Effects of Dopamine on Sinoatrial Conduction in Isolated, Blood-perfused Dog Atria

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SUMMARY

Dopamine, administered at a constant infusion rate of 1–2 μg/min into the cannulated sinus node artery of the isolated dog atrium, decreased sinus cycle length (SCL) from 630±19 to 501±22 msec (mean±SEM, 38 trials in 12 atria). However, on sinoatrial conduction time (SACT) estimated by a constant atrial pacing method, dopamine produced 2 types of response (shortening and lengthening) with sinus tachycardia. In 24 trials in 11 atria, the drug decreased SACT from 86±8 to 56±4 msec, and in 14 trials in 6 atria it increased SACT from 67±7 to 101±9 msec. In general, the effects of dopamine on SACT were dependent on the control levels of SCL: dopamine caused a reduction of SACT at small levels of SCL and a prolongation at large levels. At a control sinus rate of 120 beats/min, dopamine usually shortened SACT. Dopamine-induced shortening of SACT was blocked by a beta-adrenoceptor blocker, propranolol, and an uptake blocker, imipramine, but not by a dopaminergic inhibitor, sulpiride. Furthermore, dopamine-induced lengthening of SACT tended to be suppressed by propranolol, but not by sulpiride. It is concluded that the dopamine-induced changes in SACT are mediated via beta-adrenergic mechanism and partially due to a tyramine-like action.

Additional Indexing Words:
Isolated dog atria Dopamine Tyramine-like action
Sinoatrial conduction time Constant atrial pacing

DOPAMINE, a norepinephrine-precursor, has been widely used for the treatment of cardiogenic shock\(^1\)-\(^3\) because it has prominent positive inotropic and weak chronotropic properties.\(^4\),\(^5\) On the other hand, Furukawa et al.\(^6\) using isolated dog atria, found no differences in the chronotropic effects of dopamine and norepinephrine or epinephrine if about a 30-fold...
dosage of dopamine was used. Their finding is consistent with the observations of Homes and Fowler,7) and Schmidt et al8) in canine heart-lung preparations. Hence, in isolated preparations, it is likely that dopamine exerts some influence on sinus nodal automaticity and then sinoatrial conduction. However, to our knowledge, no one has ever shown effects of dopamine on sinoatrial conduction time. The present investigation was therefore undertaken to study the direct chronotropic and dromotropic actions of dopamine using an isolated, blood-perfused dog atrial preparation.9),10)

Methods

Mongrel dogs (8 to 27 Kg) were anesthetized with sodium pentobarbital (30 mg/Kg, i.v.). After pretreatment with 200 units/Kg of sodium heparin i.v., the right atrium was excised and plunged in Tyrode’s solution at 4°C. The sinus node artery was cannulated through the right coronary artery and perfused with heparinized blood from the carotid artery of a support dog by means of a Harvard pump (model 505-1210). Perfusion pressure was maintained at 100 mmHg. The right atrium was placed in a blood-filled glass container, which was kept at 37°C (Haake FE2). A bipolar driving electrode was sewed on the atrial epicardium near the upper part of the sulcus terminalis. A bipolar recording electrode was sewed on the caudal portion of the epicardium at a distance of 1.5 cm from the driving electrode. Sinoatrial conduction time (SACT) was measured during continuous atrial pacing consisting of a train of 8 consecutive beats at a rate 10 beats/min faster than the spontaneous rate.11) Pacing stimuli were provided by an electric stimulator (Nihon Kohden SEN-7103) at an intensity of about twice diastolic threshold and a duration of 2 msec. SACT was estimated as the length of the first postpacing cycle minus the control sinus cycle length; SACT refers to the sum of antegrade and retrograde conduction times. SACT was digitalized with a pulse counter (Nihon Kohden ET612J) and a printer (Citizen CBM Corporation). The measurement of SACT was repeated 5 times within 2 min before and after infusion of drugs and then SACT was obtained using a 20% trimmed mean.

The support dogs (9 to 32 Kg) were anesthetized with an intravenous injection of sodium pentobarbital (30 mg/Kg). The dog was ventilated through an intratracheal tube with room air and additional oxygen by a Harvard positive pressure respirator (model 607). A first dose of 500 units/Kg of sodium heparin was given i.v. prior to perfusion and additional doses of 200 units/Kg were given hourly. A detailed description of the methods employed in this study has been given elsewhere.12)
The following drugs were used: Dopamine hydrochloride (Kyowa Hakko), l-isoproterenol hydrochloride (Nikken Kagaku), tyramine hydrochloride (Tokyo Kasei), propranolol hydrochloride (Sumitomo Chemicals), imipramine hydrochloride (Fujisawa) and sulpiride (Mitsui). The drugs, dissolved in 0.9% saline, were infused with an infusion-withdrawal pump (Harvard Apparatus 901) or injected with a microsyringe (Terumo) into the sinus node artery. The data were expressed as mean±SEM and analyzed by Student's t-test, paired t-test and F-test.

