Production and Actions of Hydrogen Sulfide, a Novel Gaseous Bioactive Substance, in the Kidneys

Min Xia, Li Chen, Rachel W. Muh, Pin-Lan Li, and Ningjun Li

Department of Pharmacology & Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

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ABSTRACT

Hydrogen sulfide (H$_2$S), a novel endogenous gaseous bioactive substance, has recently been implicated in the regulation of cardiovascular and neuronal functions. However, its role in the control of renal function is unknown. In the present study, incubation of renal tissue homogenates with L-cysteine (L-Cys) (as a substrate) produced H$_2$S in a concentration-dependent manner. This H$_2$S production was completely abolished by inhibition of both cystathionine β-synthetase (CBS) and cystathionine γ-lyase (CGL), two major enzymes for the production of H$_2$S, using amino-oxyacetic acid (AOAA), an inhibitor of CBS, and propargylglycine (PPG), an inhibitor of CGL. However, inhibition of CBS or CGL alone induced a small decrease in H$_2$S production. In anesthetized Sprague-Dawley rats, intrarenal arterial infusion of an H$_2$S donor (NaHS) increased renal blood flow, glomerular filtration rate (GFR), urinary sodium (U$_{Na}$V), and potassium (U$_{K}$V) excretion. Consistently, infusion of both AOAA and PPG to inhibit the endogenous H$_2$S production decreased GFR, U$_{Na}$V, and U$_{K}$V, and either one of these inhibitors alone had no significant effect on renal functions. Infusion of L-Cys into renal artery to increase the endogenous H$_2$S production also increased GFR, U$_{Na}$V, and U$_{K}$V, which was blocked by AOAA plus PPG. It was shown that H$_2$S had both vascular and tubular effects and that the tubular effect of H$_2$S might be through inhibition of Na$^+$/K$^+$/2Cl$^-$ cotransporter and Na$^+$/K$^+$/ATPase activity. These results suggest that H$_2$S participates in the control of renal function and increases urinary sodium excretion via both vascular and tubular actions in the kidney.

In addition to NO and CO, hydrogen sulfide (H$_2$S) has recently been demonstrated to be the third gaseous bioactive substance produced in different mammalian cells (Kimura, 2002; Wang, 2002). Studies have indicated that H$_2$S plays an important role in the regulation of cardiovascular functions. In this regard, both exogenous and endogenous H$_2$S have been reported to cause vascular smooth muscle relaxation and decrease blood pressure, and inhibition of endogenous H$_2$S production induces hypertension (Hosoki et al., 1997; Cheng et al., 2004; Yan et al., 2004; Webb et al., 2008). Furthermore, accumulating evidence has shown that H$_2$S is involved in a variety of physiological and pathological processes in many other organs, such as brain (Éto et al., 2002), heart (Geng et al., 2004), lung (Bhatia et al., 2005; Baskar et al., 2007), liver (Fiorucci et al., 2005), intestine (Teague et al., 2002), pancreas (Bhatia et al., 2005; Yang et al., 2007), and cavernous (Srilatha et al., 2007).

It has been reported that mammalian cells generate H$_2$S from L-cysteine (L-Cys) mainly through two enzymes, cystathionine β-synthetase (CBS) and cystathionine γ-lyase (CGL) (Kimura, 2002; Wang, 2002; Zhao et al., 2003). The enzymatic pathways for H$_2$S production are tissue-specific. For example, CBS is the predominant enzyme generating H$_2$S in the nervous system and CGL in the vascular system (Wang, 2002; Zhao et al., 2003). Both CBS and CGL have been reported to be present in the kidneys (Stipanuk and Beck, 1982; House et al., 1997), mainly in renal proximal tubules (House et al., 1997; Ishii et al., 2004; Li et al., 2006). However, the production and actions of H$_2$S in the kidneys are not clear. The present study determined the enzymatic pathways for the production of H$_2$S in the renal tissue homogenates and examined the effects of exogenous and endogenous H$_2$S on renal hemodynamics and excretory functions. The results provide evidence showing that H$_2$S significantly participates in the control of renal functions, including glomerular and tubular functions.

