Mechanosensitive N-Methyl-d-Aspartate Receptors Contribute to Sensory Activation in the Rat Renal Pelvis

Ming-Chieh Ma, Ho-Shiang Huang, Yih-Sharng Chen, Shang-Hsing Lee

Abstract—The N-methyl-d-aspartate (NMDA) subtype of the ionotropic glutamate receptor is found in the periphery. The present study tested whether NMDA receptors (NMDARs) are present in the ends of afferent renal nerves in the renal pelvis, an area concerned mainly with transmitting sensation and the reflex regulation of body fluid. The main NMDAR subunit, NMDA$_{	ext{1}}$, was found to be more abundant in the renal pelvis than the renal cortex and medulla, and was mainly colocalized with the pan-neuronal marker PGP9.5 or the sensory nerve marker, the neurokinin-1 receptor. However, NMDA$_{	ext{1}}$ mRNA was undetectable, suggesting that it might be synthesized outside the renal pelvis. Intrarenal arterial administration of the specific ion channel blocker (+)-MK-801, but not the inactive enantiomer (−)-MK-801, decreased urine output and sodium excretion. High doses of (+)-MK-801 also caused regional vasoconstriction in the renal cortex, as determined by laser-Doppler flowmetry. Intrapelvic administration of the NMDAR ligand D-serine caused a dose-dependent increase in substance P (SP) release and afferent renal nerve activity, but had no effect on arterial pressure. The D-serine–induced sensory activation and SP release were abrogated by (+)-MK-801, the SP receptor blocker L-703,606, or dorsal rhizotomy. Increasing intrapelvic pressure resulted in an increase in afferent renal nerve activity and a diuretic/natriuretic response. Interestingly, these effects were attenuated by prior administration of (+)-MK-801. These results indicate that NMDAR-positive sensory nerves are present in the renal pelvis and contribute to the renorenal reflex control of body fluid. (Hypertension. 2008;52:938-944.)

Key Words: renal nerves • mechanoreceptors • kidney • reflex • diuresis • natriuresis

Mechanosensation is an important mechanism of signal transduction that mediates a number of biological processes ranging from the maintenance of cell volume to blood pressure regulation.1–2 Mechanically stimulating renal receptors through an increase in intrapelvic pressure (IPP) causes the release of sensory neuropeptides, such as substance P (SP), with consequent activation of afferent renal nerves.3–10 Increases in afferent renal nerve activity (ARNA) evoke an inhibitory renorenal reflex, which causes diuresis and natriuresis as a result of a reflex withdrawal of efferent renal sympathetic nerve activity.3–10 This reflex is seen not only when stimuli are directly applied to the kidney, but also during acute fluid expansion.8–10 Enhanced ARNA coincides with the increased IPP seen in association with extracellular volume expansion, indicating that an important role of ARNA is to sense the increased hydraulic pressure that occurs during massive urine formation. Intriguingly, defects in components of the SP system that cause poor sensory ability have been noted in a number of different animal models associated with fluid retention.4–10

Previous studies have shown that glutamate receptors are present in the peripheral tissues.11 The main subunit of the N-methyl-d-aspartate (NMDA) receptor, NMDA$_{	ext{1}}$, is present in the rat kidney.11–14 Activation of NMDARs by glycine evokes renal vasodilatation, which can be blocked by the specific receptor antagonist MK-801.13,14 Interestingly, inhibition of nitric oxide synthase (NOS) blocks NMDAR-mediated renal vasodilatation,15 suggesting that the receptor in the kidney is similar to that found in the central nervous system which induces Ca$^{2+}$ influx and NOS activation. These results clearly reveal the important role of the NMDAR in the regulation of renal function. However, it is not known whether NMDARs affect renal sensory responses.

