Cardiac Effects of Tyramine

By John C. Holmes, M.D., and Noble O. Fowler, M.D.

Tyramine (p-hydroxyphenylethylamine), the product of decarboxylation of tyrosine, has been known for a number of years to have pharmacological activity as a pressor substance.1-4 In a preparation of the atrium of the cat's heart in Locke-Ringer solution, Andrus, in 1924, showed that tyramine increased the rate and amplitude of atrial contractions.5 In 1926, Tainter6 reported the circulatory effects of tyramine. Its pressor action was considered to be sympathetic in cats and muscular in dogs. The isolated cat heart showed increased rate and force of contraction. In 1930, Burn demonstrated in the dog heart-lung preparation, by means of a cardiometer attached to a piston recorder, a diminution of the cardiac volume with 0.09 mg. tyramine.7 He found the action of tyramine on the heart-lung preparation to resemble that of epinephrine with the potency of tyramine being about 40 to 50 times weaker.

Müller, in 1937,8 by means of a continuous volume recorder, demonstrated in the dog heart-lung preparation an average decrease of cardiac volume of 16 cc. with 0.1 mg. tyramine. The maximum effect was reached after approximately three minutes. The duration of the effect was about 15 minutes. The heart rate was usually accelerated. The coronary circulation was augmented and the pulmonary arterial pressure reduced. Bejrablaya, Burn, and Walker, in 1958,9 showed that tyramine (0.4 to 2 mg.) in the dog heart-lung preparation increased the heart rate 25 to 82 beats per minute. This effect on the rate was slow in appearing, reaching a peak after approximately seven to eight minutes but lasting 30 to 40 minutes when the dose was 1 mg. Liebman, in 1961,10 studied the effect on heart rate of continuous infusion of tyramine in the dog heart-lung preparation, demonstrating a positive chronotropic response which was related to the rate of infusion.

These earlier studies have shown that tyramine decreases cardiac volume when measured by such instruments as a cardiometer or a continuous volume recording device. Direct measurement of the cardiac output, maintaining the baseline venous level with donor blood during the period of measurement, and the use of the strain-gauge arch to determine changes in contractile force are more specific methods of studying the cardiac action of tyramine, since the effects of changes in venous return and peripheral resistance can be avoided. By use of the Grass rectangular-wave stimulator, the effects of changes in rate upon contractile force can be eliminated. In the present study, these methods were used to evaluate the effect of tyramine on ventricular contractile force, heart rate, cardiac output, blood pressure, and atrial pressures in the normal dog heart-lung preparation.

Methods

Dogs were anesthetized with intravenous sodium pentobarbital (32 mg./Kg.). Twenty-two heart-lung preparations were made from mongrel dogs of either sex, weighing from 16 to 23 Kg. The Starling resistance was set at 85 mm. Hg; the blood entering the right atrium was kept at 38 to 39 C. The volume of blood in the preparation at the beginning of each experiment was approximately 800 ml. Each animal was given 50 mg. of heparin intravenously. All experiments lasted less than one hour after cannulations. The height of the blood in the venous reservoir was maintained at 16 cm. above the level of the right atrium, except when it was necessary to raise the height in order to maintain baseline cardiac output. Direct measurements of systemic output were made in duplicate with maintenance of baseline venous level with donor blood during period of measurement. A strain-gauge arch was sutured to the surface of the right ventricle. The right ventricle was chosen...

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because of its greater accessibility and because its lower pressure minimized bleeding. Previous reports have indicated that similar results are obtained from either ventricle. The placement and tension adjustments were as recommended by Cotton, and the tension was recorded by a Sanborn multichannel direct-writing oscillograph. In all experiments, heart rates were determined from the strain-gauge arch record. Systemic blood pressure and atrial pressures were detected by means of Statham transducers.

Each drug was injected through the venous inflow cannula of the heart-lung preparation in a volume of less than 10 ml. Both tyramine and levaterenol base were given to each preparation in amounts of 25 to 500 μg. and 1 to 2.5 μg., respectively. If drug effects were striking at the lower dosages, the higher amounts were not given. Successive doses were injected only after a steady state of cardiac output, contractile force, blood pressure, and atrial pressures had been attained. Intervals between drug injections were 2 to 5 minutes. All doses were expressed as micrograms per heart-lung preparation. In 13 of the 19 experiments, the heart rate was kept constant at a rate of 200 to 282 per minute by driving the heart through the right atrial appendage or right ventricle using a Grass rectangular wave stimulator. In six of these 13 preparations, tyramine was given before levaterenol; in the remaining seven, levaterenol was administered first. In three additional animals, reserpine 0.1 mg./Kg. body weight was given intramuscularly 48 and 24 hours prior to the experiment.

