The Effects of Dopamine on Renal Excretion of Sodium, Phosphate and Cyclic AMP in Thyroparathyroidectomized Dogs

FUMIO GOTO

Department of Anesthesiology,
Gunma University Hospital,
Maebashi, Gunma, Japan

Synopsis

With dopamine (0.5 µg/kg/min) infusion into the renal artery of thyroparathyroidectomized dogs, urine output and inorganic phosphate excretion increased significantly (p<0.05), but the increase in sodium excretion was low and not statistically significant. However, natriuresis and phosphaturia due to the infusion of dopamine were accelerated more markedly by the pretreatment with phenoxybenzamine. Dopamine was infused into the renal artery in doses too small to affect renal hemodynamics (0.02–0.05 µg/kg/min) after the treatment with phenoxybenzamine and alprenolol with the result that phosphate and sodium excretion increased significantly (p<0.05). The excretion rate of cAMP did not change. This suggests that the effect of dopamine on sodium and phosphate excretion is directly influenced by alpha adrenergic activity in the kidney. The mechanism of natriuresis and phosphaturia by dopamine is, however, independent of changes in parathyroid hormone and the adenyl cyclase-cAMP system.

Dopamine, the immediate metabolic precursor of norepinephrine, is a naturally occurring catecholamine. In addition to its alpha- and beta-adrenergic effects, dopamine has the unique effect of increasing renal and mesenteric blood flow (Goldberg, 1972). It is believed that dopamine acts on a specific receptor in the renal vascular beds (Yeh et al., 1969), but the mechanism of the natriuretic effect of dopamine remains unexplained. Vlachoyannis (1976) reported that the natriuretic effect of dopamine may be mediated by the activation of enzymes regulating cyclic adenosine 3', 5' monophosphate (cAMP) levels. However, Kuchel and Hamet (1977) pointed out that the positive correlation between the increased sodium excretion and increases in nephrogenous cAMP is not necessarily related to the mechanism of dopamine natriuresis. The excretion rate of nephrogenous cAMP is controlled by many factors (Broadus et al., 1971; Kuchel et al., 1975), the most important of these being parathyroid hormone (PTH) levels (Drezner et al., 1976). The object of the present study was to examine natriuresis and phosphaturia (Cuche et al., 1976) due to dopamine infusion; and moreover, the correlation between dopamine action and the excretion rate of cAMP in thyroparathyroidectomized dogs, as PTH secretion is stimulated by catecholamines, (Fischer et al., 1973).

Materials and Methods

Eighteen mongrel dogs of both sexes weighing 6-8 kg, were fasted for twenty-four hours before the experimental period and allowed free access to water.
The dogs were anesthetized with pentobarbital (20 mg/kg, intravenously). Tracheas were intubated and the lungs ventilated with a Harvard pump respirator with a mixture of air, oxygen and 0.7–0.9% halothane. Ventilation and gas concentration were adjusted to maintain PaCO₂ at 30–40 torr; PaO₂ at 95–130 torr. Esophageal temperature was maintained at 37 ± 0.5°C.

Cannula were inserted into the right femoral vein to sustain infusion and into the right femoral artery for blood sampling and blood pressure recording. Polyethylene cannula were passed into the left ureter via a subcostal incision for timed collection of urine. The left renal artery was exposed for the subsequent infusion of dopamine. 0.25 ml/min 0.9% saline was infused into the left renal artery via a 27 gauge curved needle. After twenty minute normal clearance periods, all dogs were thyroparathyroidectomized four hours before dopamine infusions to prevent possible altered parathyroid hormone (PTH) secretion (Fischer et al., 1973).

The dogs were divided into three groups:

**Group 1** After two 10-min control clearance periods, dopamine (0.5 μg/kg/min) was infused into the left renal artery. The infusion rate of saline (0.25 ml/min) was not altered. After allowing 10-min for equilibration, two 10-min dopamine clearance periods were obtained.

**Group 2** Following the control clearance periods, clinical doses of phenoxybenzamine (POB) (2 mg/kg) were infused intravenously. After 30 min, dopamine (0.5 μg/kg/min) was infused into the left renal artery as in group 1.

**Group 3** Following the control clearance periods, 10 mg/kg POB and 1 mg/kg alprenolol were infused intravenously. These procedures were required for the blockage of alpha- and beta-adrenergic action of dopamine. After a 30-min interval and a 10-min control clearance period, small doses of dopamine (0.02–0.05 μg/kg/min) were infused into the left renal artery.

During the experiment 200 ml/hr of a 0.9% saline solution was infused in every group.

Urine and plasma concentrations of PAH (Smith et al., 1945), creatinine (Steinitz et al., 1940) and phosphate (Fiske et al., 1925) were determined colorimetrically. The glomerular filtration rate (GFR) was determined by endogenous clearance of creatinine. cAMP was measured by radioimmunoassay (Schwarz/Mann cAMP Radioimmunoassay Kit).

Student’s t test for paired and unpaired comparisons was used for statistical analysis with a P value of less than 0.05 considered to represent a statistically significant change.