There is also evidence for a role of NMDARs in mechanical distention in internal organs, such as the stomach and colon.16,17 Furthermore, NMDARs in the Merkel cells of skin also contribute to the perception of mechanical stimuli during tactile sensation.18

Because of the existence of the NMDAR in the kidney and its unique role in sensing mechanical stimuli, we examined whether it is present in the renal pelvis and whether it contributes to the regulation of body fluid balance via the reflex function of afferent renal nerves. Understanding the role of NMDARs in the renal sensory response may help in...
eliciting the molecular mechanism associated with the pathogenesis of fluid retention, such as hypertension, and provide new therapeutic targets.

**Methods**

**Animals**

Female Wistar rats (Laboratory Animal Center, National Taiwan University, Taipei, Taiwan) weighing 200 to 220 g, were used. The experimental protocols were approved by the Institutional Animal Care and Use Committee.

**Detection of NMDAζ1 and Serine Racemase in Renal Tissues**

Rats were anesthetized with pentobarbital sodium (60 mg kg⁻¹, IP) and the kidneys removed after transcardial perfusion as described previously.³,⁹

Western blotting was performed using antibodies (Santa Cruz) against rat NMDAζ1 (1:1000), serine racemase (SR) (1:1000), or actin (1:2000) as described previously.³,⁸–¹⁰ The negative control was staining with primary antibody preincubated with specific blocking peptide (Santa Cruz).

Semiquantitative RT-PCR²⁰ was used to detect NMDAζ1 and SR mRNA using the appropriate primers. Details are available in the data supplement available online at http://hyper.ahajournals.org.

Immunohistochemistry was used to determine the intrarenal distribution of NMDAζ1, and indirect immunofluorescence was used to study the colocalization of NMDAζ1, PGP9.5, and the neurokinin-1 receptor (NK-1R) and the presence of SR in the renal pelvis as described previously.³,¹⁵

**Intrarenal Effects of NMDAR Inhibition**

Rats were anesthetized and cannulated as described previously.³ A PE-10 catheter with a fine tip was inserted into the left renal artery via the abdominal aorta and left femoral artery for intrarenal arterial (i.r.a.) infusion at a rate of 0.48 mL h⁻¹. The left ureter was cannulated near the pelvis with a combined PE-10/50 catheter to allow renal pelvic perfusion, collection of effluent for SP assay, and recording of the IPP.³

Raising the IPP to 10, 20, or 50 mm Hg elicits renorenal reflexes.³,⁸–¹⁰

Sensory responses were also examined during 5 minutes of intrapelvic infusion of 100 μg mL⁻¹ of D-serine plus i.r.a. infusion of the SP receptor blocker L-703,606 (0.5 mg min⁻¹ kg⁻¹, i.r.a.) being infused throughout.

Sensory responses were also examined during 5 minutes of intrapelvic infusion of 100 μg mL⁻¹ of D-serine plus i.r.a. infusion of the SP receptor blocker L-703,606 (0.5 mg min⁻¹ kg⁻¹), plus intrapelvic infusion of 100 μg mL⁻¹ of MK-801, and in rats with bilateral dorsal rhizotomy (DRX) at T₉-L₁ or sham-operated (Sham) rats after a 3-week induction period (n=8 for each). Measurements were made throughout each period and averaged.

**Effects of D-Serine on the Sensory Response**

The infusion protocol consisted of a 10-minute baseline period of saline infusion, a 5-minute experimental period of intrapelvic infusion of 10, 30, or 100 μg mL⁻¹ of D-serine randomly (Sigma, n=8 for each), and a 10-minute recovery period of saline infusion, MK-801 (10 μg min⁻¹ kg⁻¹, i.r.a.) being infused throughout.

**Effects of MK-801 on the Sensory Response**

MK-801 (i.r.a. 10 μg min⁻¹ kg⁻¹) was given 10 minutes before mechanostimulation and throughout the experiment (n=7 for each). The right ureter was cannulated for collection of the contralateral urine.

**Statistical Analysis**

Numeric data are presented as the mean±SEM. The Mann–Whitney U test, Friedman 2-way ANOVA, and a shortcut ANOVA were used.
to evaluate the effect of the drug or DRX on hemodynamic and excretory parameters, SP release, or ARNA responses to D-serine. Differences were regarded as significant at the level of $P<0.05$.