ABBREVIATIONS: H$_2$S, hydrogen sulfide; L-Cys, L-cysteine; CBS, cystathionine β-synthetase; CGL, cystathionine γ-lyase; AOAA, amino-oxyacetic acid; PPG, propargylglycine; GFR, glomerular filtration rate; U$_V$, urinary volume; U$_{Na}$V, urinary sodium; U$_{K}$V, urinary potassium; FF, fractional filtration; FE$_{Na}$, fractional excretion of sodium; FE$_{K}$, fractional excretion of potassium; MAP, mean arterial blood pressure; NKCC, Na$^+$/K$^+$/2Cl$^-$ cotransporter; NCC, Na$^+$/Cl$^-$ cotransporter; NKA, Na$^+$/K$^+$/ATPase; RBF, renal blood flow; ANOVA, analysis of variance; G, group; BM, basolateral membrane; HPLC, high-performance liquid chromatography; K, glomerular ultrafiltration coefficient.
Materials and Methods

Animals

Experiments were performed on male Sprague-Dawley rats, weighing between 300 and 350 g, purchased from Harlan (Madison, WI). The rats were housed in the Animal Care Facility at the Virginia Commonwealth University with free access to food and water throughout the study, with the exception that they were fasted the night before the renal function experiments. All protocols were approved by the Institutional Animal Care and Use Committee of the Virginia Commonwealth University.

Measurement of \( \text{H}_2\text{S} \) Production in Renal Tissue

The production of \( \text{H}_2\text{S} \) by renal tissue homogenates was measured using spectrophotometry as described previously with slight modifications (Stipanuk and Beck, 1982; Zhao et al., 2001; Cheng et al., 2004). In brief, renal cortical tissues were homogenized in 50 mM ice-cold potassium phosphate buffer (pH 7.4). The tissue homogenates (0.25 ml) were incubated with L-Cys (0.5, 1, and 5 mM, respectively) and pyridoxal 5'-phosphate (2 mM) at 37°C for 90 min after the reaction tubes were flushed with \( \text{N}_2 \) and sealed. Fifty percent of trichloroacetic acid (0.125 ml) was injected into the reaction tubes to stop the reaction, followed by 0.125 ml of zinc acetate (15 mM) and 0.5 ml of borate buffer (pH 10.01). The tubes were then incubated at 37°C for another 60 min. The reaction solutions were mixed with 0.5 ml of \( \text{N}N \)-dimethyl-p-phenylenediamine sulfate (20 mM, in sulfuric acid, pH 9.0) and 0.02 ml of FeCl\(_3\) (3 M) at 37°C for an additional 30 min and then centrifuged at 5000 g for 3 min and filtered with 0.45-\(\mu\)m syringe filters. The absorbance of resulting solution at 670 nm was measured with a spectrophotometer. The \( \text{H}_2\text{S} \) concentration was calculated against the calibration curve of the standard \( \text{H}_2\text{S} \) solutions.

For the measurement of endogenous \( \text{H}_2\text{S} \) levels in the kidneys, renal tissues (50 mg) were homogenized in 0.5 ml of zinc acetate (1%) and mixed with 0.5 ml of borate buffer (pH 10.01). Then, 0.5 ml of \( \text{N}N \)-dimethyl-p-phenylenediamine (20 mM) and 0.5 ml of FeCl\(_3\) (300 mM) were added into tissue homogenates. Reaction tubes were immediately sealed and incubated at 37°C for 30 min with shaking. After incubation, the samples were centrifuged, and the \( \text{H}_2\text{S} \) concentrations were measured as described above. Zinc acetate can trap \( \text{H}_2\text{S} \), and the reaction of \( \text{H}_2\text{S} \) with \( \text{N}N \)-dimethyl-p-phenylenediamine produces methylene blue that can be detected at 670 nm with spectrophotometry to represent the levels of \( \text{H}_2\text{S} \). This method is extensively used for the measurement of \( \text{H}_2\text{S} \) in the tissue (Stipanuk and Beck, 1982; Zhao et al., 2001; 2003; Cheng et al., 2004; Yan et al., 2004).

Effect of Exogenous and Endogenous \( \text{H}_2\text{S} \) on Renal Hemodynamics and Functions

Animal Preparation. Male Sprague-Dawley rats, weighing 300 to 350 g, were anesthetized with ketamine (30 mg/kg i.m.) (Phoenix Pharmaceuticals, St. Joseph, MO) and thiobotubarbital (inaction, 50 mg/kg i.p.) (Sigma-Aldrich, St. Louis, MO) and then surgically prepared for continuously monitoring mean arterial blood pressure (MAP), renal blood flow (RBF), and urine flow rate (U-V) as described previously by us and others (Zou et al., 2001; Zhang et al., 2003). After surgery, the animals received an infusion of 2% albumin saline at a rate of 1 ml/h/100 g body weight throughout the experiment to replace fluid losses and maintain a stable hematocrit of \( \pm 3% \).

