Effect of phosphodiesterase 5 inhibitor on alteration in vascular smooth muscle sensitivity and renal function in rats with liver cirrhosis

Rima Tahseldar-Roumieh,1,2 Rana Ghali-Ghoul,1 Claire Lugnier,2,* and Ramzi Sabra1,*

1Department of Pharmacology and Therapeutics, Faculty of Medicine, American University of Beirut, Lebanon; and 2Centre National de la Recherche Scientifique Unité Mixte de Recherche 7034, Université Louis Pasteur, Strasbourg, France

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CIRRHOSIS OF THE LIVER is associated with development of sodium retention by the kidney, renal vasoconstriction, and peripheral vasodilation especially in the splanchnic vascular bed, leading to a hyperdynamic circulation (26). The pathogenesis of these findings has been the subject of numerous studies. Much evidence has been provided to support a role of NO in the genesis of splanchnic vasodilation (32). The study was aimed at investigating this possible role, making use of 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)pyrazolo[3,4d]-pyrimidin-4-(5H)-one (DMPPO), a more selective and potent inhibitor of the enzyme than zaprinast (7). More specifically, the study was aimed at 1) examining the sensitivity of aortic smooth muscle to NO donors [nitroglycerin (NG) and S-nitroso-N-acetyl-penicillamine (SNAP)] and phenylephrine in the absence and presence of DMPPO, and of DMPPO itself, in rats with liver cirrhosis and in normal rats and 2) assessing the effects of DMPPO on systemic hemodynamics; nitric oxide; vasodilation; sodium retention; guanosine 3′,5′-cyclic monophosphate
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Rat models of liver cirrhosis have been used to study the effects of PDE5 inhibition on vascular sensitivity to NO donors and increased responses to vasoconstrictors. For this purpose, we used the same model of cirrhosis, i.e., the bile duct ligation and excision (BDL) model, that was used to demonstrate the role of PDE5 in the reduced response of cirrhotic rats to volume expansion and ANP and to show increased activity and expression of PDE5 in the kidney (20, 21).

METHODS

The study was approved by the Institutional Animal Care and Use Committee of the American University of Beirut. All animals received humane care according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals (National Research Council). Sprague-Dawley rats weighing 200–250 g underwent either BDL or sham operation, as previously described (29). Briefly, a midline abdominal incision was made under anesthesia and the common bile duct was identified and cut in between two sutures to achieve BDL. Sham operation consisted of manipulating the common bile duct without applying sutures or excision of the bile duct. The abdomen was double sutured, and rats were placed in separate cages for the length of the study.

In Vitro Studies

Preparation of rat aortic rings and measurement of relaxation. Four weeks after BDL, rats were killed by cervical dislocation under CO2 narcosis. The thoracic aorta was quickly dissected, cleaned of fat and connective tissues, and cut into four rings 3–4 mm in length. The rings were mounted under a resting tension in 15-ml organ baths containing Krebs solution of the following composition (mM): 118 NaCl, 4.7 KCl, 1.25 CaCl2, 1.14 KH2PO4, 1.19 MgSO4, 10 glucose, and 25 NaHCO3, gassed with 95% O2-5% CO2 and maintained at 37°C. Preparations were allowed to equilibrate for 60 min with periodic washing before the experiments started. Tension was measured with a force displacement transducer, which was connected to a Myobath system for recording (World Precision Instruments, Sarasota, FL). In some experiments, the endothelium of aortic rings was removed by gently rubbing the intimal surface; in others, care was taken to maintain the integrity of the endothelium. Nonfunctional endothelium was tested by the inability of acetylcholine (10−6 M) to induce relaxation of aortic rings precontracted with phenylephrine (1 μM). Aortic rings with functional endothelium exhibited at least 50% relaxation under identical conditions.