As shown in Table 1 and Fig. 1, fractional excretion of inorganic phosphate fell off from 13.2 to 2.3–2.4% and the positive correlation between plasma PO₄ concentration and fractional excretion (y = 2.47x + 5.25; r = 0.74, p < 0.05) during the normal periods was lost after thyroparathyroidectomy in group 2.

In Group 1, with dopamine infusion alone, urine volume and phosphate excretion increased significantly; however, increases in sodium excretion were low and not statistically significant.
Table 1. Effect of dopamine on phosphate and sodium excretion in thyroparathyroidectomized dogs (Mean±S.E.)

<table>
<thead>
<tr>
<th></th>
<th>Urine Flow m/min</th>
<th>PAH Clearance ml/min</th>
<th>GFR ml/min</th>
<th>Plasma PO₄ μg/ml</th>
<th>Phosphate Excretion μg/min</th>
<th>FEPO₄ per cent</th>
<th>Plasma Na mEq/L</th>
<th>Sodium Excretion μEq/min</th>
<th>Blood Pressure mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Period (n=18)</td>
<td>0.42±0.07</td>
<td>42.2±2.8</td>
<td>14.7±1.1</td>
<td>34.6±5.3</td>
<td>76.5±21.8</td>
<td>13.2±1.9</td>
<td>145.2±2.0</td>
<td>76.6±14.8</td>
<td>142±4</td>
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<tr>
<td>Group 1 (n=6)</td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>0.30±0.02</td>
<td>41.7±3.9</td>
<td>15.2±1.2</td>
<td>43.0±5.7</td>
<td>14.3±2.0</td>
<td>2.3±0.5</td>
<td>146.0±1.5</td>
<td>37.6±4.3</td>
<td>132±5</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.67±0.03*</td>
<td>43.5±3.1</td>
<td>15.8±1.2</td>
<td>42.4±2.7</td>
<td>24.3±5.5*</td>
<td>4.4±1.5*</td>
<td>147.0±1.4</td>
<td>60.6±12.6</td>
<td>134±6</td>
</tr>
<tr>
<td>Group 2 (n=8)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.33±0.06</td>
<td>42.1±3.2</td>
<td>15.4±1.0</td>
<td>44.2±3.5</td>
<td>16.1±2.2</td>
<td>2.4±0.9</td>
<td>146.8±1.5</td>
<td>46.4±6.1</td>
<td>135±5</td>
</tr>
<tr>
<td>POB</td>
<td>0.26±0.03</td>
<td>41.8±2.4</td>
<td>13.3±1.0</td>
<td>55.1±1.3**</td>
<td>98.4±2.4**</td>
<td>14.4±1.4***</td>
<td>147.0±1.4</td>
<td>46.6±3.1</td>
<td>118±6*</td>
</tr>
<tr>
<td>Dopamine+POB</td>
<td>0.72±0.29*</td>
<td>44.5±2.7</td>
<td>14.1±0.9</td>
<td>50.0±2.1</td>
<td>179.3±20.8***</td>
<td>27.3±3.2***</td>
<td>147.2±1.5</td>
<td>124.5±17.1**</td>
<td>121±5</td>
</tr>
</tbody>
</table>

* p<0.05  ** p<0.02  *** p<0.01; compared to control period. FE PO₄: Fractional excretion of phosphate. Normal Period: before thyroparathyroidectomy. Control: 4 hr after thyroparathyroidectomy. Dopamine: dopamine (0.5 μg/kg/min) infusion into the left renal artery. POB: 30 min after POB (2 mg/kg) was administered intravenously. Dopamine+POB: dopamine (0.5 μg/kg/min) infused into the left renal artery after POB administration.

Table 2. Effect of small dose dopamine infusion on excretion rate of inorganic phosphate, sodium and cAMP in POB and alpenolol pretreated, thyroparathyroidectomized dogs (Group 3, n=4)

<table>
<thead>
<tr>
<th>Dopamine infusion rate μg/kg/min</th>
<th>Urine Flow m/min</th>
<th>Plasma PO₄ μg/ml</th>
<th>Phosphate Excretion μg/min</th>
<th>Plasma Na mEq/L</th>
<th>Sodium Excretion μEq/min</th>
<th>cAMP Excretion pM/min</th>
<th>GFR m/min</th>
<th>PAH Clearance m/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.53±0.09</td>
<td>51.6±3.0</td>
<td>58.4±11.5</td>
<td>143.9±0.4</td>
<td>49.9±4.2</td>
<td>213.0±60.7</td>
<td>5.8±0.6</td>
<td>30.0±2.7</td>
</tr>
<tr>
<td>0.02</td>
<td>0.66±0.09</td>
<td>51.0±3.2</td>
<td>78.8±10.6</td>
<td>143.5±0.2</td>
<td>62.2±3.8</td>
<td>208.4±63.8</td>
<td>6.2±0.8</td>
<td>31.2±3.8</td>
</tr>
<tr>
<td>0.05</td>
<td>0.69±0.09</td>
<td>51.1±3.3</td>
<td>121.3±21.7*</td>
<td>143.5±0.2</td>
<td>68.9±6.4*</td>
<td>210.2±68.3</td>
<td>6.2±0.7</td>
<td>31.5±2.6</td>
</tr>
</tbody>
</table>

*; p<0.05: compared to control period.
In Group 2, mere intravenous infusion of POB (2 mg/kg) resulted in significant increases in the plasma phosphate levels and phosphate excretion. Dopamine used in combination with POB markedly increased phosphate excretion while the plasma phosphate level remained unchanged. Urine volume and sodium excretion also showed significant increases.