Experimental Protocols. After a 1.5-h equilibration period and two 20-min control collections of urine and blood samples, different reagents were infused into left renal artery for 30 min (10-min clearance period and 20-min sample collection): group 1, infusion of NaH\(\text{S} \), a \( \text{H}_2\text{S} \) donor, at 5, 10, 20, 40, and 80 nmol/min/kg; group 2, infusion of amino-oxyacetic acid (AOAA) (Sigma-Aldrich), a CBS inhibitor, and/or propargylglycine (PPG) (Sigma-Aldrich), a CGL inhibitor, to block the production of endogenous \( \text{H}_2\text{S} \); group 3, infusion of L-Cys to increase the production of endogenous \( \text{H}_2\text{S} \); and group 4, infusion of L-Cys + AOAA + PPG. At the end of the experiments, the kidneys were removed, snap-frozen in liquid \( \text{N}_2 \), and stored in \( -80^\circ\text{C} \) for measurement of \( \text{H}_2\text{S} \) concentration as described above.

Effect of \( \text{H}_2\text{S} \) on \( \text{Na}^+ / \text{K}^+ \)-ATPase Activity in Basolateral Membranes from the Kidneys by HPLC Analysis

Basolateral membranes were prepared from the kidney tissue as described previously (Sheikh et al., 1982). HPLC analysis of renal \( \text{Na}^+ / \text{K}^+ \)-ATPase activity in the basolateral membranes was performed by detecting the conversion of ATP into ADP as reported previously (Sudo et al., 2000). ATP as substrate was incubated with renal basolateral membranes at 37°C for 20 min, and then the samples were subjected to HPLC analysis of ADP concentration after being centrifuged and filtered. Effect of \( \text{H}_2\text{S} \) on ouabain-sensitive ATPase activity was used to present the effect of \( \text{H}_2\text{S} \) on \( \text{Na}^+ / \text{K}^+ \)-ATPase activity. The assays included the following groups (G): G1, ATP + basolateral membrane (BM); G2, ATP + BM + ouabain (10 mM); G3, ATP + BM + ouabain + \( \text{H}_2\text{S} \); and G4, ATP + BM + \( \text{H}_2\text{S} \). The inhibition on ATPase activity was obtained as the difference in ADP production between G1 and the other groups. The effect of \( \text{H}_2\text{S} \) on \( \text{Na}^+ / \text{K}^+ \)-ATPase activity was calculated using inhibition rate in each group according to the following formula: (G4 − (G3 − G2))/G2.

For example, if the productions of ADP in all groups are 300 (inhibition = 0) for G1, 200 (inhibition = 100) for G2, 180 (inhibition = 120) for G3, and 250 (inhibition = 50) for G4, respectively, the effect of \( \text{H}_2\text{S} \) on \( \text{Na}^+ / \text{K}^+ \)-ATPase activity will be (50 − (120 − 100))/100 = 30% ouabain. If \( \text{H}_2\text{S} \) has no effect on \( \text{Na}^+ / \text{K}^+ \)-ATPase activity, G3 = G2 + G4. If \( \text{H}_2\text{S} \) only inhibits \( \text{Na}^+ / \text{K}^+ \)-ATPase activity with no effect on other ATPase activity, G3 = G2.

Statistical Analysis

Data are presented as means \( \pm \) S.E. The significance of differences in mean values within and between multiple groups was evaluated using analysis of variance (ANOVA), and any significant differences revealed by this procedure were further investigated using the Tukey multiple-range test. Student’s \( t \) test was used to evaluate statistical significance of differences between two groups. \( P < 0.05 \) was considered statistically significant.