Measurement of aortic sensitivity to NG, SNAP, and DMPPO. The effects of NG, SNAP, and DMPPO were tested in aortic rings precontracted with phenylephrine (1 μM). Increasing concentrations of NG or SNAP were added to the bath to obtain a dose-response curve for relaxation of the aortic rings. Each experiment consisted of triplicates or duplicates, the average of which represented the result of one particular experiment. Similar dose-response curves were observed in separate aortic rings from BDL and sham-operated rats that were preincubated with DMPPO (0.1 μM), a selective inhibitor of PDE5 (7), to examine the role of PDE5 in these responses. In this study, 0.1 μM DMPPO was used to specifically and maximally inhibit PDE5 without acting on other PDE isozymes such as PDE3 and PDE4 implicated in vasorelaxation (9, 18). In separate studies, the relaxant effect of DMPPO itself and of the non-endothelium-dependent vasodilator diazoxide was investigated in aortic rings with intact endothelium, and a concentration-response curve was obtained.

Measurement of aortic sensitivity to phenylephrine. In these experiments, aortic rings were mounted as described above. Rings from BDL and sham-operated rats with intact endothelium or denuded of endothelium were exposed to increasing concentrations of phenylephrine to achieve maximal contraction. In two other groups, endothelium-denuded rings were preincubated with SNAP (0.1 μM) or with SNAP (0.1 μM) and DMPPO (0.1 μM) and then exposed to increasing concentrations of phenylephrine.

In Vivo Studies: Effect of DMPPO on Systemic Hemodynamics and Renal Function

This protocol assessed the cardiovascular response to DMPPO in sham-operated and BDL rats. Twenty-eight days after BDL or sham operation, rats were anesthetized with intraperitoneal injections of pentobarbital (25–50 mg/kg). The trachea was cannulated with PE-205 tubing to maintain a patent airway. The right jugular vein was catheterized with PE-50 tubing for administration of fluids. The right carotid artery was cannulated with PE-50 tubing and connected to a blood pressure transducer (TXD-310) attached to a BPA-100 blood pressure analyzer (Micro-Med, Louisville, KY); this was used for continuous monitoring of mean arterial pressure (MAP). A thermistor probe was introduced in the left carotid artery and advanced to the aortic arch to measure cardiac output by the thermodilution technique after administration of 200 μl of ice-cold 0.9% NaCl solution. The probe was connected to a cardiac output computer (Columbus Instruments, Columbus, OH). A spring-loaded syringe was used to ensure a constant injection rate and volume. In addition, the urinary bladder was catheterized with PE-190 tubing through the urethra for collection of urine samples. A 0.9% NaCl solution containing 1 μCi/ml of [3H]inulin was administered intravenously as a bolus of 0.75 ml, followed by an infusion of 50 μl/min, which continued until the end of the experiment. The body temperature was maintained between 37 and 38°C with a heating lamp.

A period of 45 min was allowed for stabilization after surgery, after which the experiment was started. The experiment was divided into three consecutive periods of 30 min each. During the first period baseline measurements of the cardiac output and MAP were obtained at 5-min intervals. Urine was collected for 30 min in preweighed microtubes, and a blood sample was obtained at 15 min. After this period a single intravenous dose of DMPPO (5 mg/kg) was administered over 5 min, and the same measurements were obtained over the next two periods. Plasma and urine samples were used to measure radioactivity with a beta-scintillation counter, and urine samples were used to determine urinary (UNaV) and fractional (FENa) sodium excretion. Cardiac index (CI) was calculated by normalizing the cardiac output to body weight and was expressed as milliliters per minute per 100 g of body weight. Total peripheral resistance (TPR) was estimated with the formula TPR = MAP/CI. GFR was estimated from the clearance of inulin.

Statistical Analysis

The results are expressed as means ± SE. Comparison of responses between BDL and sham-operated rats was performed with the Student’s unpaired one-tailed t-test. When more than two groups were involved, one-way ANOVA (with repeated measures for the in vivo studies) was initially performed, followed by either the Newman-Keuls test for individual comparisons or, for the in vivo studies, the Dunnett’s test for comparison of values to the control value (i.e., comparison of hemodynamic values in periods 1 and 2 with those during the baseline period). A P value of ≤0.05 was considered significant.

