Selective Peripheral Dopamine-1 Receptor Stimulation
Differential Responses to Sodium Loading and Depletion in Humans

N. Virginia Ragsdale, Marie Lynd, Robert L. Chevalier, Robin A. Felder, Michael J. Peach, and Robert M. Carey

Dopaminergic mechanisms are functionally important in the control of sodium excretion. In normal humans, urinary dopamine excretion is increased during sodium loading and, conversely, is decreased during sodium depletion. Exogenous administration of dopamine in sodium-replete humans produces renal vasodilation and increases urinary sodium excretion. In experimental animals, blockade of the renal DA1 receptor impairs the natriuretic response to acute sodium load and produces antinatriuresis by a renal tubular mechanism. Thus, it is possible that renal dopaminergic mechanisms are functionally important in the control of sodium excretion.

Fenoldopam mesylate, a benzazepine derivative, is a specific DA1 agonist. Intravenous administration of fenoldopam in humans has been reported to lower mean arterial blood pressure and to increase
renal plasma flow and urinary sodium excretion without change in glomerular filtration rate. In experimental animals, these effects have been shown to be blocked by SCH-23390, a specific D₁ antagonist.8,13

Sodium homeostasis dictates the physiological response to hormonal systems, which, in turn, regulate renal sodium excretion. For example, the renin-angiotensin system is dependent on the existing sodium balance state. Sodium deprivation decreases vascular and renal sensitivity and increases adrenal responses to angiotensin II, whereas sodium loading has the opposite effect.14,15

The effects of sodium balance on renal responses to D₁ receptor stimulation are unknown. The present study was designed to examine the renal effects of D₁ receptor stimulation by fenoldopam in normal humans during sodium loading and depletion by measurement of renal hemodynamic and tubular function.

**Methods**

**Study Design**

The experimental protocol was approved by the Human Investigation Committee of the University of Virginia School of Medicine, and written informed consent was obtained from each subject. Sixteen healthy 21–31-year-old men who passed screening evaluations participated in a single-blind, vehicle-controlled study protocol.

The 2-week study began with a 5-day outpatient phase during which the subjects received one of two isocaloric constant diets, either 300 or 10 meq sodium. The daily potassium intake was 60 meq for each diet. All meals were prepared and consumed at the metabolic kitchen of the University of Virginia Clinical Research Center, and no other food was allowed. Twenty-four-hour urine collections from days 3, 4, and 5 of the outpatient phase were analyzed for sodium, potassium, and creatinine to confirm that subjects were in sodium metabolic balance. Daily weight and orthostatic vital signs were obtained during the entire outpatient phase.

On the evening of day 5, the subjects were admitted to the Clinical Research Center, and from midnight until the protocol ended the following day, the subjects remained supine and were fasted. On day 6 at 6:30 AM, the subjects received 600 mg lithium carbonate by mouth. Between 7:00 AM and 8:00 AM, an oral load of tap water (20 ml/kg) was ingested. At 8:00 AM, a heparin lock was placed in the left antecubital vein for blood sampling; the right antecubital vein was cannulated for intravenous infusion. Priming doses of 50 mg/kg inulin in 5% dextrose–water (Taylor Pharmaceutical Co., Decatur, Illinois) and 8 mg/kg p-aminohippurate (PAH) in 5% dextrose–water (Merck Sharp & Dohme, Baltimore, Maryland) were given by bolus intravenous injection at 7:00 AM. These injections were followed by a maintenance infusion of inulin and PAH, which was calculated for the predicted glomerular filtration rate and renal plasma flow and administered at 0.3 ml/min. While the subjects remained in the supine position, urine samples were obtained every 30 minutes and were followed by oral water replacement to maintain a state of diuresis. Subjects on the high sodium diet received 170 meq sodium in tablet form during the test period.

After 2 hours for equilibration, a 2-hour precontrol period ensued; this period was followed by a 3-hour experimental period during which the subjects received intravenous infusions of either fenoldopam mesylate (0.05 μg/kg/min) in 5% dextrose–water or vehicle alone. The experimental period was followed by a 2-hour postcontrol period. Throughout the study, 30-minute urine samples were collected for analysis of PAH, inulin, sodium, potassium, and lithium concentrations and osmolality. Blood samples were obtained at the midpoint of each urine collection period for determination of plasma PAH, inulin, and serum sodium, potassium, and lithium concentrations and osmolality. Blood samples for measurement of plasma aldosterone, plasma renin activity, and atrial natriuretic peptide concentrations were collected at 10:45 and 11:45 AM and 12:45 PM. Blood pressure and heart rate were measured in duplicate every 15 minutes by using a Dinamap automatic blood pressure and heart rate recorder (model 845 XT, Critikon Inc., Tampa, Florida). At 4:00 PM, the study was terminated, and the subjects were allowed to eat and ambulate until midnight.

