Enhancement of Blood Pressure Response to Dopamine by Angiotensin II

JAIME PEREZ-OLEA, M.D., MONICA QUEVEDO, D.D.S., AND RAMON SILVA, D.D.S.

SUMMARY The interaction of dopamine and angiotensin II (AII) on blood pressure and heart rate was studied in rats. The influence of reserpine pretreatment and vagotomy was also studied. Inbred rats anesthetized with urethane received intravenous (i.v.) doses of 50, 100, 200, or 400 µg (per 100 g body weight) of dopamine HCl, before and after a single i.v. dose of 0.025 µg of AII. The same doses of dopamine were tested in vagotomized rats and in rats pretreated with reserpine. The effect of dopamine alone on blood pressure was biphasic, since 16 of 38 rats showed an early fall followed by a later rise. The early fall decreased significantly with the dose and was absent with the highest dose tested (400 µg). The late rise was observed in all experiments, and it increased significantly with the dose. Parallel to hypotension, a decrease of heart rate was observed, but both phenomena appeared not to be linked by a cause-effect relationship. Vagotomy prevented both hypotension and bradycardia induced by dopamine. Angiotensin II inhibited the early fall and increased the late rise of blood pressure induced by dopamine but had no effect on the bradycardia. Reserpine pretreatment prevented the hypotensive and enhanced the hypertensive response to dopamine, and in this situation dopamine induced cardiac arrhythmia. The interaction between dopamine and AII is inhibited by pretreatment with reserpine. The early hypotensive phase and bradycardia caused by dopamine appeared to be the consequence of a vagal reflex. (Hypertension 3 (suppl II): II-138-II-141, 1981)

KEY WORDS • dopamine • angiotensin II • blood pressure • reserpine • vagotomy

Methods

Animals and Experimental Procedures

Experiments were performed on adult Sprague-Dawley inbred rats (UCHA) obtained from the colony of the Department of Pharmacology, University of Chile. The animals were anesthetized with 1 ml/100 g of rat with 10% urethane i.p. and then heparinized (300 UI/kg i.v.). The heart rate was recorded by lead II of the electrocardiogram (ECG), and the mean carotid blood pressure was registered on a Grass Polygraph model 5D through a pressure transducer Statham Model P-23 AC. To facilitate pulmonary ventilation, a tracheal cannula was installed. Dopamine HCl (Sigma Chemical Company, Saint Louis, Missouri) dissolved in a 50 µg/ml sodium bisulfite solution and AII (Hypertensin, Ciba Company, Basel, Switzerland) in saline were injected in the femoral vein through a polyethylene catheter.

In a separate group of rats a dose-response curve to AII was performed to determine the lowest dose that should produce a regular increase in mean arterial pressure of 35 mm Hg. It was found that a dose of AII equal to 0.025 µg caused this effect (35 ± 2.4 mm Hg). This single dose was chosen to study AII-dopamine interaction once angiotensin pressure response returned to basal levels; such interaction, if present, should be revealed through a higher pressure response to dopamine.
TABLE 1. Maximum Blood Pressure Change Induced by Dopamine Before and After Angiotensin II (0.025 µg/100 g i.v.)

<table>
<thead>
<tr>
<th>Dopamine dose (µg/100 g rat)</th>
<th>No</th>
<th>Early fall (mm Hg)</th>
<th>Late rise (mm Hg)</th>
<th>No.</th>
<th>Early fall (mm Hg)</th>
<th>Late rise (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>11</td>
<td>-26.0 ± 4.8</td>
<td>+55.5 ± 5.2</td>
<td>11</td>
<td>-15.0 ± 5.0</td>
<td>+66.8 ± 4.1</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>-11.0 ± 7.8</td>
<td>+63.5 ± 6.5</td>
<td>11</td>
<td>0.0 ± 0.0</td>
<td>+84.5 ± 5.2</td>
</tr>
<tr>
<td>200</td>
<td>10</td>
<td>-15.7 ± 1.7</td>
<td>+68.0 ± 6.3</td>
<td>7</td>
<td>0.0 ± 0.0</td>
<td>+85.7 ± 4.8</td>
</tr>
<tr>
<td>400</td>
<td>7</td>
<td>0.0 ± 0.0</td>
<td>+85.0 ± 7.6</td>
<td>6</td>
<td>0.0 ± 0.0</td>
<td>+92.5 ± 5.0</td>
</tr>
</tbody>
</table>

Basal blood pressure before angiotensin injection: 122.7 ± 3.0 and after angiotensin injection: 117.4 ± 8.9 mm Hg. Significance of difference before and after pretreatment with AII.

*P < 0.025; **P < 0.05.