RESULTS

1. Changes in SCL and SACT induced by dopamine

When dopamine was continuously infused at a constant rate, stable sinus tachycardia was obtained usually within 2 min. Before and during the dopamine-infusion, atrial pacing was performed for measuring SACT. Dopamine, infused at a rate of 1−2 µg/min into the sinus node artery, shortened SCL from 630±19 to 501±22 msec (38 trials in 12 experiments), whereas it caused a decrease in SACT from 86±8 to 56±4 msec in 24 trials in 11 preparations and an increase from 67±7 to 101±9 msec in 14 trials in 6 atria. As shown in Fig. 1, at relatively low pacing rates (<130 beats/min), dopamine usually caused a shortening of SACT. Since the pacing rates were 10 beats/min faster than the spontaneous rates, dopamine decreased SACT in those trials.

![Fig. 1. Correlation between atrial pacing rates and changes in sinoatrial conduction time (ΔSACT). ΔSACT = (SACT after an infusion of dopamine) − (SACT before an infusion of dopamine). The line of best fit (obtained by the method of least squares) is given by the formula ΔSACT = 0.582 × (atrial pacing rate) − 86.7 (r = 0.4608, p < 0.01).](image-url)
preparations with rates under 120 beats/min. There was a significant correlation \( r=0.4608, p<0.01 \) between the pacing rates ranging from 80 to 210 beats/min and the changes in SACT induced by the dopamine-infusion.

2. Effects of propranolol on shortening of SCL and SACT induced by dopamine and isoproterenol

As Table I shows, when dopamine was given at an infusion rate of 1–2 \( \mu g/min \) into the sinus node artery, SCL and SACT decreased from 644±36 to 515±46 msec (\( n=7, p<0.05 \)) and from 95±16 to 60±8 msec (\( p<0.01 \)), respectively. After 10 \( \mu g \) of propranolol were injected into the sinus node artery, dopamine prolonged SCL from 659±43 to 668±25 msec and reduced SACT from 83±10 to 76±7 msec. The changes in SCL and SACT before and after a single injection of 10 \( \mu g \) of the beta-adrenergic blocking agent were significantly different (from 129±36 to 5±8 msec and from 36±8 to 7±8 msec, respectively, \( p<0.05 \)). The same dose of propranolol significantly suppressed isoproterenol-induced changes in SCL and SACT from 172±78 to 3±14 msec (\( n=6, p<0.01 \)) and from 25±5 to 5±3 msec (\( p<0.01 \)), respectively (Table I).

3. Effects of imipramine on shortening of SCL and SACT induced by dopamine and tyramine

As shown in Table II, when dopamine was infused at a rate of 1 to 2 \( \mu g/min \) into the sinus node artery, SCL and SACT decreased from 651±47 to 539±30 msec (\( n=5, p<0.05 \)) and from 81±7 to 59±6 msec (\( p<0.005 \)), respectively. After imipramine treatment (100 \( \mu g \)), dopamine altered SCL and

| Table I. Effects of Propranolol on Dopamine- and Isoproterenol-induced Shortening of Sinus Cycle Length (SCL) and Shortening of Sinoatrial Conduction Time (SACT) in Isolated Dog Atria |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Propranolol-treatment (10 \( \mu g \)) |                                |                                |
|                                | Before | SCL | Before | SCL | SACT | Before | SCL | SACT |
| Dopamine (1-2 \( \mu g/min, n=7 \)) |       |     |       |     |      |       |     |      |
| Before infusion                | 644±36 | 95±16 | 659±43 | 83±10 |
| During infusion                | 515±46 | 60±8  | 668±25 | 76±7  |
| Differences                    | 129±36 | 36±8  | 9±28a  | 7±8a  |
| Isoproterenol (10-20 ng/min, n=6) |       |     |       |     |      |       |     |      |
| Before infusion                | 634±62 | 74±5  | 711±54 | 79±10 |
| During infusion                | 463±51 | 49±3  | 683±33 | 72±9  |
| Differences                    | 172±78 | 25±5  | 3±14b  | 5±3b  |

Values represent the mean±SEM. All units in msec.