On day 7, the identical experiment was repeated with the alternate drug (fenoldopam or vehicle) regimen. The entire protocol was repeated during the next phase of the study (days 8–14) with the alternate diet. The order of administration of high or low sodium diet and infusion of fenoldopam or vehicle was assigned randomly.

**Analytical Methods**

Serum sodium and potassium concentrations were measured by an SMAC-2 instrument (Technicon, Tarrytown, New York). Urine and serum osmolalities were determined by freezing-point depression with an osmometer (model 302, Advanced Instruments, Inc., Needham, Massachusetts). Urine and plasma inulin concentrations were determined by the method of Heyrovsky.16 Urine and plasma PAH concentrations were measured by the method of Brun.17 Urine and serum lithium and serum sodium concentrations were measured by a digital flame photometer; urine sodium concentrations were detected with a NOVA 1 analyzer (NOVA Biomedical, Waltham, Massachusetts). Plasma renin activity was determined by the radioimmunoassay method of Sealey and Laragh.18 Plasma aldosterone levels were measured by a Coat-A-Count radioimmunoassay kit (Diagnostic Products Corp., Los Angeles, CA). Plasma atrial natriuretic peptide concentrations were determined by specific radioimmunoassay.19
Renal Function Calculations

Clearance values for inulin, PAH, sodium, potassium, lithium, free water, and osmolality were calculated by using standard formulas, as was the fractional excretion of each electrolyte. Distal sodium load was calculated by the following formula: $C_{H_2O} + C_{Na}$, where $C_{H_2O}$ and $C_{Na}$ are the clearance values for free water and sodium, respectively. Distal tubular sodium reabsorption was determined by using the following formula: $C_{H_2O} \times 100/(C_{H_2O} + C_{Na})$. Distal tubular sodium reabsorption was determined by using the following formula: $C_{H_2O} \times 100/(C_{H_2O} + C_{Na})$. Distal tubular sodium reabsorption was determined by using the following formula: $C_{H_2O} \times 100/(C_{H_2O} + C_{Na})$. Distal tubular sodium reabsorption was determined by using the following formula: $C_{H_2O} \times 100/(C_{H_2O} + C_{Na})$.

Statistical Analysis

Paired t tests of the mean differences between fenoldopam and vehicle control days used period means per subject and calculated significant differences in period means within the high or low sodium groups. One-way analysis of variance and Duncan's multiple range test (a fixed alpha of 0.05) were used to compare period differences within each experimental day for the four experimental conditions: high sodium–fenoldopam, high sodium–vehicle control, low sodium–fenoldopam, and low sodium–vehicle control. Data are reported as mean±1 SEM. Values of $p<0.05$ were considered significant.

Results

Metabolic Balance Before the Experimental Period

The study subjects were in metabolic balance on the fifth day of constant sodium and potassium intake, as demonstrated by urinary sodium values of $257.0\pm14.2$ meq/24 hr during high sodium intake and $11.3\pm0.7$ meq/24 hr during low sodium intake. A steady state of diuresis was present during the control period as a result of the waterloading procedure. Urinary osmolality was $86.5\pm3.4$ mOsm/kg on high sodium diet and $70.3\pm2.2$ mOsm/kg on low sodium diet.

Renal Responses to DA$_1$ Receptor Stimulation

Administration of fenoldopam increased urine flow rate (Figure 1) during high sodium intake compared with vehicle time control values ($p<0.05$). After termination of fenoldopam infusion, urine flow rate decreased to control values within 30 minutes. No significant changes were observed during low sodium intake. Urine flow rate was consistently higher with sodium loading compared with sodium depletion ($p<0.05$).

Urine sodium excretion (Figure 2) and fractional excretion of sodium (Figure 3) were increased substantially and in parallel with fenoldopam infusion during high sodium intake compared with vehicle time control values ($p<0.001$ and $p<0.005$, respectively). Urinary sodium excretion and fractional excretion of sodium returned to control values within 30 and 60 minutes, respectively, during the postcontrol period. Urinary sodium excretion and fractional excretion of sodium were unchanged during low sodium intake. As expected, urinary sodium excretion and fractional excretion of sodium were higher during high sodium intake compared with vehicle time control values ($p<0.05$).
Fractional excretion of sodium (Figure 3) showed a significant increase during high rather than during low sodium balance (p<0.05 for both parameters).