Animals were divided into two controls and three groups as follows: intact (n = 22), bilaterally vagotomized (n = 10), and 2) reserpine-treated (n = 11).

Control Groups
In 22 intact rats, four doses of dopamine (50, 100, 200, or 400 µg/100 g rat in volumes of 0.1, 0.2, 0.4, and 0.8 ml respectively) were injected before and after a single dose of angiotensin (0.025 µg/100 g) in 0.05 ml saline solution. Every injection of dopamine was given when the mean blood pressure reached baseline levels. The four doses were also tested on 10 other animals with cut vagi.

Reserpine-Treated Rats
Eleven other rats received i.p. 1.25 mg/kg reserpine (Serpasil, Ciba Company, Basel, Switzerland) 12 and 24 hours before the experiments. In these rats, pressor levels obtained with serial single doses of dopamine before and after AII (0.025 µg/100 g) were recorded. Statistical significance was studied by means of Student's t test, and r correlation coefficient. Results were expressed in difference with the basal levels either in absolute values or in percentages.

Results
Effect of Dopamine on Blood Pressure Before and After Vagotomy
The effect of different doses of dopamine on blood pressure with and without prior administration of AII is summarized in table 1. The data show that the effect of dopamine appears to be biphasic. In 16 of 38 total cases, an initial maximal decrease of blood pressure was observed after 17.6 ± 2.0, 8.8 ± 1.7, and 15.6 ± 5.4 seconds following dopamine injections of 50, 100, and 200 µg/100 g respectively. No initial decrease of blood pressure was observed after injection of 400 µg/100 g of dopamine. In every case, the depressor response was followed by an increase in mean pressure with peak values at 34.8 ± 3.0, 27.0 ± 5.1, 32.9 ± 3.9, and 29.6 ± 3.6 seconds after injection of the four doses respectively. The early pressure fall was inversely related to the dose (r = +0.73, P < 0.001, n = 38) while the late rise was dose-dependent (r = +0.45, P < 0.005, n = 38).

Interaction of Dopamine and Angiotensin
Prior administration of AII (0.025 µg/100 g) prevented the early drop in blood pressure induced by dopamine when dopamine was administered immediately after blood pressure had returned to basal levels. The only exception was observed in a small proportion (two of 11) of cases with the lowest tested dose (50 µg/100 g). The peak of the increase in blood pressure induced by 100 or 200 µg/100 g of dopamine was significantly higher after angiotensin administration (table 1).

The data showing dopamine effects on heart rate appear in table 2. As observed with the blood pressure, the dopamine effect upon heart rate was biphasic before the administration of AII. A transient early phase of bradycardia was present in 30 of 40 cases and was then followed by a slight increase of frequency.

TABLE 2. Maximum Heart Rate Change Induced by Dopamine Before and After Angiotensin II (0.025 µg/100 g i.v.)

<table>
<thead>
<tr>
<th>Dopamine dose (µg/100 g rat)</th>
<th>No</th>
<th>Early decrease (%)</th>
<th>Late increase (%)</th>
<th>No.</th>
<th>Early decrease (%)</th>
<th>Late increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>12</td>
<td>-11.9 ± 2.5</td>
<td>+4.6 ± 2.1</td>
<td>8</td>
<td>-16.98 ± 4.4</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>100</td>
<td>11</td>
<td>-9.4 ± 0.9</td>
<td>+8.2 ± 4.3</td>
<td>7</td>
<td>-14.73 ± 5.1</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>200</td>
<td>11</td>
<td>-23.6 ± 7.8</td>
<td>+1.7 ± 0.9</td>
<td>5</td>
<td>-33.54 ± 10.5</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>400</td>
<td>6</td>
<td>-20.0 ± 10.6</td>
<td>0.0 ± 0.0</td>
<td>6</td>
<td>-18.75 ± 10.4</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

Basal heart rate before angiotensin injection, 372.5 ± 21, after angiotensin injection, 408.5 ± 10 beats/min.
TABLE 3. Influence of Vagotomy on the Effect of Dopamine on Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th>Dopamine (g/100 g)</th>
<th>Intact Blood Pressure</th>
<th>Vagotomy Blood Pressure</th>
<th>Intact Heart Rate</th>
<th>Vagotomy Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease</td>
<td>Increase</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>50</td>
<td>-26.0 ± 4.8</td>
<td>+55.5 ± 5.2</td>
<td>-26.0 ± 4.8</td>
<td>0.0 ± 0</td>
</tr>
<tr>
<td>100</td>
<td>-11.0 ± 7.8</td>
<td>+63.5 ± 6.5</td>
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<td>0.0 ± 0</td>
</tr>
<tr>
<td>200</td>
<td>-15.7 ± 1.7</td>
<td>+68.0 ± 6.3</td>
<td>-15.7 ± 1.7</td>
<td>0.0 ± 0</td>
</tr>
<tr>
<td>400</td>
<td>0.0 ± 0</td>
<td>+85.0 ± 7.6</td>
<td>0.0 ± 0</td>
<td>0.0 ± 0</td>
</tr>
</tbody>
</table>

