Dopamine-2 Receptor Blockade Potentiates the Renal Effects of Nitric Oxide Inhibition in Humans

Alberto Montanari, Enrico Tateo, Elena Fasoli, Anna Donatini, Barbara Cimolato, Patrizia Perinotto, Pierpaolo Dall’Aglio

Abstract—In eight young healthy subjects on a 240 mM Na diet mean arterial pressure (MAP), renal hemodynamics and renal handling of Na and exogenous Li were measured at baseline and during acute nitric oxide (NO) inhibition with 90-minute infusion of 3 0 μg/kg min⁻¹ of N⁰-L-arginine methyl ester (L-NAME). The same experiment was repeated with infusion of 50 μg/kg min⁻¹ of DA₂ receptor blocker L-Sulphide (L-SULP) alone and, finally, with simultaneous infusion of both L-NAME and L-SULP. L-SULP alone did not elicit any effect. L-NAME alone produced no changes in MAP from 0 to 45 minutes (P₁) and a 6% increase at 45 to 90 minutes (P₂) of infusion. Effective renal plasma flow (ERPF, PAH clearance) and glomerular filtration rate (GFR,ulin clearance) declined by 10% and 7.6%, respectively, in P₁, and by 15% and 11.5% in P₂. Filtration Fraction (FF) rose by 7.2% in P₁, calculated renal vascular resistance (RVR) increased by 13% to 25.6%. Fractional excretion of Na (FENa) and Li (FELi) fell by 20% and by 16%, respectively, in P₁, and by 40% and 25% in P₂. All these variations, except for MAP and GFR, were significantly greater during infusion of L-NAME and L-SULP. ERPF declined by 17% to 33.7%, FENa by 26% to 53.3%, FELi by 13% to 34.8%, while RVR rose by 22.5% to 59.1% and FF by 10% to 29.3%. The present data confirm that NO blockade with low-dose systemic infusion of L-NAME promotes renal vasoconstriction, reduced GFR, with slight increase in FF, and enhanced tubular Li and Na reabsorption. Since increase in RVR and FF and decrease in FENa and FELi are markedly potentiated by the simultaneous infusion of DA₂ blocker L-SULP, which exerts no effects by itself, we suggest that DA interactions between DA at the level of DA₂ receptors and basal NO production play a physiological role in the regulation of renal function in humans (Hypertension, 1998;31[part2]:277-282.)

Key Words: DA₂ receptor ■ L-SULP ■ L-NAME ■ human ■ kidney ■ nitric oxide ■ hemodynamics

The endogenous catecholamine dopamine (DA) is involved in a wide variety of physiological processes and contributes to modulation of many functions including behavior, movement, nerve conduction, hormone synthesis and release, blood pressure and renal hemodynamics, and sodium handling. Outside of the central nervous system, DA receptors have been divided on the basis of their localisation into two major groups, the presynaptic (DA₂) and postsynaptic (DA₁) subtypes.²³ Within the kidney, DA₂ receptors have been localized postsynaptically in blood vessels, proximal convoluted tubule, and collecting duct.¹⁻³ Increase in adenylcyclase activity, renal vasodilation and natriuresis, inhabitable by DA₂ antagonists, are known to follow DA₁ receptor stimulation by infusion of DA or specific DA₁ agonistic drugs.¹⁻³

DA₂ receptors have been identified presynaptically on sympathetic nerve terminals in the adventitia of the renal vasculature.¹⁻³ Due to their prejunctional localisation, DA₂ receptor activation is thought to inhibit the release of NE from the terminal, thus modulating RSNA.¹⁻² The physiological role of presynaptic DA₂ receptors on the regulation of renal hemodynamics and sodium reabsorption has been questioned since neither activation by endogenous DA of these receptors nor potentiation by DA₂ blockade of the effects of renal nerve stimulation in animals has been demonstrated.¹⁻⁴ Nonetheless, pharmacological DA₂ blockade has been shown to blunt markedly the renal responses to a number of different renal vasodilating and natriuretic manoeuvres, including low-dose DA infusion,⁶ extracellular fluid volume expansion with saline solution,⁷ central blood volume expansion with lower body negative pressure⁸ or head-out water immersion,⁹ and amino acid infusion.¹⁰ These effects have been obtained with DA₂ inhibiting drugs at doses that exert usually almost no effect on baseline renal hemodynamics and sodium excretion.