Urinary potassium excretion (Table 1) and fractional excretion of potassium (Table 1) were unchanged by fenoldopam and did not vary with sodium diet; however, an overall trend of decreasing urinary potassium excretion and fractional excretion of potassium was observed throughout all phases of the study (p<0.05). Fractional excretion of lithium (Figure 4) increased with fenoldopam during high sodium intake and returned to vehicle control values 30 minutes into the postcontrol period. During high sodium intake, the incremental increases in response to fenoldopam were 78.9±13.2% for fractional excretion of sodium and 14.4±5.4% for fractional excretion of lithium (p<0.0001).

Renal plasma flow (Table 1) was increased by fenoldopam during both high and low sodium intake (p<0.005 and p<0.0001, respectively). Renal plasma flow returned to vehicle control values within 30 minutes after termination of fenoldopam administration. Overall, renal plasma flow values were higher with high sodium intake (p<0.05). Glomerular filtration rate (Table 1) was not affected by fenoldopam and did not vary with sodium intake.

As expected, distal sodium load (Figure 5) was higher during high than low sodium intake (p<0.005). Distal sodium load was increased by fenoldopam during high sodium intake (p<0.05) and returned to vehicle control values within 30 minutes after cessation of fenoldopam infusion. No changes in distal sodium load were observed during low sodium intake. Distal sodium reabsorption (Figure 6) was decreased during high as compared with low sodium intake (p<0.005). Distal sodium reabsorption decreased with fenoldopam infusion during high sodium intake; however, this decrease was not significant statistically compared with corresponding vehicle control values. Distal sodium reabsorption was unchanged during low sodium intake.

Hormonal Responses to DA<sub>1</sub> Receptor Stimulation

Table 2 shows that plasma renin activity and plasma aldosterone concentration were increased with dietary sodium depletion (p<0.0005 and p<0.0001, respectively) and that plasma concentrations of atrial natriuretic peptide were slightly higher in the presence of high sodium intake (p<0.05) during the precontrol period but were not significantly different during the experimental period. Administration of fenoldopam did not cause any significant changes in plasma renin activity, plasma aldosterone concentration, or atrial natriuretic peptide.

Table 1. Selected Renal Responses to Dopamine-1 Stimulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diet</th>
<th>Precontrol</th>
<th>Experimental</th>
<th>Postcontrol</th>
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<tr>
<td>RPF (ml/min)</td>
<td>V</td>
<td>F</td>
<td>V</td>
<td>F</td>
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<tr>
<td>HS</td>
<td>681.8±28.9</td>
<td>670.7±31.7</td>
<td>630.5±19.4</td>
<td>717.3±21.0</td>
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<td>LS</td>
<td>623.3±17.8</td>
<td>569.0±17.8</td>
<td>549.7±12.9</td>
<td>624.8±17.0</td>
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<tr>
<td>GFR (ml/min)</td>
<td>V</td>
<td>F</td>
<td>V</td>
<td>F</td>
</tr>
<tr>
<td>HS</td>
<td>113.1±3.4</td>
<td>118.1±4.4</td>
<td>107.6±3.2</td>
<td>110.0±2.9</td>
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<tr>
<td>LS</td>
<td>107.0±3.3</td>
<td>109.7±3.7</td>
<td>107.5±2.8</td>
<td>110.6±3.8</td>
</tr>
<tr>
<td>UaV (μeq/min)</td>
<td>V</td>
<td>F</td>
<td>V</td>
<td>F</td>
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<tr>
<td>HS</td>
<td>65.5±3.1</td>
<td>67.0±2.3</td>
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<td>73.0±4.2</td>
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<td>61.9±3.4</td>
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<td>FEX (%)</td>
<td>V</td>
<td>F</td>
<td>V</td>
<td>F</td>
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<tr>
<td>HS</td>
<td>15.7±0.8</td>
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<td>15.0±0.5</td>
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<tr>
<td>LS</td>
<td>19.4±1.4</td>
<td>16.8±1.1</td>
<td>17.0±0.9</td>
<td>15.6±0.8</td>
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</tbody>
</table>

Values are mean±1 SEM. V, vehicle group; F, fenoldopam group; RPF, renal plasma flow; GFR, glomerular filtration rate; UaV, urinary potassium excretion; FEX, fractional excretion of potassium; HS, high salt diet; LS, low salt diet.

*p<0.05 compared with vehicle.

†p<0.005 compared with vehicle.

‡p<0.0001 compared with vehicle.
Fractional Excretion of Lithium (\%)

Time (hrs)

1 2 3 4 5

-20

-18

-16

-14

-12

-10

-8

-6

-4

-2

0

2

4

6

8

10

12

14

16

18

FIGURE 4. Graph showing response of fractional excretion of lithium to fenoldopam or vehicle during high (300 meq/day) sodium balance in normal male subjects (n=16). Value of p refers to the difference between fenoldopam and vehicle control values of the experimental period (0-3 hours). Results are plotted as mean±1 SEM. C, precontrol period; PC, postcontrol period.