RESULTS

Vascular Sensitivity to NG, SNAP, diazoxide, and DMPPO

In endothelium-denuded aortic rings from sham-operated and BDL rats precontracted with phenylephrine, NG induced concentration-dependent relaxation (Fig. 1). Aortic rings from BDL rats had a reduced sensitivity to NG, with a shift of the dose-response curve to the right. Aortic rings that were incu-
bated with DMPPO (0.1 μM) had an enhancement of the relaxant responses to NG in both sham-operated and BDL rats, such that the difference between the two curves was eliminated except at one concentration (10 nM), at which aortic rings from cirrhotic rats remained less sensitive to NG than those from sham-operated rats. The relaxant responses to SNAP in the BDL group were, like those to NG, attenuated compared with the responses in the corresponding sham-operated group. This difference in sensitivity was eliminated by treatment with DMPPO (0.1 μM) (Fig. 2). The relaxant response to diazoxide was not different in aortic rings with intact endothelium from cirrhotic or control rats (Fig. 3). In endothelium-denuded aortic rings, however, the responses to diazoxide were significantly attenuated relative to intact rings. Nevertheless, the effect of diazoxide remained similar in rings from BDL and sham-operated rats. The relaxant response to DMPPO in aortic rings with intact endothelium precontracted with phenylephrine (1 μM) was attenuated in the cirrhotic rats compared with the sham-operated rats (Fig. 4). In endothelium-denuded aortic rings, there was no discernible relaxant effect of DMPPO in any of the groups at the concentrations used in this study (data not shown).

Vascular Sensitivity to Phenylephrine

In aortic rings with endothelium, the phenylephrine dose-response curve was right-shifted in BDL rats, showing a significantly reduced response to phenylephrine in cirrhotic rats compared with sham-operated rats (Fig. 5). Aortic rings denuded of endothelium had an enhanced response to phenylephrine in both sham-operated and cirrhotic rats, and the difference between the two groups was no longer observed (Fig. 5). Preincubation of aortic rings with DMPPO attenuated the vasoconstriction in both groups: it shifted the dose-re-
response curve to the right and decreased the maximal response to phenylephrine in both the sham-operated and cirrhotic groups, and it eliminated the differences between them that were observed in aortic rings with endothelium (Fig. 6). When endothelium-denuded rings were incubated with SNAP or with SNAP and DMPPO and then exposed to phenylephrine, there was no difference in response between cirrhotic rats and sham-operated rats, contrary to the response observed in aortic rings with intact endothelium, nor were there changes in the responses observed within either the sham-operated or the cirrhotic group after these pretreatments (Figs. 7 and 8).

**Effects of DMPPO on Systemic Hemodynamics**

At the time of the experiment there was no difference in body weight between cirrhotic (265.5 ± 8.4 g) and sham-operated (255 ± 3.9 g) rats. The values of MAP, CI, and TPR in the two groups of rats before and after administration of DMPPO are shown in Table 1. Baseline values in BDL compared with sham-operated rats showed significantly higher CI and lower TPR, but there was no significant difference in MAP. Administration of DMPPO resulted in a decrease in MAP and TPR in both groups compared with the basal values, but no changes occurred in CI, such that the significant differences in both CI and TPR between sham-operated and cirrhotic rats that were observed before DMPPO administration remained valid after administration.

**Effects of DMPPO on Renal Function**

GFR, U_{Na}V, and F_{E_{Na}} are shown in Table 1. No significant difference was observed in the basal value of GFR between BDL rats and sham-operated rats, and administration of DMPPO had no effect on GFR in either group. In contrast, BDL rats tended to have lower basal values of U_{Na}V and F_{E_{Na}} compared with the sham-operated controls, but this was not statistically significant. After DMPPO administration, there were significant, almost threefold, increases in U_{Na}V and F_{E_{Na}} values in BDL rats. In contrast, in sham-operated rats, although there tended to be similar responses in U_{Na}V, this did not reach statistical significance by repeated-measures ANOVA (P = 0.07). As for F_{E_{Na}} in the sham-operated group, repeated-measures ANOVA revealed a significant difference from baseline (P = 0.03), which was evident during the first experimental period only. Comparison of values in the two groups during corresponding experimental periods with the Student’s unpaired t-test did not reveal a significant difference.