It is worth noting that under conditions known to be sensitive to DA₂ blockade, such as amino acid load and saline infusion,⁷,¹⁰-¹² renal vasodilation and natriuresis have been shown to be at least in part dependent on the integrity of L-Arginine-NO pathway. In addition, possible interactions between SNS and NO have been investigated to explain renal vasoconstriction and sodium retention following inhibition of basal NO synthesis with L-Arginine analogues, such as L-NMMA, L-NAME and L-NNA.¹³⁻¹⁸

Until now, no studies have been made in humans on the relationship between tonic NO-dependent regulation of renal function and DA or SNS. Thus, we have conducted the present study in healthy humans to investigate the effects of...
Dopamine and Nitric Oxide Interactions on Kidney Function

Methods

Subjects

Eight healthy subjects, three males and five females, chosen among the medical staff of Istituto di Patologia Medica at the University of Parma, participated in the study, after the study protocol had been approved by the Ethical Committee of our institution, and written informed consent had been obtained by each subject. The following inclusion criteria were used: All the subjects were aged less than 40 years, had no evidence or history of disease of heart, liver, kidneys, or endocrine organs, had not abused alcohol or drugs, and were not currently under medical treatment. Prior to the study, all subjects had maintained a controlled diet providing 2400 to 2800 kcal and 240 to 300 mmol sodium and 60 to 90 mmol potassium per day. At 8 00 AM After a blood sample was drawn for the control of para-aminomethylphenlic acid (PAH) and inulin measurement and hematocrit, a plastic indwelling catheter was placed into a cubital vein and a priming dose of 3000 mg/L 73m2 body surface area inulin (Inufest® 25% solution) and 600 mg/L 73m2 of PAH (20% solution) was infused. Then an infusion of PAH and inulin in saline solution was initiated using a 50 ml precision pump (Perfusion Secura, Braun) at a rate adjusted to obtain plasma levels around 1.5 mg/dL for PAH and 20 mg/dL for inulin. The infusion continued throughout the entire study, which was performed with the subjects in a sitting position. A second indwelling catheter for blood sampling was immediately placed at the controlateral arm and kept patent by constant infusion of 1.0 mL/h of saline solution.

After 60 minutes of equilibration (~45 minutes time), subjects emptied their bladders, then a 45 minute baseline clearance period was initiated. After 45 minutes, subjects voided, then a pump infusion of either 5 0 µg/kg min-1 L-SULP or 3 0 µg/kg min-1 of L-NAME in saline solution or both drugs, respectively, was initiated and maintained until the end of the study. Two further 45 minute clearance periods were performed (0 to 45 minutes, P1, and 45 to 90 minutes, P2, respectively), at which time the experiment was stopped. A 300 mL tap water load was administered hourly throughout the study in order to ensure an appropriate urine flow. Blood pressure and pulse rate were monitored every 5 minutes using an automatic monitoring device (TM 2421, A and D Co Ltd). Samples from urine excreted during each clearance period were taken for Na, Li, and NO2. Samples for plasma PAH and inulin were drawn every 15 minutes during the entire study. Samples for plasma Na and Li were taken at -45, 0, +45 and +90 minutes and for plasma PRL at 0, +45 and +90 minutes.

Calculations

A satisfactory steady-state plasma concentration of PAH and inulin was obtained with our infusion technique. The variability in plasma PAH and inulin measured throughout infusion was of the same order of magnitude as the coefficient of variability found in duplicate analysis of single plasma samples (2.4% for PAH and 3.6% for inulin). Thus, ERPF and GFR were calculated without measuring urinary PAH and inulin. For this purpose, PAH and inulin were measured in the inusate, and infusion rates were calculated by multiplying their concentrations for the volume of infusion solution per minute. By dividing the infusion rate for each measured plasma concentration, we obtained four values in the baseline period and three in each drug infusion period for both ERPF and GFR.