**Results**

**Localization of NMDAR in Renal Tissues**

Figure 1A shows that NMDA$\zeta$1 was present in the rat kidney, being most abundant in the pelvis. In the cortex and medulla, NMDA$\zeta$1 was expressed, respectively, at $14\pm2$ and $36\pm4\%$ of renal pelvis levels. NMDA$\zeta$1 mRNA transcripts were undetectable in the renal pelvis of the 3 animals examined, but were present in the brain cortex positive control (Figure 1B).

NMDA$\zeta$1 was not homogeneously distributed throughout the kidney, being found in the glomeruli, arteriole, and, to a lesser extent, in the tubules of the renal cortex and medulla (Figure 1C). In the renal pelvis, NMDA$\zeta$1 was found mainly in the fibrous structures between the uroepithelial and smooth muscle layers, and also just beneath the smooth muscle layer. Most nerve bundles in the renal pelvis contained NMDA$\zeta$1, as shown by double-labeling with antibodies against NMDA$\zeta$1 and a panneuronal (PGP9.5) or sensory nerve (NK-1R) marker (Figure 1D).

**Intrarenal Effects of MK-801**

Figure 2 shows the effects of i.r.a. infusion of MK-801. MK-801 had no significant effect on the mean arterial blood pressure (MABP), but (+)-MK-801 dose-dependently decreased the LDF at a dose of 30 or 100 $\mu$g min$^{-1}$ kg$^{-1}$, compared to the same dose of (-)-MK-801. (+)-MK-801 at 10, 30, or 100 $\mu$g min$^{-1}$ kg$^{-1}$ also significantly decreased the UV and UNaV, with maximal reduction at 30 $\mu$g min$^{-1}$ kg$^{-1}$. We therefore chose the dose of 10 $\mu$g min$^{-1}$ kg$^{-1}$ to study the effects on sensory function, as this dose lowered the UV and UNaV, but had no significant effect on the LDF.

**D-Serine Induces Sensory Activation**

As shown in Figure 3, i.r.a. or intrapelvic infusion of the test drugs did not affect the MABP or heart rate. Intrapelvic infusion of D-serine caused a dose-dependent increase in ARNA and SP release, which was blocked by i.r.a. infusion of (+)-MK-801, but not the (-)-MK-801 (left panel). The increase in ARNA, but not the increased SP release, caused by infusion of 100 $\mu$g ml$^{-1}$ of D-serine was also blocked by i.r.a. infusion of L-703 606 (second panel from left) or intrapelvic infusion of (+)-MK-801 (third panel from left).

DRX had no effect on the daily intake of food and water and body weight compared to sham-operated rats (data not shown), but blocked the ARNA increase and SP release seen after administration of 100 $\mu$g min$^{-1}$ of D-serine (right panel).

**NMDAR Inhibition Attenuates the Mechanostimulation-Induced Reflex Response**

Figure 4 (left panel) shows the effects of mechanostimulation of the renal pelvis. During i.r.a. infusion of 10 $\mu$g min$^{-1}$ kg$^{-1}$ of (-)-MK-801, the MABP was unaffected by the 2 lower IPPs (10.5±1.4 and 20.6±1.8 mm Hg), but was significantly decreased at the high IPP (51.2±2.6 mm Hg), and the ARNA in the left kidney and the UV and $U_{NaV}$ of the contralateral kidney increased in an IPP-dependent manner. The same dose of (+)-MK-801 abolished the increases in the ipsilateral ARNA and contralateral diuretic/natriuretic response at IPP 10 mm Hg and the decrease in the MABP at IPP 50 mm Hg. Although the ARNA, UV, and $U_{NaV}$ were significantly increased at IPPs of 21.1±1.6 and 50.8±2.1 mm Hg in the presence of (+)-MK-801 (with the exception of the UV at IPP 20 mm Hg), these responses were largely attenuated compared to those when (-)-MK-801 was used (all $P<0.05$).

