Effects of Small Oral Doses of Reserpine on Vascular Responses to Tyramine and Norepinephrine in Man

By François M. Abboud, M.D., and John W. Eckstein, M.D.

In animals, reserpine depletes tissues of catecholamines,4 5 reduces the response of smooth muscle to tyramine,4 5 and potentiates the action of norepinephrine.4 6 7 The decreased response to tyramine probably results from depletion, since the action of this sympathomimetic amine appears to be mediated through the release of norepinephrine.4 6 The cause of hypersensitivity to exogenous norepinephrine after reserpine is not known.5 8

It seemed important to determine if the two phenomena, namely, the subsensitivity to tyramine and the hypersensitivity to norepinephrine, occur in men receiving small doses of reserpine orally. Such findings would have important clinical implications.9

Methods

Materials

Seven healthy young medical students served as subjects. They were studied while lying in the supine position, lightly clothed and covered with a sheet. The left forearm was placed in a water plethysmograph. The technic for enclosing the limb has been described previously.30 Room temperature was 82 to 84 F. and water temperature in the plethysmograph was 89 F. The water level in the instrument was adjusted so that water pressure on the arm was slightly higher than venous pressure. This reduced transmural venous pressure to a constant low value, so that the veins could be distended freely when venous congestion was produced by suddenly inflating a pneumatic cuff around the arm proximal to the plethysmograph. The minimal venous occlusion pressure needed to produce the maximal rate of increase in arm volume was used. A second cuff was placed at the wrist distal to the plethysmograph and inflated to suprasystolic pressures during observations on blood flow. The increase in forearm volume during occlusion of venous return caused a rise of the column of water in an open tube connected to the top of the plethysmograph. The resulting change in pressure was measured with a Statham strain-gage and recorded on a Sanborn direct-writing oscillograph. Pulse rate was continuously recorded from the dorsalis pedis artery. Brachial arterial pressure was measured in the right arm by auscultation. Toe and room temperatures were monitored with a thermistor.

Procedure

The subjects rested for 20 to 30 minutes before the experiment was begun to allow blood flow, arterial pressure, heart rate, and temperature to stabilize. Observations on blood flow, arterial pressure, and heart rate began 4 minutes before and ended 3 minutes after the intravenous administration of the sympathomimetic amines. Tyramine sulfate (0.1 mg./Kg.) was injected first and L-norepinephrine bitartrate was given thereafter at rates of 0.037, 0.075, and 0.15 μg. of base per Kg. per minute. The injection of tyramine lasted 3 minutes. Each infusion of norepinephrine lasted 6 minutes. A 20-minute recovery period was allowed between injections. Three flow curves and two blood pressure readings were obtained during each minute. Blood flow was calculated from the rate of increase in forearm volume during venous occlusion and expressed in milliliters per minute per 100 ml. of forearm volume. The mean blood pressure (diastolic plus one third of the pulse pressure) was divided by the corresponding blood flow to obtain an expression of forearm vascular resistance in arbitrary units.

This procedure was repeated in each subject on three separate occasions. The first session was a pretreatment control. The second session followed 14 days of treatment with reserpine, 1 mg. orally per day, and the third session was a posttreatment control and took place more than 4 weeks (average 8 weeks) after the treatment with reserpine had been discontinued. The dose of reserpine had to be reduced to 0.75 mg. in one subject (D.L.) and 0.25 mg. in another (J. Mc.) because of side effects.

Resting values were calculated from observa-
tions made at the beginning of each experiment during 4-minute periods before the injection of tyramine. The effects of tyramine were obtained from observations made during the third minute of injection of tyramine and the two succeeding minutes. The responses to norepinephrine were calculated from observations made during 4-minute periods beginning from the fourth minute of norepinephrine infusion. The results of the second session (after reserpine) were compared to those of the first and third control sessions.

Results

Effect of Reserpine
All subjects complained of nasal stuffiness, conjunctival injection, fatigue, and orthostatic weakness. Two were allowed to reduce the daily dose of 1 mg. because of side effects. One student (D.L.) took only 0.75 mg. per day after the first 3 days because he suffered from diarrhea, nausea, and lethargy. At the end of the 2 weeks of treatment he had gained 7 pounds. The other subject (J. Mc.) became lethargic and had orthostatic hypotension and ankle edema. His dose was reduced to 0.25 mg. per day after 3 days.

Reserpine reduced resting blood pressure and heart rate significantly; it did not alter forearm vascular resistance (tables 1 and 2).

Effect of Tyramine
During control sessions tyramine increased mean blood pressure and forearm vascular resistance and reduced heart rate significantly. After reserpine, the effect of tyramine on blood pressure was greatly reduced (table 1), and its effects on resistance and heart rate were not significant (table 2). The changes in forearm blood flow were variable both before and after reserpine.