The mean values were used in the expression of data for each clearance period. Filteration Fraction (FF) was calculated by dividing GFR for ERPF, RBF by dividing ERPF for (1-hematocrit) and RVR from MAP and RBPF. Clearances of Li (ClLi) and Na (ClNa) were calculated with standard formula using the mean plasma value between the beginning and the end of each period. Baseline plasma Li ranged 0.10 to 0.18 mmol/L, according to the subject body size. Fractional excretion of Li and Na (FEli and FENA) were obtained by dividing CNa and CLi for GFR.

Study Drugs

PAH (20% solution) was purchased from J Monoce, Venice, Italy and Inute® from Laevosan Gesellschaft. Commercially available L-SULP (Levopral® 25mg/7ml ampoules, Ravizza) was used, whereas pharmaceutical-grade L-NAME was obtained from Clinalfa.

Analytical Methods

Na was measured by flame photometry, Li by atomic absorption spectrophotometry, and plasma and inusate PAH and inulin as previously described. PRL was measured by radioimmunoassay and NO, after NADPH oxidation also as previously described.
**Discussion**

The aim of the present human study was to investigate whether renal changes following acute L-NAME-induced inhibition of basal NO production are potentiated by blockade of DA system with L-SULP.

Plasma PRL, used as an indirect marker of DA blockade, increased substantially, as expected, with infusion of L-SULP alone. L-NAME alone did not alter basal PRL, as previously observed in rats. With L-SULP plus L-NAME infusion, changes in PRL were essentially the same as those observed with L-SULP alone. Although complex interactions between NO and local systems controlling PRL release in hypothalamus have been recently discovered, this latter finding indicates that the potent stimulus produced by DA2-blockade on PRL release overwhelmed any other interference potentially dependent on NO blockade.

Infusion of L-SULP alone did not affect baseline renal hemodynamics and cation handling. This is in agreement with that observed in most, although not in all, human studies on the effect of DA2 blockade by itself on renal function. Bughl et al. showed that DA2 blockade with domperidone can reduce ERPF in normal humans maintained at a low or intermediate Na intake, but is not effective at a 220 mmol Na intake, which is very close to that adopted in the present study.

Low-dose L-NAME infusion alone resulted in significant changes in basal renal hemodynamics and tubular reabsorption. These include substantial renal vasoconstriction, slight reduction in GFR and elevation in FF, relatively independent of changes in MAP, which rose significantly (+6%) only after 45 minutes of L-NAME infusion. In addition, both absolute and fractional excretion of Li and Na fell progressively. These variations are consistent with previous animal and human investigations, including our own recent study performed with the same L-NAME infusion technique as that presented here. During infusion of L-NAME and L-SULP, UNO,V fell at the same extent as during L-NAME alone. This indicates

**Statistical Methods**

Data are expressed as the mean ± SEM. Analysis of variance (ANOVA) and paired Student t test were used to compare the results obtained in different study periods in the same experiment and those of the same study period between the three experiments.

**Results**

No adverse effect due to L-SULP or L-NAME administration was observed.

Table 2 summarizes the results of our experiments for MAP and renal hemodynamics. While L-SULP alone did not exert any effect, L-NAME alone was followed by a slight, but significant rise in MAP only after 45 minutes of infusion. Renal hemodynamics was widely altered by L-NAME even at 0 to 45 minutes (P1), when MAP was unchanged. In that period, GFR diminished by about 8%, ERPF declined by 10.2%, and RVR increased by 13%. All these changes were more pronounced in the 45- to 90- minute infusion period (P2), when RVR was 25% higher than at baseline. With L-NAME plus L-SULP, changes in MAP were the same, while those in ERPF, RBF, and RVR were all significantly greater than with L-NAME alone in both P1 and P2. In P2 RVR was 59% higher than at baseline. Conversely, the fall in GFR was not different between L-NAME alone and L-NAME plus L-SULP. By consequence, FF, which showed only a modest increase in P1 with L-NAME (+4%), was markedly augmented even in P2 during L-NAME plus L-SULP infusion with a further significant rise during P2 (+29.3% versus baseline).