Intrapelvic infusion of 100 $\mu$g ml$^{-1}$ of (+)-MK-801 also resulted in blockade of the IPP-induced renorenal reflex response at $\approx$50 mm Hg (Figure 4, right panel).

**Intrapelvic Expression of Serine Racemase**

Figure 5A (left panel) shows that serine racemase (SR), the critical enzyme for the synthesis of D-serine, was expressed predominantly in, or below, the muscle layer of the renal pelvis, and, to a lesser extent, in the uroepithelial layer. Little fluorescence was seen in the negative control (right panel). Western blots showed that SR was distributed throughout the kidney and was more abundant in the renal pelvis and medulla (107±6% of renal pelvis level) than in the renal cortex (26±3% of renal pelvis level; Figure 5B). The expression pattern of SR mRNA was similar to that of protein expression (Figure 5C).
Discussion
Figure 6 shows schematically, for the first time, evidence that NMDARs are present in the renal pelvis and sense increases in the IPP. It is interesting that the key enzyme responsible for synthesizing D-serine, SR, was also found in the renal pelvis. When the renal pelvic wall is stimulated by an increase in IPP, D-serine activates NMDARs, which act as mechanoreceptors, allowing SP to be released, possibly via a mechanism involving cation ion influx and sensory nerve activation. The important function of NMDARs as an initiator of renal

![Figure 3. D-serine induces renal sensory activation. B, E, and R are baseline, experimental, and recovery periods. D-serine at the doses indicated in brackets was infused into the renal pelvis during the experimental period. i.r.a. infusion of MK-801 (left panel) or L-703,606 (second panel) or intrapelvic infusion of MK-801 (third panel) was performed in all periods. Right panel: D-serine was tested in Sham or DRX rats. n=8 for each test. *Significant difference (P<0.05) compared to the basal period. †Significant difference (P<0.05) between the 2 treatments.](image)

![Figure 4. Effects of NMDAR inhibition on the renorenal reflex. MK-801 was given via the i.r.a. (left) or intrapelvic (right) route throughout the experiment and the IPP elevation-induced renorenal reflex was measured (n=7 for each). *Significant difference (P<0.05) compared to the basal period. †Significant difference (P<0.05) between the 2 MK-801 treatments.](image)
sensory activation also has a profound effect on the reflex response, as NMDAR blockade reduced diuresis/natriuresis in the renorenal reflex and acute saline loading (please see http://hyper.ahajournals.org).

In the present study, we first examined the expression of NMDA<sub>1</sub>, as it is an obligatory subunit of NMDARs and essential for channel activity. However, NMDAe (NR2) is known to confer modulatory properties on receptors. Leung et al<sup>13</sup> showed that NR2C protein, but not other NR2 subunits, are present in rat kidneys. Further studies are required to determine whether NMDAe modulates receptor function in the ARNA response. The NMDA<sub>1</sub> subunit was found to be unevenly distributed within the rat kidney. Although the vascular or tubular function of NMDARs is unknown, activation of NMDARs by glycine causes a vasodilatory response.<sup>14,15</sup> Blockade of the NMDAR by (-)-MK-801 gradually reduced renal regional blood perfusion, supporting the idea that activation of NMDARs causes renal vasodilatation. Increased nitric oxide formation and activation of tubuloglomerular feedback have been postulated to contribute to NMDAR-mediated intrarenal vasodilation.<sup>14,15</sup> Our results showed that the NMDA<sub>1</sub> subunit was located in the cortical arterioles and glomeruli. This localization could directly affect glomerular perfusion or filtration via a vascular effect, as suggested previously.<sup>14,15</sup> In a micropuncture study, Sломовиц et al<sup>23</sup> showed that glycine infusion to activate NMDARs resulted in significant increases in the single-nephron GFR and blood flow which were attributable to significant decreases in afferent and efferent arteriolar resistance. We therefore speculate that intrarenal administration of (+)-MK-801 blocks receptor function in the arteriole and glomerulus and may cause a reduction in GFR.