Basal blood pressure, with intact vagi 122.7 ± 3 and after vagotomy 109.7 ± 9 mm Hg. Basal heart rate: with intact vagi 372.5 ± 2.0; after vagotomy 426 ± 13 beats/min

Neither the early decrease nor the late increase in heart rate were significantly related to the dose either before or after administration of AI; hence, for the purpose of statistical analysis, four doses of dopamine either before or after AI administration can be taken together. No significant difference in the percentage between both conditions was observed (−15.20 ± 3.19 vs −19.97 ± 3.29, t = 0.98 N.S.). The magnitude of the early bradycardia did not correlate with the fall in blood pressure.

Effect of Vagotomy

Bilateral vagotomy prevented the early decrease of blood pressure in all cases but it did not influence the rise in blood pressure (table 3). Also, the early reduction of heart rate was prevented by vagotomy. In fact, the mean beat/min decrease induced by the four doses of dopamine was −64.75 ± 13.15 with intact vagi and only −8.65 ± 2.65 after vagotomy (p < 0.001).

Reserpine-Treated Rats

In reserpine-treated animals, the effect of dopamine on blood pressure was clearly different. The data summarized in table 4 show that under reserpine the early fall in blood pressure did not occur. Moreover, the increase in blood pressure due to AI was much higher in animals treated with reserpine with all tested doses of dopamine. No influence of previous administration of AI was observed in this case. In fact, even the dose of 50 µg/100 g of dopamine proved to be the maximum in raising blood pressure, both with or without exposure to AI.

In reserpine-pretreated animals, dopamine induced cardiac arrhythmia, including different degrees of AV conduction delay and ventricular premature depolarization. Such features made it impossible to study the influence of these drugs on the heart rate accurately.

Discussion

The present findings show that dopamine induced a biphasic effect upon the blood pressure and heart rate of rats, namely, an early fall in pressure and bradycardia followed by a later rise in pressure and an increase in heart rate. The late rise in pressure and heart rate was dose-dependent. In this respect the behavior of the rat is similar to that of the dog. Previous studies by McDonald and Goldberg showed that dopamine causes a biphasic response in the dog. The drop in blood pressure, as well as lowering of the heart rate, were prevented by bilateral section of the vagus nerve. In fact, both phenomena appeared to be independent, since the early fall of blood pressure tended to decrease with higher doses of dopamine, while the bradycardia was more pronounced. Prevention of bradycardia by vagotomy supports the idea that the bradycardia was mediated by an increase in vagal tone to the heart and was not produced by the direct action of dopamine on the physiological pacemaker. On the
other hand, the possibility of a reflex mechanism secondary to blood pressure change is not tenable, because the low heart rate is coincident with the hypertensive phase.

Alternatively, the early blood pressure fall prevented by vagotomy suggests a peripherally mediated vagal reflex. The original source of the reflex could be located in the heart itself, as in the Bezold-Jarish reflex or in the lung, as has been postulated by others to explain the abrupt hypotension induced by intravenous injection of morphine in the rat.

It has been stated that the pressor effect of angiotensin can be explained by direct vasoconstriction and noradrenaline release from the sympathetic nerve endings. After angiotensin exposure, dopamine failed to produce the early hypotensive phase whereas the pressor effect was potentiated. The higher pressor response to dopamine might be due to the norepinephrine-releasing effect of angiotensin. This effect would be produced by stimulation of presynaptic angiotensin receptors. No significant changes were observed in heart rate; bradycardia was recorded both with and without angiotensin.

In reserpine-pretreated animals the hypotensive phase caused by dopamine was not observed and the hypertensive phase was potentiated. All tested doses of dopamine produced maximum pressor levels in reserpine-treated rats, which can be ascribed to the well-known catecholamine supersensitivity induced by reserpine. In reserpinized animals angiotensin was unable to potentiate the pressor effect of dopamine in the dose scale range assayed. Although the mechanism underlying the loss of dopamine-angiotensin interaction is unknown, it may well be due to exhaustion of norepinephrine stores by reserpine. This effect would deprive angiotensin of its epinephrine-releasing properties.

References
1 McDonald RH Jr, Goldberg LI. Analysis of the cardiovascular effects of dopamine in the dog. J Pharmacol Exp Ther 140: 60, 1963
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