Results

During control observations, the peak systolic tension recorded by the strain-gauge arch did not vary more than 2 mm. out of 10 to 15-mm. response in each experiment. After the injection of the drug, increases or decreases of 1 mm. or more beyond this limit were interpreted as positive or negative inotropic effects, respectively.

In each of six uncontrolled rate preparations, tyramine (250 to 500 μg.) increased the contractile force, the cardiac rate, and the cardiac output (table 1). The effects of smaller doses of tyramine (25 and 50 μg.) were variable and inconsistent. A significant decrease in both right and left atrial pressures occurred in all but one animal with tyramine (250 to 500 μg.).

Figure 1 shows the effects of tyramine and levaterenol on cardiac output in 13 heart-lung preparations with the heart rate held constant by the Grass stimulator. With 100 to 250 μg. of tyramine, increase in cardiac output was consistent; increased output was observed in some but not all preparations with the smaller amounts. Levaterenol (1 to 2.5 μg.) in the same rate-controlled animals increased the cardiac output in all but two preparations (fig. 1). With successive doses of tyramine, there was some increase in the baseline cardiac output and ventricular force, with a fall in right atrial pressure. The baseline cardiac output during the course of the experiments changed from −56 to +116 ml./min., averaging 33 ml. increase. The baseline ventricular force deflection changed from 0 to +7 mm., averaging +2.7 mm. The control right atrial pressure changed from +1.6 to −5.6 mm. Hg, averaging −1.3 mm. Hg.

With 100 to 250 μg. tyramine, the increase of contractile force was consistent (fig. 2); increased ventricular force was observed in some but not all preparations after the smaller doses. Levaterenol (1 to 2.5 μg.) increased the ventricular force with one exception (fig. 2). Tyramine (25 to 50 μg.) increased the blood pressure in six of 13 preparations 2 to 9.5 per cent, whereas 100 to 250 μg. increased the blood pressure in the 13 animals by 1.5 to 18 per cent. Levaterenol (1 to 2.5 μg.) given after tyramine increased the blood pressure 1.5 to 25 per cent in 11 of 13 preparations.

In the majority of preparations, tyramine (100 to 250 μg.) produced a prompt decrease in right atrial pressure and in left atrial pressure (fig. 3). With 25 μg. of tyramine, small and inconsistent changes in both right and left atrial pressures were observed. Tyramine (50 μg.) in eight of 13 preparations produced a decrease in right atrial pressure of 2 to 15 per cent and a decrease in the left atrial pressure in 10 of 13 preparations (fig. 3). Levaterenol (1 to 2.5 μg.) produced a...
consistent decrease in left atrial pressures (fig. 3) and also in right atrial pressures.

The effect of prior administration of 1 to 2.5 μg. of levarterenol upon the response to tyramine is shown in table 2. There were slightly greater hemodynamic effects after 50 μg. tyramine in the animals receiving levarterenol first, but this group showed no significant difference in response to 100 μg. tyramine.

In the animals receiving tyramine first, 1 μg. levarterenol produced an average increase of 15 per cent in cardiac output and in ventricular force and an average 16 per cent decrease in right atrial pressure. In the animals receiving 1 μg. levarterenol before tyramine, cardiac output showed an average increase of 28 per cent; cardiac force, an average increase of 25 per cent; and right atrial pressure, an average decrease of 9 per cent.

It was shown consistently in these experiments that the onset of effect of tyramine was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of Effects of Tyramine in Six Heart-Lung Preparations with Uncontrolled Cardiac Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>25 μg.</td>
</tr>
<tr>
<td>Cardiac rate</td>
<td>0 to +4</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>-3 to +5</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>-21 to +31</td>
</tr>
<tr>
<td>Left atrial pressure</td>
<td>-21 to +11</td>
</tr>
</tbody>
</table>

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FIGURE 2
Effect of tyramine and levarterenol on ventricular force in heart-lung preparations with controlled cardiac rate.

Later than that of levarterenol, but that the duration of effect of tyramine exceeded that of levarterenol. Following the maximum effect of levarterenol, there was observed in many preparations a decline of cardiac output which was not observed with tyramine.

In the three reserpinized animals, 25 to 500 
\(\mu g\). doses of tyramine had little effect. In two of the three animals, there was no significant change in ventricular force, heart rate, cardiac output, or atrial pressure. One of the three animals showed a slight effect; cardiac output and ventricular force increased 9 per cent, and atrial pressure decreased 13 per cent. On the other hand, 250 and 500 
\(\mu g\). of dopamine increased cardiac output somewhat better than 30 per cent in two reserpinized animals.

In three heart-lung preparations, DOPA (dihydroxyphenylalanine), 0.5 to 10 mg., produced no positive inotropic or chronotropic effects.