**DISCUSSION**

The results of this study reveal that in this model of cirrhosis in rats, there is a decreased sensitivity to the vasodilator effects of NG, an NO donor, compared with control rats. It is well established that the relaxant effect of NO is due to the action of cGMP produced as a result of stimulation of guanylate cyclase. PDE5 is the primary phosphodiesterase responsible for hydrolysis of cGMP in vascular smooth muscle. Theoretically, this...
The difference in response may be due to one of several factors: 1) decreased release of NO from the NO donor, 2) decreased formation of cGMP due to decreased activation of guanylyl cyclase by NO, possibly due to downregulation of soluble guanylate cyclase as a result of increased NO release in vessels from cirrhotic rats (14), and 3) increased hydrolysis of cGMP due to increased activity of PDE5 in cirrhotic rats. To examine whether this decreased responsiveness was limited to NG or extended to other NO donors, we conducted experiments with SNAP. These revealed essentially the same pattern of response, with decreased response in the BDL group compared with the sham-operated group, a difference that was eliminated by pretreatment of endothelium-denuded aortic rings with DMPPO. These results are consistent with a recent study that showed a decreased response to acetylcholine in mesenteric vessels from BDL rats (6) but contrary to other studies that found no difference between vessels from cirrhotic and control animals in their response to bethanecol or NG (16). Colle et al. (6) attributed this reduced response to impaired endothelium-dependent relaxation or to dysfunction at the level of vascular smooth muscle. However, two findings in the present study argue against this. 1) This decreased response was observed in endothelium-denuded rings; hence it was independent of the endothelium. 2) The similar response to diazoxide in vessels from BDL and control rats suggested that there was a specific decrease in sensitivity to the NO-cGMP pathway and not a nonspecific decline in vascular smooth muscle reactivity. The fact that DMPPO corrected the decreased sensitivity to NG and SNAP suggests that of the three mechanisms proposed above to explain this difference, the last, i.e., an increase in PDE5 activity, is the most plausible. Interestingly, the response to diazoxide was attenuated in endothelium-denuded vessels, suggesting that a small part of the response may be endothelium dependent. This was reported previously for low concentrations of diazoxide (30 μM) and was linked to NO production; higher concentrations of diazoxide were not affected by endothelium removal or by treatment with a NOS inhibitor (11). Others have reported that removal of the endothelium enhances the vasodilating effects of potassium channel openers like pinacidil and levromakalim (19). On the other hand, Deka et al. (8), using these same compounds, reported differential modulation by NO of their effects, such that removal of the endothelium led to enhancement of the effects of pinacidil and inhibition of the effects of levromakalim. It is obvious that this requires further investigation, but the fact remains that the major component of vasodilatation by diazoxide is endothelium independent, and there was no difference between BDL and sham-operated rats in response to diazoxide.

