Effect of Desmethylimipramine on the Canine SA Node

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CHIBA, S. Effect of Desmethylimipramine on the Canine SA Node. Tohoku J. exp. Med., 1974, 113 (4), 337-341 — Direct perfusion of the sinus node artery at constant pressure of 100 mmHg was performed in eleven canine hearts in situ. The injection of desmethylimipramine (DMI) into the sinus node artery caused an initial short deceleration followed by markedly long-lasting acceleration of the heart rate. The initial deceleration was not influenced by treatment with atropine. The secondary acceleration was inhibited by propranolol, and, furthermore, suppressed by tetrodotoxin. After the treatment with propranolol or tetrodotoxin, DMI produced only a negative chronotropic effect dose-relatedly. It was difficult to observe the blocking effect of DMI on tyramine action, because DMI alone induced marked sinus acceleration. On the other hand, tyramine action was not influenced by tetrodotoxin. Therefore, the use of both DMI and tetrodotoxin is beneficial to observe blocking effect of DMI on tyramine-like action in the in situ SA node preparation.

It has been established that DMI exerts its effect not only by inhibiting uptake of norepinephrine but also by direct depressant action in the isolated heart preparation (Greeff and Wagner 1969; Langslet et al. 1971; Babulova et al. 1973). In the clinical medicine, it was reported that the cardiac side effects were induced by tricyclic anti-depressant treatment in depressed patients (Edwards 1964; Freyschuss et al. 1970; Moir et al. 1972). Therefore, it is of interest to investigate the effect of DMI on the SA node in situ of the dog heart. In the present study, it was attempted to analyze chronotropic responses to DMI when injected into the cannulated sinus node artery of the in situ canine heart.

METHODS

Eleven mongrel dogs of either sex, weighing 9 to 18 kg, were anesthetized with sodium pentobarbital, 30 mg/kg, i.v. Artificial respiration was maintained with a Harvard respirator. The chest was opened at the right 4th intercostal space. Both vagi were cut at the mid-cervical level. The methods of the direct perfusion of the canine sinus node artery were described in previous papers (Hashimoto et al. 1967, 1968). The systemic blood pressure was measured by an electric manometer (Nihon Kohden RT-2). The electrocardiogram (lead II) was recorded with an electrocardiograph (Nihon Kohden ME-20-TR). The heart rate was continuously recorded on a cardiograph (Nihon Kohden RT-2) which was triggered by the R wave of the lead II.

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Drugs used were acetylcholine chloride (Daiichi), DL-norepinephrine (Sumitomo Chemicals), desmethylimipramine hydrochloride (DMI, Fujisawa), tyramine hydrochloride (Waco), atropine sulfate and tetrodotoxin (Sankyo). The volume of injected drug solution was 0.01–0.03 ml which was administered in a period of 4 sec through a microinjector (Terumo Co.).

**RESULTS**

*Effect of DMI on the SA node*

When a relatively small dose of DMI was injected into the sinus node artery, an acceleration of sinus rate was usually observed. The threshold dose for inducing sinus acceleration was about 1 µg. At a higher dose, DMI induced an initial deceleration of sinus rate followed by a long-lasting sinus acceleration. The threshold dose for inducing sinus deceleration was about 10 to 30 µg. The duration of sinus deceleration was 1 to 2 min and that of following sinus acceleration was usually more than 30 min at doses of 10–30 µg. Tachyphylaxis was not so clear when injected at 1-hour intervals. Fig. 1 shows a typical response to 30 µg of DMI. Summarized data are shown in Table 1.

![Fig. 1. Typical chronotropic response to 30 µg of desmethylimipramine (DMI) injected into the sinus node artery of the dog. SBP, systemic blood pressure; HR, heart rate.](image)

**Table 1. Effect of desmethylimipramine (DMI) on the SA node of the dog**

<table>
<thead>
<tr>
<th>Dose of DMI (µg)</th>
<th>Number of dogs</th>
<th>Control heart rate (beats/min)</th>
<th>PCE (% increase in heart rate)</th>
<th>NCE (% decrease in heart rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>141±7.2</td>
<td>6.3±1.9</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>141±7.2</td>
<td>11.8±3.1</td>
<td>2.5±1.4</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>146±4.3</td>
<td>19.8±3.0</td>
<td>4.4±1.6</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>148±4.6</td>
<td>27.6±6.0</td>
<td>3.4±3.2</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>144±4.7</td>
<td>34.8±11.1</td>
<td>29.8±4.8</td>
</tr>
<tr>
<td>300</td>
<td>3</td>
<td>145±7.6</td>
<td>39.0±16.3</td>
<td>44.7±5.2</td>
</tr>
<tr>
<td>1000</td>
<td>2</td>
<td>150</td>
<td>50</td>
<td>61</td>
</tr>
</tbody>
</table>

The values represent mean ±s.e.