Systemic Hemodynamic Responses to DA₁ Receptor Stimulation

Table 3 shows systolic and diastolic blood pressure and heart rate responses to DA₁ receptor stimulation. Systolic blood pressure was not affected significantly by fenoldopam during either high or low sodium intake. Systolic blood pressure was slightly increased by high sodium intake during the experimental and postcontrol periods of the vehicle control day (p<0.05 for both periods). Diastolic blood pressure decreased slightly but significantly with fenoldopam during low sodium intake only (p<0.05) and returned to vehicle control values during the postcontrol period. Diastolic blood pressure did not vary significantly with sodium balance and was not affected by fenoldopam during high sodium intake. Heart rate was very slightly increased by fenoldopam during both high and low sodium intake (p<0.05 for both compared with vehicle control) and returned to vehicle control values during the postcontrol period.

Discussion

The results of this study show that during dietary sodium loading, DA₁ receptor stimulation with fenoldopam leads to an increase in urinary flow rate, urinary sodium excretion, and renal plasma flow without alteration in glomerular filtration rate or induction of kaliuresis. Fractional excretions of sodium, potassium, and lithium were evaluated as indicators of tubular function beyond the glomerulus. Since the fractional excretion of sodium increased significantly in response to fenoldopam, the data were evaluated to separate tubular effects with respect to proximal and distal sites. A decrease in proximal tubular sodium reabsorption in response to DA₁ stimulation was demonstrated by the calculated distal sodium load, which approximates the quantity of sodium not reabsorbed in the proximal portion of the nephron. This response was confirmed by a simultaneous increase in the fractional excretion of lithium. In the sodium-replete or sodium-loaded state, lithium is reabsorbed quantitatively in parallel with sodium and almost exclusively in the proximal tubule. Lithium is not transported in the distal portions of the nephron. Consequently, in the sodium-replete state, fractional excretion of lithium is a direct marker of proximal tubular sodium reabsorption, and the fractional excretions of sodium and lithium, taken together, are an indirect marker of distal tubular sodium reabsorption. Our study shows that fractional excretion of sodium and lithium both rose in parallel in response to DA₁ receptor stimulation. However, the increment of change of the fractional excretion of sodium engendered by fenoldopam was larger than that of the fractional excretion of lithium; this difference indicates a natriuretic effect of fenoldopam at distal as well as proximal tubular sites. The reduction of distal sodium reabsorption in response to fenoldopam, although not achieving statistical significance, supports the above-
mentioned evidence that DA₁ receptor stimulation also decreases sodium reabsorption at the distal tubule. DA₁ receptors and dopamine-stimulated adenylate cyclase have been measured in the cortical collecting duct (R.A. Felder, unpublished observations). Taken altogether, these results strongly suggest DA₁-induced natriuresis at distal as well as proximal renal tubular sites.

Although the mechanisms of DA₁-induced natriuresis are not well defined, dopamine has been reported to inhibit both active (Na,K-ATPase) and passive (Na-H antiporter) sodium exchange mechanisms in the proximal tubule.25,26 Similar mechanisms could pertain for distal DA₁-mediated natriuresis as well.

During dietary sodium depletion, DA₁ receptor stimulation with fenoldopam did not elicit a renal tubular response. Maximum tonic inhibition of sodium excretion as a result of sodium depletion was not likely, because natriuresis may be attained during sodium depletion by other experimental maneuvers, such as administration of saralasin (angiotensin II receptor blockade), teprotide (angiotensin converting enzyme inhibition), or the statine-containing renin inhibitor ACRIP (renin inhibition).27-29 Since sodium depletion would be expected to decrease renal dopamine production,3 it is unlikely that the abrogation of fenoldopam-induced natriuretic responses was due to down-regulation of the renal tubular DA₁ receptor by the endogenous agonist. Therefore, possible mechanisms for the abrogation of DA₁-induced renal sodium excretion during sodium depletion include a direct inhibition by the low sodium state of postreceptor DA₁ mechanisms in the renal tubular cell or an overriding effect of renal compensatory factors, including the renin-angiotensin system, with increased renal tubular sodium reabsorption during sodium depletion. In this regard, plasma renin activity and plasma aldosterone concentration were increased as expected during sodium depletion and were not altered during DA₁ receptor stimulation with fenoldopam.