In Table 3, we summarize the effects of different infusion experiments on plasma PRL, renal handling of Li and Na, and excretion rate of NO (UNO,V). L-SULP alone produced, as expected, a marked rise in plasma PRL, thus showing an effective blockade of DA2 receptors, without any significant variation in Li, Na and NO excretion. Infusion of L-NAME alone did not affect PRL, while it elicited a progressive decline in both absolute and fractional excretion of Li and Na with values of UNaV, FENa, CLi, and FELi significantly lower in P2 than in P1.

These changes in Na and Li handling were markedly greater with the combined infusion of L-NAME and L-SULP, which produced the same rise in PRL as that with L-SULP alone and decrements in UNO,V comparable to those observed with L-NAME alone.

**Table 2. Effect of 90-minute Infusion of 5.0 μg/Kg.min⁻¹ L-Sulpride, 3.0 μg/Kg.min⁻¹ L-NAME and Both Drugs, Respectively on MAP and Renal Hemodynamics in 8 Na Repleted Healthy Subjects**

<table>
<thead>
<tr>
<th></th>
<th>b</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-SULP</td>
<td>76 ± 2</td>
<td>2.1</td>
<td>76 ± 2.3</td>
</tr>
<tr>
<td>L-NAME</td>
<td>76 ± 0.2</td>
<td>2.0</td>
<td>77 ± 0.2</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>76 ± 2</td>
<td>3.3</td>
<td>77 ± 0.2</td>
</tr>
<tr>
<td>GFR mL/min 1 73m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-SULP</td>
<td>103 ± 2</td>
<td>0.2</td>
<td>103 ± 2.3</td>
</tr>
<tr>
<td>L-NAME</td>
<td>104 ± 2</td>
<td>0.2</td>
<td>96 ± 2.3</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>104 ± 2</td>
<td>0.4</td>
<td>94 ± 2.3</td>
</tr>
<tr>
<td>ERPF mL/min 1 73m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-SULP</td>
<td>474 ± 18</td>
<td>0.8</td>
<td>480 ± 18</td>
</tr>
<tr>
<td>L-NAME</td>
<td>469 ± 19</td>
<td>0.0</td>
<td>439 ± 18</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>477 ± 19</td>
<td>0.0</td>
<td>302 ± 17</td>
</tr>
<tr>
<td>RBF mL/min 1 73m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-SULP</td>
<td>817 ± 40</td>
<td>0.7</td>
<td>830 ± 36</td>
</tr>
<tr>
<td>L-NAME</td>
<td>843 ± 37</td>
<td>0.7</td>
<td>757 ± 40</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>822 ± 38</td>
<td>0.7</td>
<td>676 ± 38</td>
</tr>
<tr>
<td>RVR mm Hg mg/min/mL 10º</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-SULP</td>
<td>02 ± 8</td>
<td>0.6</td>
<td>01 ± 6</td>
</tr>
<tr>
<td>L-NAME</td>
<td>90 ± 7</td>
<td>0.8</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>93 ± 8</td>
<td>0.8</td>
<td>114 ± 8</td>
</tr>
</tbody>
</table>

*b = baseline, P1 = 0 to 45 min of infusion, P2 = 45 to 90 min of infusion, Mean ± SEM.*

Table 3 summarizes the results of our experiments for PRL, renal handling of Na and Li, and excretion rate of NO (UNO,V). L-SULP alone produced, as expected, a marked rise in plasma PRL, thus showing an effective blockade of DA2 receptors, without any significant variation in Na and Li excretion. Infusion of L-NAME alone did not affect PRL, while it elicited a progressive decline in both absolute and fractional excretion of Na and Li with values of UNaV, FENa, CLi, and FELi significantly lower in P2 than in P1.