Results

Enzymatic Pathways for the Production of \( \text{H}_2\text{S} \) in Renal Tissue Homogenates. As shown in Fig. 1A, incuba-
There was no change in MAP after infusion of NaHS into the renal artery also markedly increased the H2S levels in the kidney tissues after different treatments. After each experiment, the kidney was removed and saved, and the H2S levels within the kidney were measured. The data are summarized in Fig. 4. Intrarenal arterial infusion of AOAA plus PPG substantially reduced the H2S levels in the kidneys. Infusion of l-Cys significantly increased the FF, FENa, and FEK, which was blocked by AOAA plus PPG. In addition, infusion of NaHS into the renal artery also markedly increased the levels of H2S in the kidneys.

Effect of H2S on Specific Sodium Transporters in the Kidneys. The major renal sodium transporters include Na+/H+ exchanger, Na+/K+2Cl− cotransporter (NKCC), Na+/Cl− cotransporter (NCC), and epithelial Na+ channel on the apical side and Na+/K+2Cl−-ATPase (NKA) on the basolateral side of the tubule. Carbonic anhydrase is also an important contributor to the Na+ reabsorption. In the current study, a substantial increase in UNa+/V indicated that epithelial Na+ channel might not play an important role in H2S-induced tubular effects. There was no significant change in urine pH.

<table>
<thead>
<tr>
<th>NaHS (nmol/min/kg)</th>
<th>C</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (nmol Hg)</td>
<td>107.5 ± 1.74</td>
<td>107.7 ± 1.72</td>
<td>107.5 ± 1.80</td>
<td>107.8 ± 1.79</td>
<td>107.2 ± 1.89</td>
<td>105.5 ± 1.58</td>
</tr>
<tr>
<td>RBF (ml/min/g kwt)</td>
<td>8.99 ± 0.01</td>
<td>9.12 ± 0.04</td>
<td>9.12 ± 0.03</td>
<td>9.25 ± 0.03</td>
<td>9.73 ± 0.03</td>
<td>10.59 ± 1.03</td>
</tr>
<tr>
<td>GFR (ml/min/g kwt)</td>
<td>1.02 ± 0.10</td>
<td>1.04 ± 0.07</td>
<td>1.09 ± 0.08</td>
<td>1.26 ± 0.02*</td>
<td>1.32 ± 0.04*</td>
<td>1.57 ± 0.08*</td>
</tr>
<tr>
<td>UV (µl/min/g kwt)</td>
<td>17.7 ± 1.70</td>
<td>17.2 ± 0.89</td>
<td>19.8 ± 2.07</td>
<td>26.0 ± 1.31*</td>
<td>39.1 ± 4.94*</td>
<td>53.7 ± 5.87*</td>
</tr>
<tr>
<td>UNa+/V (µmol/min/g kwt)</td>
<td>2.72 ± 0.35</td>
<td>2.71 ± 0.53</td>
<td>2.96 ± 0.22</td>
<td>3.69 ± 0.21*</td>
<td>5.27 ± 0.70*</td>
<td>12.28 ± 1.31*</td>
</tr>
<tr>
<td>UF (µmol/g kwt)</td>
<td>1.69 ± 0.16</td>
<td>1.73 ± 0.26</td>
<td>1.82 ± 0.22</td>
<td>2.14 ± 0.26*</td>
<td>2.37 ± 0.19*</td>
<td>4.46 ± 0.33*</td>
</tr>
<tr>
<td>FE(Na) (%)</td>
<td>20.39 ± 1.47</td>
<td>20.65 ± 1.36</td>
<td>21.51 ± 1.31</td>
<td>24.71 ± 1.06*</td>
<td>25.77 ± 1.28*</td>
<td>28.95 ± 1.29*</td>
</tr>
<tr>
<td>FE(K+)(%)</td>
<td>33.53 ± 7.39</td>
<td>33.65 ± 3.30</td>
<td>34.37 ± 5.19</td>
<td>37.13 ± 2.14*</td>
<td>45.88 ± 4.33*</td>
<td>57.77 ± 6.04*</td>
</tr>
</tbody>
</table>

* P < 0.05 vs. control (C) by repeated measures ANOVA.
Therefore, we examined the effects of H2S on NKCC, NCC, due to the strong vessel constrictor effect of induced increases in UNaV/H9262 mol/min/kg) and PPG (4/H11001/11021 mol/min/kg). We were unable to conduct the similar in vivo experiment to produce H2S in the kidneys and that the inhibition of CBS or CGL alone could be compensated by the increase in the activity of the other enzyme in H2S production. This is consistent with a previous study, which showed that inhibition of CGL activity by 93% lowered H2S production by only 30% (Stipanuk and Beck, 1982). A recent report suggested that CGL was an essential enzyme for the synthesis of endogenous H2S in the kidneys based on the findings that PPG prevented the recovery of renal function after ischemic injury, whereas exogenous H2S protected the kidney from ischemic injury (Tripatha et al., 2008). The results from this report might not be able to rule out that inhibition of endogenous H2S production requires blockade of both CBS and CGL in the kidneys, because the enhanced renal injury after PPG administration could be a nephrotoxic effect of PPG (Konno et al., 2000) under the ischemic conditions.