Effect of Norepinephrine
The absolute levels of blood pressure attained with the infusions of norepinephrine after reserpine were the same or lower than those observed during control sessions (table 1). Ascending doses of norepinephrine caused progressive increments in mean blood pressure and forearm vascular resistance with progressive decrements in blood flow and heart rate during control sessions (table 2). After reserpine the responses to norepinephrine were not altered significantly (table 2).

Discussion
The results indicate that the oral administration of small doses of reserpine to normo-

Table 1
Effect of Oral Administration of Reserpine on the Absolute Levels of Mean Systemic Arterial Pressure Obtained during Intravenous Infusions of Tyramine and Norepinephrine in Each Subject*  

<table>
<thead>
<tr>
<th>Subject</th>
<th>R (resting)</th>
<th>Tyr. (tyramine)</th>
<th>NE (norepinephrine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.F.</td>
<td>86</td>
<td>87</td>
<td>116</td>
</tr>
<tr>
<td>D.E.</td>
<td>102</td>
<td>101</td>
<td>117</td>
</tr>
<tr>
<td>D.L.</td>
<td>96</td>
<td>102</td>
<td>118</td>
</tr>
<tr>
<td>D.P.</td>
<td>86</td>
<td>85</td>
<td>117</td>
</tr>
<tr>
<td>M.W.</td>
<td>86</td>
<td>96</td>
<td>118</td>
</tr>
<tr>
<td>M.G.</td>
<td>103</td>
<td>92</td>
<td>114</td>
</tr>
<tr>
<td>J.Mc.</td>
<td>101</td>
<td>93</td>
<td>114</td>
</tr>
<tr>
<td>Average</td>
<td>94</td>
<td>93</td>
<td>114</td>
</tr>
</tbody>
</table>

*Abbreviations: R, resting values; Tyr., effects of tyramine (0.1 mg/Kg.); NE, effects of the highest of the three doses of norepinephrine (0.15 mg/Kg./min.). All values are means of observations obtained over a period of a few minutes (see text). Session I was before reserpine; session II was after 14 days of treatment with reserpine; and session III took place more than 4 weeks after the drug had been discontinued. The results obtained in session II were compared to those obtained in sessions I and III by an analysis of variance and the symbols and $ indicate the significance of the difference between the sessions: $ = p<0.05$, and $ = p<0.01$.  

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Table 2
Effects of Oral Administration of Reserpine on the Changes in Mean Arterial Pressure, Pulse Rate, Forearm Blood Flow and Resistance in Response to Intravenous Tyramine and Norepinephrine

<table>
<thead>
<tr>
<th></th>
<th>Control observations (n = 14) *</th>
<th>After reserpine (n = 7) †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAP mm. Hg</td>
<td>BF ml./min./100 ml.</td>
</tr>
<tr>
<td>Resting values</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>93.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Responses to tyramine</td>
<td>(1.9)</td>
<td>(0.2)</td>
</tr>
<tr>
<td>(0.1 mg/Kg.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses to norepinephrine (μg/Kg/min.)</td>
<td>+21.4</td>
<td>-0.16‡</td>
</tr>
<tr>
<td></td>
<td>(2.3)</td>
<td>(0.30)</td>
</tr>
</tbody>
</table>

SAP, mean systemic arterial pressure; BF, forearm blood flow; R, forearm vascular resistance in arbitrary units; PR, pulse rate. Entries are mean values and the standard errors are in parentheses below each mean.

* Includes observations made during the pre- and post-treatment control sessions (first and third sessions).
† Includes observations made during the second session.
‡ Indicates that the response to tyramine or norepinephrine is not significant (p>0.05).
§ Indicates that the difference between the group of control observations and the group of observations made after reserpine is significant (p<0.05 and t = X1-X2 \( \sqrt{\frac{n_1 n_2 (n_1+n_2-2)}{(n_1+n_2)\Sigma x^2}} \)).

Responses in session II were compared also to responses in sessions I and III separately by calculating the relative potencies (table 3).

tensive subjects reduced the effect of tyramine on arterial blood pressure by 75% per cent and suppressed its actions on forearm vascular resistance and heart rate. The data do not permit us to conclude that the responses to norepinephrine were augmented by treatment with reserpine.

Tyramine acts by releasing norepinephrine from tissues. The decreased response to tyramine provides indirect evidence for depletion of endogenous catecholamines in man. Reduction in neurotransmitter substance could impair cardiovascular reflexes in the presence of increased demands on the circulation. In animals, depletion of norepinephrine decreases the effects of tyramine and other sympathomimetic amines, such as methamphetamine, ephedrine, and mephentermine, which act indirectly by releasing endogenous catecholamines. The results suggest that in man also the pressor amines which act as tyramine may be ineffective after treatment with reserpine.