These changes in Na and Li handling were markedly greater with the combined infusion of L-NAME and L-SULP, which produced the same rise in PRL as that with L-SULP alone and decrements in UNO,V comparable to those observed with L-NAME alone.
TABLE 3. Effect of 90-minute infusion of 5.0 μg/kg.min⁻¹ L-Sulpiride, 3.0 μg/kg.min⁻¹ L-NAME and Both Drugs, Respectively on Plasma PRL, Renal Handling of Na and Li and Urinary Excretion of NO₂ Plus NO₃ (NOₓ) in 8 Na Repleted Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>b</th>
<th>P₁</th>
<th>P₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRL ng/mL</td>
<td>9.1±0.8</td>
<td>64.3±5.3*</td>
<td>75.3±7.1*</td>
</tr>
<tr>
<td>L-SULP</td>
<td>8.3±1.0</td>
<td>7.8±0.8</td>
<td>7.7±1.4</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>10.2±1.4</td>
<td>61.2±5.6*</td>
<td>68.3±7.0*</td>
</tr>
<tr>
<td>FENa</td>
<td>0.14±0.02</td>
<td>0.14±0.02</td>
<td>0.15±0.02</td>
</tr>
<tr>
<td>L-NAME</td>
<td>0.15±0.02</td>
<td>0.12±0.01*†</td>
<td>0.09±0.001**†</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>0.15±0.02</td>
<td>0.11±0.01*†</td>
<td>0.07±0.011***†</td>
</tr>
<tr>
<td>UNaV μmol/min</td>
<td>391±0.02</td>
<td>382±0.19</td>
<td>388±0.22</td>
</tr>
<tr>
<td>L-SULP</td>
<td>374±0.08</td>
<td>314±0.17*†</td>
<td>280±0.020***†</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>385±0.19</td>
<td>332±0.21*†</td>
<td>251±0.191**†</td>
</tr>
<tr>
<td>UNaV μmol/min</td>
<td>209±19</td>
<td>200±20</td>
<td>212±18</td>
</tr>
<tr>
<td>L-NAME</td>
<td>215±20</td>
<td>156±15*†</td>
<td>115±17††</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>217±18</td>
<td>148±19††</td>
<td>92±16††</td>
</tr>
<tr>
<td>Cl⁻ mL/min</td>
<td>40.3±2.1</td>
<td>39.4±1.7</td>
<td>40.4±1.9</td>
</tr>
<tr>
<td>L-SULP</td>
<td>38.9±1.8</td>
<td>30.1±2.2††</td>
<td>25.8±2.0**††</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>40.0±2.0</td>
<td>31.2±1.9††</td>
<td>22.3±1.8***††</td>
</tr>
<tr>
<td>UNaV μmol/min</td>
<td>1.16±19</td>
<td>1.22±21</td>
<td>1.23±23</td>
</tr>
<tr>
<td>L-NAME</td>
<td>1.30±20</td>
<td>0.88±18*</td>
<td>0.57±15*</td>
</tr>
<tr>
<td>L-SULP + L-NAME</td>
<td>1.02±19</td>
<td>0.75±21*</td>
<td>0.40±19*</td>
</tr>
</tbody>
</table>

*b = baseline, P₁ = 0 to 45 min of infusion, P₂ = 45 to 90 min of infusion, Mean ± SEM * P< 0.01 vs b, † P< 0.01 vs L-SULP, ‡ P< 0.05 vs P₁, § P< 0.01 vs P₀, || P< 0.05 vs L-NAME

Soares da Silva et al²⁵ reported an increased urinary DA excretion in long-term, L-NAME-treated rats. Conversely, Haynes et al²⁶ observed a reduction in urinary DA in humans acutely infused with L-NMMA. This latter finding, obtained under experimental conditions close to those adopted by us, may suggest that a reduced renal DA production may participate in Na retention following NO inhibition. We did not measure urinary DA. Whatever the change, if any, elicited by our experimental procedure on renal DA production, any significant relationship between potentiating effects of L-SULP and urinary DA excretion is very unlikely. Indeed, urinary DA reflects almost exclusively the DA production by tubular cells. Tubular DA does not elicit any demonstrated modulation on renal hemodynamics and exerts its native effect at the tubular level as an autocrine-paracrine substance through an activation of DA₂ receptors,¹,²,³ while blockade of DA system with L-SULP takes place mainly at the level of presynaptic DA₃ receptors.