Discussion

Our results indicated that both CBS and CGL were functioning to produce H2S in the kidneys and that the inhibition of CBS or CGL alone could be compensated by the increase in the activity of the other enzyme in H2S production. This is consistent with a previous study, which showed that inhibition of CGL activity by 93% lowered H2S production by only 30% (Stipanuk and Beck, 1982). A recent report suggested that CGL was an essential enzyme for the synthesis of endogenous H2S in the kidneys based on the findings that PPG prevented the recovery of renal function after ischemic injury, whereas exogenous H2S protected the kidney from ischemic injury (Tripatha et al., 2008). The results from this report might not be able to rule out that inhibition of endogenous H2S production requires blockade of both CBS and CGL in the kidneys, because the enhanced renal injury after PPG administration could be a nephrotoxic effect of PPG (Konno et al., 2000) under the ischemic conditions.

Given the facts that H2S plays an important role in the regulation of vascular function (Hosoki et al., 1997; Zhao et al., 2003; Cheng et al., 2004; Yan et al., 2004; Webb et al., 2008) and that the control of renal function is largely associated with the regulation of renal vascular functions, H2S may significantly participate in the control of renal functions. In the present study, intrarenal arterial infusion of an H2S donor increased RBF and GFR, which was accompanied by increases in FF, indicating that H2S may produce greater vasodilation in preglomerular arterioles than in postglomerular arterioles. In addition, the present study demonstrated that H2S increased U/V, UNaV, and UcV much more than RBF and GFR, implying that H2S has direct effects on renal tubular functions. Indeed, both FENa and FEK were increased by NaHS, suggesting an inhibitory effect of H2S on ion transport in the renal tubules. It was also shown that H2S exhibited more potent effects on tubular activity than vascular activity.
Although the above results from exogenous H₂S indicate that H₂S may play an important role in the regulation of renal function, the conclusion cannot be drawn until the role of endogenous H₂S is confirmed. Our results showed that combined inhibition of CBS and CGL significantly attenuated GFR, U-V, U₆₅-V, and U₅₋₆₋₅-V, revealing that endogenous H₂S is important in the maintenance of basal renal filtration and tubular functions. Inhibition of either CBS or CGL alone did not have a marked effect on renal hemodynamics and excretory functions. This is probably due to the observation that inhibition of either one of these two enzymes only reduced a small portion of H₂S production; the effect of this small change in H₂S production could not be detected in the complicated in vivo environment.

It should be noted that although PPG, an inhibitor of CGL used in the present study, was shown to be toxic to renal proximal tubular cells (Konno et al., 2000), the effects of PPG in the present study were unlikely due to its nephrotoxicity, because nephrotoxicity of PPG needs a large dose (300 versus 13.6 mg/kg in the present study) and induces an increase in urine volume (Konno et al., 2000). It has been shown that PPG at a dose of 50 mg/kg does not cause histological abnormalities in the kidneys (Triguero et al., 1997).

To further evaluate the physiological significance of H₂S in the regulation of renal function, we infused L-Cys into the renal artery to determine the effect of increased endogenous H₂S production on renal functions. Previous studies have documented that incubation of isolated arteries with L-Cys increases H₂S production and induces vasodilation (Cheng et al., 2004). Our results showed that L-Cys dose-dependently increased GFR, V, U₆₅-V, and U₅₋₆₋₅-V. Because there was no significant increase in RBF after infusion of L-Cys, the increase in GFR was probably due to the increases in FF and glomerular ultrafiltration coefficient (K₅). It has been documented that glomerular mesangial cells and podocytes contain contractile proteins and respond to vasoactive hormones, thereby modulating the K₅ (Stockand and Sansom, 1998; Pavenstädt, 2000). It is possible that H₂S has a direct effect on mesangial cells or through an unknown mechanism increases K₅ and consequently GFR. Our results also confirmed that L-Cys-induced changes in renal functions were attributed to increased production of H₂S, because inhibition of CBS and CGL in combination abolished the L-Cys-induced effects on renal hemodynamics and excretions. This was consistent with the results in our biochemical analyses. These data further demonstrate that endogenous H₂S participates in the regulation of renal functions. The results from the measurement of renal H₂S concentrations showed that renal H₂S concentrations were well associated with the changes in
renal functions, which additionally indicates an important role of H$_2$S in the regulation of renal functions.