It was noticeable that the magnitude of the difference in the response to SNAP between sham-operated and BDL rats was less than that observed for NG. These results support recent reports of decreased vascular responsiveness to NG and SNAP in cirrhotic livers (10). Those authors suggested that this decreased sensitivity was due to both decreased metabolism of NG to NO and the inability of the hepatic vasculature to respond to NO. Our results suggest that the observed inability to respond to NO may be due to increased PDE5 activity in the
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Table 1. Effect of DMPPO on systemic hemodynamic and renal parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Period 1</th>
<th>Period 2</th>
<th>RM-ANOVA</th>
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<tr>
<td>Mean arterial pressure,</td>
<td></td>
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<td>mmHg</td>
<td>118±4</td>
<td>97±4*</td>
<td>99±5*</td>
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<td>Sham</td>
<td>121±5</td>
<td>98±4*</td>
<td>96±4*</td>
<td>&lt;0.0001</td>
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<td>Cardiac index, g·min⁻¹·100 g⁻¹</td>
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<tr>
<td>Sham</td>
<td>26.6±1.1</td>
<td>27.4±1.1</td>
<td>27.0±1.1</td>
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<tr>
<td>BDL</td>
<td>37.8±1.9</td>
<td>39.3±2.4†</td>
<td>40.1±1.9†</td>
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<td>Total peripheral resistance, mmHg·min⁻¹, 100 g⁻¹</td>
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<td>Sham</td>
<td>4.4±0.2</td>
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<td>3.6±0.2*</td>
<td>&lt;0.0001</td>
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<td>BDL</td>
<td>3.3±0.2†</td>
<td>2.6±0.2*†</td>
<td>2.5±0.2*†</td>
<td>&lt;0.0001</td>
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<td>Glomerular filtration rate, μeq/min</td>
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<tr>
<td>Sham</td>
<td>0.61±0.06</td>
<td>0.56±0.05</td>
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<td>BDL</td>
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<td>0.90±0.21</td>
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<td>Urinary Na excretion, %</td>
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<tr>
<td>Sham</td>
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<td>1.88±0.54</td>
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<tr>
<td>BDL</td>
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<td>4.03±0.85†</td>
<td>3.16±0.56*</td>
<td>0.01</td>
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<td>Fractional Na</td>
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<tr>
<td>excretion, %</td>
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<td></td>
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<tr>
<td>Sham</td>
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<td>BDL</td>
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<td>1.24±0.26*</td>
<td>1.13±0.15*</td>
<td>0.003</td>
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Values are means ± SE of the effects of 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)pyrazolo[3,4-d]pyrimidin-4(SH)-one (DMPPO) on systemic hemodynamic and renal parameters in bile duct ligation (BDL; n = 9) and sham-operated (Sham; n = 16) rats during a 30-min baseline period and 2 consecutive 30-min periods after administration of DMPPO (5 mg/kg iv). Comparisons among the 3 periods within the same group were conducted by repeated-measures ANOVA (RM-ANOVA). *P < 0.05 comparing baseline values with periods 1 and 2 (after DMPPO administration); †P < 0.05 comparing Sham and BDL rats.

hepatic vasculature. The fact that the difference between sham-operated and cirrhotic rats was greater for NG in our study is in agreement with the suggestion that there is, in the aorta as in the liver, an additional decrease in the conversion of NG to NO in cirrhotic rats.

Consistent with these findings was the reduced responsiveness of aortic rings to the relaxant effect of DMPPO itself. This vasodilator effect of DMPPO is likely due to enhancement by the drug of the relaxant effects of endothelium-derived NO, because it was absent in endothelium-denuded aortic rings (data not shown). The reduced response to DMPPO in cirrhotic rats may thus be explained by the increased activity of PDE5 in that tissue. Alternatively, the decreased response to DMPPO may be due to lower NO generation in the aorta. This, however, is contrary to the results of many studies that suggest that NO production is increased, rather than decreased, in the extrahepatic vasculature of cirrhotic rats (32). For example, Niederberger et al. (22) demonstrated an increase in both eNOS expression and cGMP levels in the aorta of cirrhotic rats. Cahill et al. (4) also showed increase in eNOS activity in superior mesenteric artery, thoracic aorta, and portal vein of portal hypertensive rats after partial portal vein ligation. Alternatively, it has been shown that cGMP itself activates PDE5, and that this activated form of PDE5 has a lower sensitivity to sildenafil (24). It is possible, therefore, that in cirrhotic vessels, which produce increased amounts of NO, the effectiveness of DMPPO is less because of increased cGMP levels, leading to inefficient inhibition of PDE5 and consequently a lower dilator effect.

The studies involving phenylephrine were particularly revealing. In endothelium-rich aortic rings, the responses to phenylephrine were attenuated in cirrhotic rats. One would have expected a greater response to phenylephrine based on the above discussion (increased PDE5 activity). However, this result is consistent with previous findings in the mesenteric vasculature and aorta of cirrhotic rats, which demonstrated decreased sensitivity to vasoconstrictors attributed to increased NO production (2, 3, 23, 32). Thus vessels from cirrhotic animals appear to have both an increase in NO synthesis and an increase in PDE5 activity that antagonizes the effects of NO; however, the increased NO synthesis predominates over the increased cGMP hydrolysis and leads to a reduced response to phenylephrine. In support of this explanation is the finding that in endothelium-deficient rings responses to phenylephrine were similar in the two groups. Interestingly, when endothelium-denuded rings were incubated with SNAP or with SNAP + DMPPO, thus eliminating the contribution of the differences in NO production and providing a constant and similar NO tone, the responses to phenylephrine remained similar to those in the sham-operated group, indicating that restoring a basal NO tone is not sufficient to reveal the difference in response based on a difference in PDE5 activity. This suggests that phenylephrine induces novel NO synthesis in the endothelium that partially antagonizes its direct vasoconstrictor effect and that differences in NOS activities in the two groups account for the observed differences in response to phenylephrine, as previously suggested (22).