SULP is known to be a highly specific inhibitor of DA receptors¹,²,³ Moreover, studies on SULP enantiomers have indicated that L-SULP is much more potent than the D-SULP on DA₂ receptors in various vascular tissues²,³,²⁷-²⁹ In addition, L-SULP showed marked stereoselective antagonisms upon presynaptic DA₂ receptors in different vascular tissues,²,²⁷-²⁹ including those of the kidney.²² Finally, recent work by Rump et al³⁰ has demonstrated that both L-SULP and domperidone, but not DA₁ blockers, do prevent in human kidney tissue the inhibition of electrically induced NE release produced by activation of DA₂ receptors with specific presynaptic DA₃ agonists. This confirms not only the existence of presynaptic DA₃ receptors in man, but also their functional properties of modulation of neuronal NE release.

Thus it seems reasonable to assume that L-SULP affects L-NAME-induced changes in renal function mainly through the inhibition of presynaptic DA₂ receptors in the kidney, with subsequent absolute or relative increase in NE release at the presynaptic level and enhancement of RSNA. However, the physiological role of presynaptic DA₂ receptors in controlling renal function is still uncertain.¹,²,³

Based on several animal studies in which DA₂ blockade failed to enhance the effects of electrical stimulation of renal nerves,⁴ the conclusion has been reached that there is no physiological role for DA₂ receptors and, more generally, for DA containing nerves in regulating renal hemodynamics and tubular function.⁴,⁵ Even in recent studies by Rump et al.³⁰ L-SULP and domperidone did not prevent the increase in NE release due to electrical stimulation of human kidney tissue unless DA₂ receptors were activated by specific agonistic drugs. Agnoli et al.⁶ observed that L-SULP, which is usually devoid of DA₂ antagonistic properties, essentially blocks DA₂ receptors in controlling renal function. The present study, is much more effective than D-SULP in inhibiting renal vasodilation and natremia induced by low-dose DA infusion in humans. This may suggest that activation of DA₂ receptors (in this case by the physiological, but exogenous substrate DA) is necessary to unmask their vasodilatory and natriuretic properties, whereas a direct demonstration of a physiological activation of presynaptic DA₂ receptors by endogenous DA is not yet available.⁴,⁵,³⁰

that the different magnitude of renal changes between the two infusions was not due to variations in the degree of NO synthesis inhibition, at least into the limits of UNaV as an approximate marker of whole body and, presumably, renal metabolism of NO₃.

As the main finding from the present study, changes in renal hemodynamics and cation handling due to L-NAME were markedly potentiated by the simultaneous infusion of L-SULP, which produced a two-times amplification of the fall in ERPF and RPF and the rise in RVR, subsequent to L-NAME alone. Since the drop in GFR was roughly the same with or without confused L-SULP, the small (+4%) but significant rise in FF with L-NAME alone was enormously potentiated (+29%).

Such a change in FF may explain, at least in part, the accentuated increase in fractional reabsorption of both Na and Li following L-NAME plus L-SULP infusion. Actually, a great increase in FF with consequent elevation in peritubular oncotic pressure and a fall in peritubular hydrostatic pressure owing to glomerular vasoconstriction may act as hemodynamically mediated physical forces to further increase reabsorption...
On the other hand, when pharmacological DA₂ blockade has been performed in humans under experimental conditions associated with reduced rather than increased RSNA, such as central blood volume expansion by lower body negative pressure or head-out water immersion, the consequent natriuretic and renal vasodilating responses have been found to be significantly inhibited. Thus, presynaptic DA₂ receptors seem to play an important physiological role at least under these particular conditions, where their blockade could be effective by preventing the appropriate reflex decrease in RSNA, following activation of mechanoreceptors due, in turn, to the centralization of blood volume.