There was a concern that infusion of L-Cys, unlike NaHS, did not increase RBF despite the fact that it increased H$_2$S in the kidney. This discrepancy indicates that L-Cys may produce other effects in addition to the enhancement of H$_2$S production. L-Cys has been reported to be a weak inhibitor of S-adenosylhomocysteine hydrolase (Knudsen and Yall, 1972), an enzyme that produces adenosine (Kloor et al., 2003). Adenosine is well known for increasing afferent arteriolar resistance and decreasing efferent arteriolar resistance, which is accompanied by little change in total RBF (Spielman and Thompson, 1982). Infusion of L-Cys may decrease the production of adenosine within the kidneys, resulting in a preglomerular vessel relaxation and postglomerular vessel constriction. This postglomerular vessel constriction may then counteract the effect of H$_2$S on RBF.

As a result, L-Cys induced little change in RBF in the current study. Slightly higher FF in L-Cys-infused rats may be taken in support of the notion that there are adenosine-mediated effects of L-Cys. However, this adenosine-mediated effect may not be a major portion of L-Cys-induced action because inhibition of CBS and CGL abolished the effect of L-Cys on renal function, suggesting that H$_2$S-mediated action of L-Cys is predominant. The speculation concerning the effect of L-Cys on RBF needs to be proven in future studies.

To determine which sodium transporter is responsible for the inhibitory effect of H$_2$S on sodium reabsorption, we performed experiments to dissect the effects of H$_2$S on specific
sodium transporters along the renal tubule. Our results demonstrated that the tubular effects of H$_2$S might be partially through inhibition of NKCC and NKA activity. The inhibitory effects of H$_2$S on both NKCC and NKA are similar to those of NO (Ortiz and Garvin, 2002). The interaction between H$_2$S and NO in this regard may need further attention. It should be noted that H$_2$S exhibits both vascular and tubular effects and that the inhibitors of NKCC, NCC, and NKA also have effects on renal hemodynamics (Langård et al., 1984; Okusa et al., 1989; Sawaya et al., 1991; Dobrowolski et al., 2000; Dobrowolski and Sadowski, 2005; Lorenz et al., 2006). Therefore, there is a possibility that there are interactions/counteractions between the vascular effects of H$_2$S and those of Na$^+$ transport inhibitors. These interactions/counteractions can also change U$_{Na,V}$ and may be responsible for the further increases or no further effect in U$_{Na,V}$ when NaHS is infused in combination with different Na$^+$ transport inhibitors. Moreover, it cannot be ruled out that H$_2$S affects other tubular transporters simultaneously in addition to its effects on NKCC and NKA, because such effects, if there are any, may be covered in the complicated signal interactions/counteractions in the in vivo experiments. Thus, the results from the current study are not conclusive regarding the effects of H$_2$S on specific tubular transporters. A study using isolated and perfused different tubular segments will clarify the effects of H$_2$S on specific tubular transporters in the future.

In summary, the present study demonstrated that the kidney tissues were capable of producing H$_2$S from L-Cys via CBS and CGL: exogenous H$_2$S produced dose-related increases in RBF, GFR, and urinary excretion; inhibition of endogenous H$_2$S reduced GFR, U$_V$, U$_{Na,V}$, and U$_{K,V}$; induction of endogenous H$_2$S production increased GFR, U$_V$, U$_{Na,V}$, and U$_{K,V}$; F$_{Na}$, and F$_{K}$ were also increased by H$_2$S; and the inhibitory effect of H$_2$S on tubular reabsorption involved NKCC and NKA. These results suggest that H$_2$S participates in the control of renal function via both vascular and tubular actions in the kidney.

References

Address correspondence to: Dr. Ningjun Li, Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, P.O. Box 980615, Richmond, VA 23298. E-mail: nl2f@vcu.edu