\( a p<0.05, b p<0.01 \), as compared to the values before and after propranolol-treatment.
Table II. Effects of Imipramine on Dopamine- and Tyramine-induced Shortening of Sinus Cycle Length (SCL) and Shortening of Sinoatrial Conduction Time (SACT) in Isolated Dog Atria

<table>
<thead>
<tr>
<th>Imipramine-treatment (100 µg)</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td></td>
<td>SCL</td>
<td>SACT</td>
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<tr>
<td>Dopamine (1-2 µg/min, n=5)</td>
<td>Before infusion</td>
<td>651±47</td>
</tr>
<tr>
<td></td>
<td>During infusion</td>
<td>539±30</td>
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<tr>
<td></td>
<td>Differences</td>
<td>111±41</td>
</tr>
<tr>
<td></td>
<td>Before infusion</td>
<td>675±58</td>
</tr>
<tr>
<td></td>
<td>During infusion</td>
<td>411±30</td>
</tr>
<tr>
<td></td>
<td>Differences</td>
<td>234±61</td>
</tr>
<tr>
<td></td>
<td>SCL</td>
<td>621±43</td>
</tr>
<tr>
<td></td>
<td>SACT</td>
<td>552±53</td>
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<tr>
<td></td>
<td>SCL</td>
<td>68±28</td>
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<tr>
<td></td>
<td>SACT</td>
<td>68±10</td>
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<td></td>
<td>SCL</td>
<td>65±65a</td>
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</tbody>
</table>

Values represent the mean±SEM. All units in msec.

SACT from 621±43 to 552±53 msec and from 64±4 to 65±8 msec, respectively. The uptake blocker suppressed the changes in SACT induced by dopamine from 22±3 to -1±9 msec (p<0.05) and those in SCL from 111±41 to 68±28 msec. The same dose of imipramine significantly depressed changes in SACT and SCL produced by an infusion of tyramine (3 µg/min) from 26±5 to 1±3 msec (n=5, p<0.01) and from 234±61 to 65±65 msec (p<0.05), respectively (Table II).

4. Effects of sulpiride on shortening of SCL and SACT induced by dopamine

SCL was decreased by the infusion of dopamine (1 to 2 µg/min) from 689±81 to 450±82 msec (n=5) in the absence and 680±80 to 539±82 msec in the presence of sulpiride (30 µg). SACT was decreased by dopamine from 88±26 to 52±11 msec in the absence and from 88±23 to 55±12 msec in the presence of sulpiride. Neither the changes in SCL (139±52 to 141±52 msec) nor those in SACT (36±15 to 32±12 msec) were inhibited by sulpiride.

5. Effects of propranolol and sulpiride on lengthening of SACT induced by dopamine

Dopamine, as described above, frequently lengthened SACT in the preparations where the drug induced tachycardia over about 120 beats/min. In this study, we used cases of dopamine-induced lengthening of SACT. As Table III shows, SCL was decreased by the dopamine infusion (1 to 2 µg/min) from 542±50 to 447±24 msec (n=6, p<0.05) in the absence and from 608±56 to 582±41 msec in the presence of propranolol (10 µg). In contrast, SACT was increased by dopamine from 78±18 to 114±16 msec in the ab-
Table III. Effects of Propranolol and Sulpiride on Dopamine-induced Shortening of Sinus Cycle Length (SCL) and Lengthening of Sinoatrial Conduction Time (SACT) in Isolated Dog Atria

<table>
<thead>
<tr>
<th>Dopamine (1-2 μg/min, n=6)</th>
<th>Propranolol-treatment (10 μg)</th>
<th>Sulpiride-treatment (30 μg)</th>
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<tr>
<td></td>
<td>Before</td>
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<td></td>
<td>SCL</td>
<td>SACT</td>
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<tr>
<td>Before infusion</td>
<td>542±50</td>
<td>78±18</td>
</tr>
<tr>
<td>During infusion</td>
<td>447±24</td>
<td>114±16</td>
</tr>
<tr>
<td>Differences</td>
<td>96±33</td>
<td>-36±12</td>
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</table>

Values represent the mean±SEM. All units in msec.

sence and from 75±17 to 95±23 msec in the presence of the beta-adrenolytic drug. Subsequently, propranolol suppressed the changes in SCL and SACT from 96±33 to 26±35 msec (p<0.05) and from -36±12 to -20±9 msec, respectively. On the other hand, sulpiride did not affect a dopamine-induced reduction of SCL and prolongation of SACT. As Table III shows, SCL was decreased by dopamine from 539±43 to 404±20 msec (n=6, p<0.05) in the absence of sulpiride and from 530±37 to 405±17 msec (p<0.05) in the presence of sulpiride. SACT was increased by dopamine from 74±10 to 85±13 msec (p<0.05) in the absence and from 65±12 to 76±10 msec (p<0.05) in the presence of the dopaminergic blocker. However, sulpiride did not influence the shortening of SCL or the lengthening of SACT induced by dopamine.