It is of interest that a presumed reflex decrease in SNS activity has also been demonstrated in humans submitted to NO-inhibition with acute L-NAME infusion with subsequent rise in MAP. Thus the hypothesis may be advanced, although not demonstrated, that a NO inhibition-induced reduction in SNS activity, similar to that operating in central blood volume expansion, allows DA₂ receptor blockade to exert its effects on renal function.

The relationship between SNS (or RSNA) activity and renal effects of NO synthesis inhibition has been widely investigated. Studies in rats have indicated that renal denervation or chemical sympathectomy delay the onset or reduce the severity of L-NAME-induced hypertension. Moreover, when RSNA in rats is increased with carotid artery occlusion systemic and renal effects of L-NAME are markedly potentiated. Studies in conscious dogs and chronically instrumented, conscious rats with renal denervation have shown, however, that basal RSNA is not involved in renal vasoconstriction induced by L-NAME. On the other hand, investigations of dogs and rats infused intrarenally with NO have demonstrated that NO inhibition markedly exaggerates renal responses to acute NE and that these changes are not sustained chronically unless renal NO production is inhibited. Thus led the authors to suggest that basal renal NO production substantially modulates renal actions of NE.

Taken together, all these findings indicate that basal, not stimulated SNS activity by itself, has little effect on renal changes to NO inhibition, while marked potentiation follows stimulation of SNS secondary to carotid occlusion or even to stress due to surgical preparation or anesthesia. In addition, since renal hemodynamic effects of intrarenal NE are markedly accentuated by NO inhibition, basal NO production may serve as a physiological antagonist of increased RSNA.

A combination of an increased RSNA (or elevated renal content of NE) and an inhibited NO production, such as that obtained in the above mentioned experimental studies, may resemble the conditions of the present human study. In fact, when renal NO production is inhibited by L-NAME and DA₂ receptors are simultaneously blocked by L-SULP with subsequent increase (or, perhaps, impaired decrease) in RSNA, renal vasoconstriction and Na retention take place at an extent much greater than with L-NAME alone.

On the other hand, DA₂ blockade by itself has no effect on basal renal function, and it produces renal vasoconstriction and antinatriuresis only under NO inhibition. If we assume that presynaptic DA₂ blockade per se may stimulate RSNA, we might suggest that NO may act as a physiological buffering mechanism for increase in RSNA, thus confirming the findings obtained in animal studies. Of course, a major limitation of this interpretation rests as previously pointed out, on the uncertainty of the physiological activation by endogenous DA of presynaptic DA₂ receptors and, by consequence, of the effect of their blockade under both baseline conditions and NO inhibition.

In conclusion, we demonstrate in the present study that simultaneous blockade of both DA system at the level of presynaptic DA₂ receptors and NO synthesis produces in the human kidney profound changes in hemodynamic and tubular functions, with intense vasoconstriction and marked sodium retention. Since these changes are much greater that those observed with NO inhibition alone, while DA₂ blockade by itself has no effect, we suggest that interactions between presynaptic DA₂ receptors and NO system play a physiological role in the regulation of renal hemodynamics and tubular function.

Further investigation is required in order to clarify whether this interaction is mediated by the interplay between NO production and modulation of SNS activity in the kidney operated by the neural presynaptic DA₂ receptors.

References

Dopamine and Nitric Oxide Interactions on Kidney Function


16


17


18


19


20


21


22


23


24


25


26


27


28


29

Shepperson NB, Duval N, Mssingham R, Langer S. Differential blocking effect of several dopamine receptor antagonists for presynaptic pre- and postsynaptic dopamine receptors in anesthetized dogs. *J Pharmacol Exp Ther* 1982;221:753-761

30


31

Dopamine-2 Receptor Blockade Potentiates the Renal Effects of Nitric Oxide Inhibition in Humans
Alberto Montanari, Enrico Tateo, Elena Fasoli, Anna Donatini, Barbara Cimolato, Patrizia Perinotto and Pierpaolo Dall’Aglio

Hypertension. 1998;31:277-282
doi: 10.1161/01.HYP.31.1.277

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/31/1/277

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/