The hypersensitivity to norepinephrine after reserpine is a complex phenomenon which is poorly understood and not observed consistently in animals. Burn and Rand attributed the sensitivity to exogenous norepinephrine after denervation and after treatment with reserpine to the "disappearance of a store of noradrenaline." Their hypothesis has been challenged recently by several groups of investigators who found that hypersensitivity is not directly related to depletion of endogenous catecholamines. Kirpekar, Cerfonti, and Furchgott provided analytical data to show that the decrease in tissue content of catecholamines was not related to the sensitivity. A decreased response to tyramine has been observed at a time when there was no hypersensitivity to norepinephrine. In animals, the cardiovascular effects of norepi-
norepinephrine have been reported as increased,\textsuperscript{4, 6, 17} unchanged,\textsuperscript{18} or decreased\textsuperscript{19} after treatment with reserpine.

In the experiments reported here the pressor, forearm vasoconstrictor, and bradycrotic actions of norepinephrine were not augmented significantly even though the responses to tyramine were suppressed. A suggestive trend toward a greater pressor and forearm vasoconstrictor response to norepinephrine after reserpine may be noted from data in table 2 in which the two control sessions (I and III) were compared with session II. The reason for this is that the pressor and vasoconstrictor effects of norepinephrine in session II were slightly greater than in session I, but equal to or slightly less than those in session III (table 3). It was fortunate that the experimental design included the second control session (III). Without session III we would have been led to believe that hypersensitivity existed even though the differences between the responses in sessions I and II were small. We must conclude that hypersensitivity, if it existed, was not sufficient to be detected by our methods. The excessive responses to norepinephrine, which might be expected from the work of Burn and Rand,\textsuperscript{6, 14} did not oc-
cur in human subjects receiving small doses of reserpine orally. The two subjects M.G. and J. Mc. had the largest reductions in resting mean arterial pressure after reserpine; their responses to norepinephrine were similar to those of other subjects and were not much greater after reserpine than during one or both control sessions (table 1).

Two additional observations should be discussed. The first is that reserpine reduced blood pressure without changing forearm vascular resistance (table 2). Unchanged forearm vascular resistance or caliber in face of a fall in distending pressure indicates decrease in forearm vascular tone. If vascular tone were unchanged, forearm vascular resistance would have increased passively with the fall in distending pressure.

The second observation concerns the comparison between the actions of tyramine and norepinephrine during control sessions. In the doses used norepinephrine decreased forearm blood flow significantly while tyramine did not (table 1). The intermediate dose of norepinephrine (0.075 \textmu g. per Kg. per minute) caused approximately one half of the pressor response seen after tyramine and yet the vasoconstrictor and bradycrotic actions of this dose of norepinephrine were similar to those of tyramine (table 1). These results indicate that, in equipressor doses, norepinephrine produces greater vasoconstriction, greater reduction in forearm blood flow, and more reflex bradycardia than tyramine.

Table 3

Relative Potencies with Respect to the Changes in Mean Arterial Pressure and Forearm Vascular Resistance in Response to Norepinephrine during Session II vs Sessions I and III\textsuperscript{*}

<table>
<thead>
<tr>
<th></th>
<th>(\Delta) Mean blood pressure</th>
<th>(\Delta) Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session II vs 1</td>
<td>1.47</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>(1.77-1.23)</td>
<td>(2.34-1.07)</td>
</tr>
<tr>
<td>Session II vs III</td>
<td>1.15</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>(1.37-0.96)</td>
<td>(1.12-0.53)</td>
</tr>
</tbody>
</table>

\* The figures represent the estimated relative potencies; the 95-per cent fiducial limits for the relative potencies are in parentheses.\textsuperscript{12} Relative potency

\[ a = \text{antilogarithm of log dose difference (m). } m = \frac{a}{b} \]

where: \(a = \) increase in response as measured at the mid-points of the log dose response lines; \(b = \) average slope of two parallel log dose response lines. If the relative potency and its 95-per cent fiducial limits do not include unity the difference between the sessions is statistically significant.

Summary

Experiments were done to see if reserpine, in small oral doses, alters the responses to tyramine and norepinephrine in man. Each of seven normotensive subjects was studied on three occasions. The first and third sessions served as pre- and post-treatment control sessions; the second session was held after oral administration of reserpine (0.25 to 1 mg. per day) for 2 weeks. Blood pressure was measured with a sphygmomanometer, and forearm blood flow was measured with a water plethysmograph. Reserpine reduced resting blood pressure and heart rate but forearm blood...
flow did not change. The pressor, forearm vasoconstrictor, and bradycrotic actions of intravenous tyramine were suppressed by reserpine, but the pressor, vasoconstrictor, and bradycrotic actions of three intravenous doses of norepinephrine were not augmented significantly. The results indicate that oral administration of small doses of reserpine may cause depletion of endogenous catecholamines in man as suggested by the suppressed response to tyramine. The decreased response to tyramine was not accompanied by hypersensitivity to exogenous norepinephrine. In equipressor doses norepinephrine produced greater forearm vasoconstriction and more reflex bradycardia than did tyramine.

References
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FRANCOIS M. ABBOUD and JOHN W. ECKSTEIN

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