We also showed that the low dose (10 μg min<sup>-1</sup> kg<sup>-1</sup>) of (+)-MK-801 reduced renal excretion, with no effect on cortical perfusion. Increases in absolute proximal tubular reabsorption were also seen during glycine infusion by

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**Figure 5.** Expression of serine racemase in the kidney. A, Serine racemase was expressed in the renal pelvis (left panel, green color). Horizontal bar = 10 μm. Negative control in the right panel. B, Upper panel: Typical blots showing serine racemase expression in renal tissues in 2 kidneys. Lower panel: statistical results for 6 rats. C, Upper panel: Typical gels showing serine racemase mRNA level in renal tissues from 2 kidneys. Lower panel: statistical results for 6 rats. NTC indicates no template control. *Significant difference (P<0.05) compared to the renal cortex.

**Figure 6.** Scheme showing how the NMDAR interacts with the NK-1R to affect ARNA generation. On mechanostimulation through an increase in IPP, activation of the NMDAR in the sensory nerve terminals allows cation influx and increases SP release into the pelvic space. SP activates NK-1Rs and the activation of both NMDARs and NK-1Rs generates ARNA. NMDARs are synthesized and transferred outside the renal pelvis, as indicated by the dashed line.
peripheral NMDARs causes hypotension or increases the activation of presynaptic NMDARs facilitates SP release as an indirect measure of SP release, it has been shown that the internalization of spinal SP receptors as an indicator of SP release.

Morphological studies have shown that NMDARs are present in unmyelinated and myelinated axons in the periphery. By calculating the conduction velocity of the single-unit ARNA, we showed that renal sensory nerves are C-fibers. This suggests that NMDARs are probably present in the unmyelinated C-fibers of afferent renal nerves. By monitoring the internalization of spinal SP receptors as an indirect measure of SP release, it has been shown that activation of presynaptic NMDARs facilitates SP release from primary afferents. Consistent with this, the present results showed that D-serine caused a dose-dependent increase in SP release. In addition to MK-801, an NK-1R blocker, and DRX also completely abolished D-serine–mediated sensory activation, suggesting that the functional presence of afferent renal nerves is necessary for NMDAR function and that the neurokinin system acts downstream of the NMDAR.

D-serine has been proposed as an endogenous agonist that binds to the glycine-binding site of the NMDA \( \alpha \) subunit. D-serine is up to 3- to 100-fold more effective than glycine in activating NMDARs expressed in hypoglossal motoneurons or recombinant receptors expressed in Xenopus oocytes. These results suggest that it might be a preferential agonist for NMDARs. With regard to the endogenous amount of D-serine, a previous study showed that, in some brain areas, extracellular levels of D-serine are similar to, or greater than, those of glycine, as determined by in vivo microdialysis. Furthermore, an important function of D-serine in the renal pelvis is strongly supported by our new observation of the presence of SR, the key enzyme in D-serine synthesis. SR is known to be present in human cardiac myocytes and the convoluted tubules of the kidney. These results strongly suggest a potential role for D-serine in the regulation of NMDAR activity in the kidney, especially in the renal pelvis.

There is considerable evidence that NMDARs present at the central end of primary afferent nerves modulate the baroreceptor reflex. However, stimulation or blockade of peripheral NMDARs causes hypotension or increases the blood pressure, suggesting that peripheral NMDARs are involved in the regulation of the systemic pressure. Kłoda et al. showed that membrane stretch exerted by either positive hydrostatic pressure or cytoskeletal deformation potentiates the NMDAR response and that membrane deformation frees the Mg\(^{2+}\) block on the NMDA channel, thus triggering Ca\(^{2+}\) influx. Although the in vivo range for pressure monitoring by NMDARs is not precisely known, the NMDAR contributes to responses of sensory afferent fibers innervating the distal stomach and colon during distension at pressures of 5 to 80 mm Hg. Consistent with this, the possible presence of NMDARs in renal C-fibers could detect a pressure range of 10 to 50 mm Hg. Moreover, our results showed that NMDARs detect an IPP range broader than that detected by the transient receptor potential vanilloid type 1 channel (TRPV1), another mechano-sensitive channel present in the renal pelvis. In contrast to TRPV1 inhibition, inhibition of NMDARs reduced the increase in ARNA seen at an IPP of 50 mm Hg.

