA receptors are important routes in mediating NF-\( \kappa \)-B activation during brain ischemic injury. Active NF-\( \kappa \)-B may, in turn, lead to excitotoxin-induced cell death (31). Moreover, overstimulation of NMDA receptors modulates glutamate postsynaptic neurotransmission by generating \( \text{Ca}^{2+} \) channel openings, and overloaded (3, 36) and excessive reactive oxygen species generation (8, 9) may participate in ischemia-reperfusion cell death. Leung et al. (30) have indicated that NMDA receptor NR1 subunit expression is increased in gentamicin-treated rats, and this receptor likely mediates cell damage via the endothelin-endothelin type B receptor-nitric oxide pathway. NMDA antagonism ameliorates renal damage after exposure to short-term gentamicin. Previous studies have shown that glutamate (10 or 100 nmol), NMDA, and AMPA, by microinjections into the median preoptic nuclei or nucleus of the tractus solitarius of conscious rats, elicited systemic and hemodynamic effects consisting of increased blood pressure and constriction of renal blood vessels (41, 47). In contrast, Deng et al. (13) demonstrated the presence of renal NMDA receptors and observed significant functional effects of inhibiting NMDA receptors in the kidneys that are not related to central nervous effects. Inhibiting these receptors by an NMDA calcium channel blocker (75 mg/kg MK-801 ip) or a glycine binding to NMDA inhibitor (30 mg/kg 5,7-dichlorokynurenic acid ip) causes marked renal vasoconstriction and a reduction in RBF. The RBF/GFR response to one of the normal agonists, glycine, which normally increases RBF, is nearly abolished in rats pretreated with two different types of NMDA receptor antagonists (57).

In the kidneys, systemic infusion of l-glycine causes NO-dependent renal vasodilation (32). NOS-I, colocalized with the NMDA receptor, is prominently expressed in renal macula densa cells (14), where it exerts a tonic vasodilatory effect on the glomerular microvasculature by modulating tubuloglomerular feedback (25, 57). In the present study, however, the use of local, intrarenal arterial administration of an NMDA agonist reduces GFR, UV, \( \text{UNaV} \), and \( \text{UKV} \) but has no effect on blood pressure and RBF. This discrepancy may be due to the fact that the systemic effect of NMDA by the intravenous or intraperitoneal route is the suppression of central and peripheral sympathetic reflex discharges (28, 37), possibly including renal sympathetic nerve activity. On the other hand, an NMDA agonist may have a direct effect on NMDA receptors located in the glomeruli to affect GFR. However, the detailed mechanism needs to be further investigated.

Taken together, the NMDA NR1 subunit is abundant in the outer medulla, cortical brush-border membrane, and glomeruli. Ischemia-reperfusion injury enhances NRI expression in the outer medulla, a major damaged area after ischemia-reperfusion. An intrarenal NMDA agonist significantly reduces glomerular and tubular function. Glomerular and tubular dysfunction, after exposure to ischemia-reperfusion injury, can be ameliorated by pretreatment with the NMDA receptor blocker D-AP-5, which is suggestive of a definitive role for the NMDA receptor in renal injury.

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