How do these results suggesting increased PDE5 activity in the aorta and kidneys of cirrhotic animals relate to the hemodynamic disturbances in cirrhosis? Although the aorta may not be the ideal vessel to study, being a conduit rather than a resistance vessel, it has been used frequently as a model to examine the mechanisms of vascular dysfunction in liver cirrhosis and other diseases (4, 16, 22, 23). The peripheral vasodilation hypothesis of ascites formation in cirrhosis suggests that splanchnic vasodilation is the primary event that leads to activation of compensatory mechanisms, including the renin-angiotensin and sympathetic nervous systems, to result in sodium retention by the kidney and eventually renal vasoconstriction, culminating in the hepatorenal syndrome (26). Many studies have provided evidence to support a role for NO in splanchnic vasodilation (32). This conclusion was based in many instances on correction of the hemodynamic abnormality by NOS inhibitors, with some studies demonstrating increased levels of NO metabolites or increased NOS activity in that vascular bed. Taking the thoracic aorta as a model, we have provided evidence to suggest increased activity of PDE5, which manifested functionally as a reduced responsiveness to NO donors. This is consistent with previous studies that demonstrated increased activity and expression of PDE5 in the kidney (20, 21). These changes in PDE5 will tend to counteract the effect of increased NO generation or of any process that is mediated by cGMP, such as the effect of ANP in the kidney. It is possible therefore that the increased PDE5 activity may be an adaptive mechanism to the increased NO generation. This is
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in cirrhotic rats, although control rats also sustained an increase in sodium excretion (1). It should be noted, however, that this was an acute intervention, and that the chronic effect of administration of PDE5 inhibitors in cirrhosis may be different and may actually worsen sodium retention because it will potentiate vasodilation, which may further stimulate the compensatory sodium-retaining mechanisms. This is especially relevant considering recent findings in which a single dose of sildenafil administered to patients with liver cirrhosis and ascites reduced sodium excretion and arterial pressure and was associated with increases in plasma renin activity and angiotensin II and aldosterone levels (28). The reasons for these contradictory results are not clear, but it should be noted that all these patients had advanced stages of cirrhosis (with ascites), indicating severe sodium retention and activation of compensatory mechanisms. Any further vasodilation and reduction in arterial pressure could cause a marked worsening of their renal function. Furthermore, the dose of the PDE5 inhibitor may be an important consideration because a relatively high dose may lead to a marked reduction in arterial pressure that will counteract the direct, intrarenal natriuretic effect of the drug. Specific studies are needed to address these issues in the future.

In conclusion, this study revealed novel findings suggesting a role for PDE5 in regulating vasomotor reactivity, hemodynamics, and renal function in cirrhotic rats. In at least two tissues (the aorta and kidney), there is evidence to suggest an increase in activity of PDE5 that has important functional consequences. Further studies are warranted to examine the usefulness of chronic administration of PDE5 inhibitors in ameliorating the renal complications of cirrhosis, especially sodium retention.

REFERENCES


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The present study, despite the decrease in arterial pressure induced by DMPPO, there was an increase in sodium excretion in both the cirrhotic and control groups. Although unpaired analysis did not show a difference between the sham-operated and cirrhotic groups at any time point, likely because of the wide variability in values, repeated-measures analysis within each group revealed that the increase in sodium excretion was more consistent and reproducible in the cirrhotic group, resulting in a significant increase from baseline sustained during the two periods after DMPPO administration. These results emphasize the role of PDE5 activity locally in the kidney and the influence of PDE 5 inhibition on sodium handling by the kidney, both under control and, more prominently, under cirrhotic conditions. They are in agreement with previous findings that also showed a more consistent and more significant increase in sodium excretion after PDE5 inhibition with zaprinast in cirrhotic rats, although control rats also sustained
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