In conclusion, our results clearly show that NMDARs in the renal pelvis monitor changes in IPP. The receptor profile includes stimulation by D-serine and inhibition by (+)-MK-801. SP release and NK-1R activation are essential for NMDAR-mediated sensory activation in the inhibitory renorenal reflex.

**Perspectives**

The discovery of mechanoreceptors in the renal pelvis has revealed that the kidney performs an important function in monitoring the intrarenal transmission of hydrostatic pressure from the beginning of the renal artery to the end of the renal tubule during urine formation. Activation of mechanoreceptors in afferent renal nerves triggers an inhibitory renal reflex and causes a diuretic and natriuretic response by reflex withdrawal of efferent renal sympathetic nerve activity. Impaired sensory function in the renorenal reflex can lead to abnormal fluid retention, particularly in various rat models of hypertension. As shown in this study, blockade of NMDARs attenuates urine excretion in the renorenal reflex. Moreover, inappropriate expression of NMDARs results in renal injury, as seen in gentamicin-induced nephrotoxicity. Thus, it is important to know whether altered function or expression of NMDARs is involved in the impaired renorenal reflex and excretory response in the pathogenesis of hypertension or other kidney diseases.

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**Disclosures**

None.

**References**


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Data Supplement

Mechanosensitive NMDA receptors contribute to sensory activation in the rat renal pelvis

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**Running title:** Renal NMDA receptors act as mechanoreceptors
Primers for RT-PCR.

The cDNA was synthesized using 10 μg of the total RNA sample and amplified as previously described.\(^1\) The NMDAζ1 primer sequences were 5’-ACG GAA TGA TGG GCG AGC-3’ (sense) and 5’-GGC ATC CTT GTG TCG CTT GTA G-3’ (antisense) (transcript product of 1,033 bp, NM_017010), those for SR were 5’-CCC AAA GCC GTT GTT ACT CAC A-3’ (sense) and 5’-CAT TGG AAG GTT CAG CAG CGT ACA-3’ (antisense) (395 bp, NM_198757), and those for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were 5’-TTA GCA CCC CTG GCC AAG G-3’ (sense) and 5’-CTT ACT CCT TGG AGG CCA TG-3’ (antisense) (535 bp, XR_007956).

Acute saline loading.

Saline was infused intravenously in amounts equal to 1, 2, or 3% of the body weight over 10 min as described previously (n=8).\(^2\)\(^-\)\(^3\) MK-801 (10 μg min\(^{-1}\) kg\(^{-1}\)) was infused via the i.r.a. catheter as above for 10 min before saline loading and throughout the experiment.

NMDAR inhibition reduces diuresis and natriuresis after saline loading.

As shown in Figure S1, saline loading induced a transient increase in the MABP, the magnitude of which was dependent on the volume administered. Neither (-)-MK-801 nor (+)-MK-801 had any effect on the pressor responses and the increases in LDF and IPP due to saline loading. (+)-MK-801 attenuated the peak ARNA and UV responses at 20, 10-20, and 10-30 min for 1, 2, and 3% of saline loading, respectively, when compared to (-)-MK-801. Cumulative urine output in the (+)-MK-801-treated kidneys was 66.3±7.2, 58.2±8.9, and 48.1±10.7% of the values seen in the (-)-MK-801-treated kidneys for 1, 2, and 3% of saline loading,
respectively (all P<0.05).

References


Figure S1. Renal response to acute saline loading and NMDAR inhibition. Saline was infused intravenously for 10 min as indicated by the horizontal bar, and MK-801 was infused by the i.r.a. route. †Significant difference (P<0.05) between the two treatments.