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TABLE 2

Effect of Prior Levartenol on Response to Tyramine

<table>
<thead>
<tr>
<th></th>
<th>Cardiac output (average per cent increase)</th>
<th>Force (average per cent increase)</th>
<th>Right atrial pressure (average per cent decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Tyramine 50 µg. (6)*</td>
<td>+0.8</td>
<td>+8</td>
<td>0</td>
</tr>
<tr>
<td>After Levartenol Tyramine 100 µg. (6)</td>
<td>+33</td>
<td>+39</td>
<td>-15</td>
</tr>
<tr>
<td>After Levartenol Tyramine 50 µg. (7)</td>
<td>+12</td>
<td>+11</td>
<td>-6</td>
</tr>
<tr>
<td>After Levartenol Tyramine 100 µg. (6)</td>
<td>+35</td>
<td>+35</td>
<td>-18</td>
</tr>
</tbody>
</table>

*Figures in parentheses indicate numbers of animals.

Discussion

Goldberg and Sjoerdsma, in 1959, demonstrated in open-chest intact dogs a 5 to 22 mm. Hg increase of carotid blood pressure and an average 39 per cent increase above control levels in heart contractile force after tyramine 20 µg./Kg.12 In the open-chest intact dog, measuring contractile force by a strain-gauge arch, Goldberg and Sjoerdsma determined the relative potency of the five naturally occurring amines in the dog.12 The relative potency of the five amines, when compared at equivalent dosage, was in the following order: levartenol > serotonin > dopamine > tyramine > tryptamine. Tyramine had the longest duration of action; levartenol, the shortest.

A number of studies have been made to clarify the mechanism of action of tyramine. Tainter and Chang4 showed that cocaine abolished the action of tyramine. Burn and Tainter3 demonstrated that the denervated pupil did not react to tyramine, but was supersensitive to epinephrine. Burn2 showed that denervation of the cat's foreleg caused loss of the constrictor response to tyramine, but not to epinephrine. Bülow and Burn13 found that the contraction of the denervated nictitating membrane of the spinal cat was decreased to large doses of tyramine, but maintained or increased to small doses. Burn and Rand14 showed that the pressor action of tyramine was largely lost in reserpinized cats, but that the response to dopamine was increased following reserpine. Paasonen and Krayer15 showed that reserpine decreased the norepinephrine content of the right atrium and left ventricle in the dog heart-lung preparation. Liebman10 showed that pretreatment with reserpine reduced, but did not completely abolish, the chronotropic effect of tyramine in the dog heart-lung preparation. He postulated that the sympathomimetic action of tyramine is indirect and depends upon the release of norepinephrine from its stores. Our failure to observe the usual inotropic or chronotropic effects of tyramine in three reserpin pretreated preparations agrees with this hypothesis. The amount of tyramine used in these three animals produced consistent effects in the preparations not pretreated with reserpine. Our observations were consistent with those of Burn and Rand14 in that reserpine did not diminish the cardiac effects of dopamine.

From the present studies, it is apparent that tyramine has significant positive inotropic and chronotropic cardiac effects in the dog. In the dog heart-lung preparations, a considerably larger dosage of tyramine than of levartenol was required to produce positive inotropic and chronotropic effects. Previous studies from this laboratory on the cardiac effects of dopamine16 indicate that the relative potency of tyramine is less than that of dopamine in the dog heart-lung preparation. The onset of effect of tyramine in the heart-lung preparations was considerably slower than levartenol. Although the rate of dissipation of these two sympathomimetic amines may be different in the intact animal, the present studies suggest that the duration of effect of tyramine is significantly longer than levartenol and that the rebound fall of cardiac output seen with levartenol is not present with tyramine. It is possible that tyramine may have useful clinical applica-
tion; however, additional studies of the effects of tyramine on the peripheral circulation and the circulation of isolated organs such as the kidney and lung are needed to evaluate further the possible clinical applications of this drug.

Summary
The cardiac effects of tyramine (p-hydroxyphenylethylamine) were studied in 22 dog heart-lung preparations. In six uncontrolled rate preparations, tyramine 250 to 500 μg. increased the heart rate an average of 21 percent. In controlled rate preparations, tyramine 100 to 250 μg. consistently increased ventricular contractile force, cardiac output, and blood pressure; there was a consistent decrease of right and left atrial pressures. Comparable hemodynamic effects were produced by 1 to 2.5 μg. of levarterenol, except that the effects of tyramine tended to be of longer duration and were less likely to be followed by cardiac depression. It is concluded that tyramine has significant positive inotropic and chronotropic effects in the dog heart-lung preparation. In three animals pretreated with reserpine, tyramine had little effect. Its action appears to depend to a large extent upon the presence of myocardial catecholamines.

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