In Table 2, the results of intrarenal infusion of small amounts of dopamine following the administration of large doses of POB and alprenolol are shown. PAH clearance and GFR remained unchanged with mild increases in urine volume; however, sodium and phosphate excretion significantly increased. Excretion of cAMP remained unchanged.

Discussion

The objective of the present study was to evaluate the possible effect of exogenous dopamine on sodium and phosphate excretion even when administered in doses so small as to induce no renal hemodynamic change. Frick (1968, 1969) demonstrated suppression of fractional reabsorption of inorganic phosphate following saline infusion and showed that inorganic phosphate diuresis initiated by saline infusions depended on the presence of intact parathyroids; in thyroparathyroidectomized animals, fractional inorganic phosphate reabsorption was independent of fractional sodium reabsorption. The clearance studies described in this report were performed with thyroparathyroidectomized dogs undergoing saline diuresis.

Dopamine acts as a vasoconstrictor or as a vasodilator in the renal artery depending on dose levels. Vasoconstriction is not affected by cocaine or by reserpine pretreatment, indicating that it is due to direct action on alpha-adrenergic receptors (Mark et al., 1970). After administration of POB, vasoconstriction was eliminated and vasodilation was observed at all dose levels (McNay et al., 1965). McGiff (1967) also observed that phentolamine and renal nerve stimulation abolished dopamine natriuresis without altering renal blood flow. He suggested that the effect of dopamine on sodium excretion was directly influenced by the autonomic nervous system and perhaps by intrarenal blood distribution.

The increases in sodium excretion induced by doses of dopamine too small to cause significant changes in systemic and renal hemodynamics have been considered to be due to changes in intrarenal blood distribution, as is so with acetylcholine and para- verine (Meyer et al., 1967; Carriere et al., 1971). However, May (1970) showed that cholinmimetic agents like acetylcholine inhibited sodium reabsorption in the proximal renal tubule even when administered in doses so small as to induce no intrarenal hemodynamic change. Using the micropuncture method, Seely (1967) reported that dopamine infusion resulted in decreased sodium reabsorption in the proximal convoluted tubule.

It is well known that the kidneys have an abundant sympathetic nerve supply (Müller et al., 1972). Slick (1975) showed that the renal sympathetic nerves directly influenced the proximal tubular sodium transport in the absence of alterations in renal hemodynamics. Thus, renal sympathetic activity is also an inhibitor of proximal tubular phosphate as well as sodium reabsorption. Moreover, as distal phosphate reabsorption appears to be relatively small, most of the phosphate not reabsorbed in the proximal tubule is excreted in the final urine (Agus et al., 1973).

In the present study, during the infusion of dopamine alone, urine volume and excretion of phosphate increased significantly. Increases in sodium excretion were small and statistically insignificant (Group 1). Following the blockage of alpha- or/and
beta-adrenergic action (group 2 and group 3), increases in both sodium and phosphate excretion were insignificant and did not affect GFR or PAH excretion rates. This suggests that dopamine does not induce changes in renal hemodynamics in small doses, but acts directly on the renal tubule to inhibit sodium and phosphate reabsorption which are directly influenced by alpha adrenergic activity.

Regarding the diuretic mechanism of dopamine, Deis (rats) (1970) and Bentley (toad bladder) (1972) reported that dopamine activity is antagonistic to antidiuretic hormone. This is contrary to later reports (Goldberg, 1973; Cadnapaphornchai, 1977) of parallel increases in osmotic clearance and sodium excretion in urine in man and dogs.

Vlachoyannis (1976) administered dopamine to patients with impaired renal function and found that there was a significant correlation between increased sodium and nephrogenous cAMP excretion, suggesting that the adenyl cyclase-cAMP system was related to dopamine diuresis. The presence of adenyl cyclase in homogenates of isolated renal cortical tubules has been well established. However, only that fraction of total urinary cAMP secreted by the proximal nephron (renal cAMP) is influenced by PTH (Drezner et al., 1976), the secretion of which is altered by beta-adrenergic activity (Fisher et al., 1973).

In our study, following the complete blockage of alpha- and beta-adrenergic action, no increase in cAMP excretion was observed; however, sodium and phosphate excretion increased following the infusion of small doses (0.02–0.05 μg/kg/min) of dopamine close to the physiological blood level (Christensen, 1973) into the renal artery. These findings suggest that the mechanism of depression of sodium and phosphate reabsorption in the renal tubule by dopamine is independent of changes in parathyroid hormone activity and the adenylcyclase-cAMP system in alpha- and beta-adrenergic receptor blocked thyroparathyroidectomized dog kidneys.

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References