DISCUSSION

The present study shows the following results: (1) Change in SACT caused by dopamine depend on atrial pacing rates. At high frequencies dopamine frequently induced prolongation of SACT and at low frequencies (>130 beats/min), it caused only a reduction of SACT. (2) Both propranolol and imipramine depress dopamine-induced shortening of SACT and SCL.
Moreover, propranolol suppresses dopamine-induced lengthening of SACT. (3) Neither reduction of SACT and SCL nor prolongation of SACT caused by dopamine are influenced by sulpiride. Several factors can conceivably be involved in the phenomenon that dopamine produced both positive and negative dromotropic effects. First, dopamine is categorized as a "mixed amine", which causes cardiac effects both by acting directly on beta-adrenergic receptors and by releasing norepinephrine from the labile pool of sympathetic nerve terminals, like tyramine. The positive dromotropism of dopamine, therefore, can be explained by the fact that dopamine, like other catecholamines, increases the amplitude of the action potential recorded from subsidiary pacemakers, accelerating conduction velocity of the sinoatrial junction. Second, as there is general agreement that sympathetic agents shift the dominant pacemaker group within the sinoatrial node, dopamine may bring about a shift of the dominant pacemaker sites, which may have caused the changes in SACT measured in this study. This speculation is supported by our data that propranolol diminished both the shortening and the lengthening of SACT caused by dopamine, probably because propranolol prevents the pacemaker-shift induced by the catecholamine. Third, Plumb et al reported that as pacing intervals decreased to shorter than about 240 msec, the conduction time of the human atria increased. In experiments with rabbit hearts, as the pacing rates increased, the conduction time from the crista terminalis to the dominant pacemaker cells lengthened. These findings may account for our observation that the faster the pacing rates, the greater the prolongation of SACT produced by dopamine, although the SACT in the present study (the sum of antegrade and retrograde conduction times) was different from the human atrial conduction time and the retrograde conduction time of the rabbit atrium. Fourth, our findings that dopamine exerts both positive and negative dromotropic effects may be a result of interaction of the above factors. This interpretation is supported by our previous report that catecholamines did not produce a dose-dependent positive dromotropic effect in spite of dose-dependent positive chronotropic and inotropic effects. It may be speculated that mechanisms of overdrive suppression contribute to prolonged SACT by dopamine, but this possibility seems unlikely because the post-return cycle was almost the same as the control sinus cycle in the majority of the present experiments.

As stated earlier, it is known that the cardiac effects of dopamine are the result of directly stimulating beta-adrenoceptors and displacing norepinephrine from sympathetic nerve cells. Chiba, using the same isolated atrial preparation as ours, reported that the positive chronotropic and inotropic actions of dopamine were in part due to tyramine-like effects that re-
leased norepinephrine from the sympathetic nerve storage site. The present
findings are in agreement with his results, because the positive chronotropic
action of dopamine-infusion was blocked by propranolol and imipramine.
Furthermore, the findings of the present experiments that the positive dromotropism
of dopamine was significantly inhibited by both propranolol and imipramine indicate that
the accelerating effect of dopamine on sinoatrial conduction is also related to the same mechanism responsible for its chronotropism. In addition, propranolol blocked the negative dromotropic effect of
dopamine. A possible explanation for this finding is that the beta-adrenergic
blocking agent inhibits the dopamine-induced pacemaker shift which delays
sinoatrial conduction. Another possibility is that slower pacing rates for measure-
ment of SACT in the presence than those in the absence of propranolol
may be associated with the suppressive effect of propranolol on the negative
dromotropism of dopamine as discussed above.

We attempted to examine the effects of a dopaminergic blocking drug,
sulpiride, on dopamine-induced chronotropic and dromotropic actions, and
found that there were no effects of sulpiride, as used in the present experi-
ments, on the actions of dopamine.

In conclusion, the present study suggests that the changes in SACT ind-
duced by dopamine are dependent on the pacing rates and that dopamine
exerts its chronotropic and dromotropic actions through cardiac beta-adre-
nergic receptors like tyramine but not through dopaminergic receptors.

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