The rise in renal plasma flow in response to fenoldopam during dietary sodium depletion is noteworthy. In 1988, Hughes et al30 reported a similar dissociation of tubular and hemodynamic effects after 24 hours of continuous DA₁ stimulation with fenoldopam in normal male subjects on a 150 meq (normal) sodium diet. Under these conditions, renal tubular refractoriness to continuous long-term (24-hour) DA₁ receptor stimulation may have been related to the large cumulative sodium deficit brought about by continuous DA₁-induced natriuresis. The present study shows that the aforementioned dissociation of renal hemodynamic and tubular responses to DA₁ stimulation is mimicked by fenoldopam-induced DA₁ responses during dietary sodium depletion. That is, renal plasma flow remains elevated while natriuresis is abrogated during fenoldopam infusion. These results suggest that sodium homeostasis directly influences the affinity or density of renal tubular, but not renal vascular, DA₁ receptors or that sodium balance influences DA₁-induced cellular responses distal to the DA₁ receptor.

In addition to the further understanding of renal physiological responses to DA₁ mechanisms, the results of the present study may be important clinically. Selective DA₁ stimulation with a quantity of fenoldopam too low to affect systemic hemodynamic or hormonal function appreciably produces renal impairment.

### Table 2. Hormonal Responses to Dopamine-1 Stimulation

<table>
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<th>Parameter</th>
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<th>Experimental</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>V</td>
<td>F</td>
</tr>
<tr>
<td>PAC (ng/dl)</td>
<td>HS</td>
<td>4.5±0.5</td>
<td>4.1±0.3</td>
</tr>
<tr>
<td></td>
<td>LS</td>
<td>19.8±2.2*</td>
<td>17.4±1.8*</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>HS</td>
<td>0.68±0.12</td>
<td>0.54±0.04</td>
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<tr>
<td></td>
<td>LS</td>
<td>3.5±0.4*</td>
<td>3.2±0.4*</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>HS</td>
<td>28.7±3.3</td>
<td>30.6±3.1</td>
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<tr>
<td></td>
<td>LS</td>
<td>21.7±2.0*</td>
<td>22.6±2.2*</td>
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*Values are mean±1 SEM. V, vehicle group; F, fenoldopam group; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ANP, plasma atrial natriuretic peptide; HS, high salt diet; LS, low salt diet. *p<0.05 compared with high salt diet.

**FIGURE 6.** Graph showing response of distal sodium reabsorption to fenoldopam or vehicle during high (300 meq/day) or low (10 meq/day) sodium balance in normal male subjects (n=16). Values of p refer to differences between fenoldopam and vehicle control values for the experimental period (0–3 hours). Results are plotted as mean±1 SEM. C, precontrol period; PC, postcontrol period; NS, not significant.
vasodilation and natriuresis/diuresis. These renal effects would potentially correct increased renal vasoconstriction and renal tubular sodium reabsorption in disorders of increased extracellular fluid volume, such as congestive heart failure. Whether the kidneys of patients with edema-forming states respond to DA₁ stimulation with natriuresis/diuresis, as do kidneys of sodium-loaded normal subjects, or whether they behave as kidneys of sodium-depleted subjects refractory to DA₂-induced renal tubular responses remains to be determined.

In conclusion, DA₁ receptor stimulation mediates natriuresis by renal hemodynamic and tubular mechanisms. The renal tubular effects of DA₁ stimulation are a result of an action at both proximal and distal tubular sites and are independent of the circulating renin-angiotensin-aldosterone system or atrial natriuretic peptide. Abolition of the DA₁ natriuretic response during sodium depletion suggests a direct inhibition by low sodium of cellular DA₁ mechanisms in the renal tubule or recruitment of compensatory homeostatic mechanisms within the kidney.

Acknowledgments

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<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Experimental</th>
<th>Postcontrol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>V</td>
<td>F</td>
<td>V</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>HS</td>
<td>120.3±2.3</td>
<td>122.6±2.2</td>
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<tr>
<td></td>
<td>LS</td>
<td>116.7±1.5</td>
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<td>DBP (mm Hg)</td>
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<td>69.6±1.3</td>
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<tr>
<td></td>
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<td>67.9±1.2</td>
<td>67.0±1.3</td>
<td>63.7±1.3*</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>HS</td>
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<td>55.6±1.1*</td>
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<td>56.4±1.5</td>
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</table>

Values are mean±1 SEM. V, vehicle group; F, fenoldopam group; SBP, systolic blood pressure; DBP, diastolic blood pressure; HS, high salt diet; LS, low salt diet. *p<0.05 compared with vehicle.

KEY WORDS • dopamine • kidney • sodium • fenoldopam • dopamine receptors
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