PCE, positive chronotropic effect; NCE, negative chronotropic effect.
Desmethylimipramine and SA Node

Fig. 2. Effect of 10 μg of tetrodotoxin on the sinus acceleration induced by 10 μg of desmethylimipramine (DMI). Norepinephrine action is not inhibited by tetrodotoxin treatment.

Fig. 3. Negative chronotropic effect induced by desmethylimipramine (DMI) after treatment with 3 μg of tetrodotoxin. SBP, systemic blood pressure; HR, heart rate; AVNR, atrioventricular nodal rhythm.

Effect of propranolol or tetrodotoxin on DMI-induced chronotropic responses

The positive chronotropic response to DMI (10 to 30 μg) was completely blocked by treatment with an adrenergic beta-blocking agent, propranolol (1 to 3 μg). This acceleration response to DMI was also suppressed by tetrodotoxin treatment. The sinus acceleration induced by 10 to 30 μg of DMI was significantly suppressed by 1 to 10 μg of tetrodotoxin treatment. Fig. 2 shows that DMI-induced sinus acceleration is interrupted by injection of 10 μg of tetrodotoxin into the sinus node artery.

After treatment with propranolol or tetrodotoxin, a higher dose of DMI induced only a negative chronotropic response. Fig. 3 shows that DMI dose-relatedly induces a negative chronotropic effect in the preparation treated with 3 μg of tetrodotoxin. In this case, 1000 μg of DMI induces complete suppression of SA node pacemaker activity and atrio-ventricular rhythm appears for about 5 min.

The sinus deceleration response to DMI was not modified by atropine treatment. A negative chronotropic response to 30 μg of DMI was not influenced by 100 μg of atropine which completely blocked the negative chronotropic response to 1 μg of acetylcholine as shown in Fig. 4.

Effect of DMI on tyramine-induced sinus acceleration

When tyramine was administered into the sinus node artery, sinus acceleration was dose-dependently induced as reported previously (James and Nadeau 1964; Chiba et al. 1973). It is well known that this tyramine action is blocked by DMI treatment. However, DMI alone induced a marked sinus acceleration.
Fig. 4. Effect of 100 μg of atropine on negative chronotropic responses to 1 μg of acetylcholine (Ach) and 100 μg of desmethylimipramine (DMI). SBP, systemic blood pressure; HR, heart rate.

**TABLE 2. Effect of desmethylimipramine (DMI) and tetrodotoxin (TTX) on tyramine-induced sinus acceleration**

<table>
<thead>
<tr>
<th>Dose (μg)</th>
<th>Treatments with DMI (10–30 μg) and TTX (1–3 μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (% increase in heart rate)</td>
</tr>
<tr>
<td>Tyramine 0.1–0.3</td>
<td>19.8±5.7</td>
</tr>
<tr>
<td>Norepinephrine 0.01–0.1</td>
<td>25.5±6.8</td>
</tr>
</tbody>
</table>

Control sinus rate is 133±8.7 (mean±s.e.) beats/min in 4 experiments in 4 dogs.

Therefore, after suppression of DMI-induced sinus acceleration by tetrodotoxin, tyramine action was readily investigated in the in situ preparation. By treatment with both tetrodotoxin and DMI, it was clearly observed that tyramine-induced sinus acceleration was inhibited. At that time, norepinephrine action was not inhibited. Summarized data are shown in Table 2.

**DISCUSSION**

It was well documented that over-dose with tricyclic antidepressants produces the acute cardiac effects. In this study, it was demonstrated that DMI at small doses induced only a slight positive chronotropic effect and at increasing doses induced an initial negative chronotropic response followed by a secondary long-lasting positive chronotropic one. The DMI-induced negative chronotropic effect was not inhibited by atropine and its secondary positive response was blocked either by an adrenergic beta-blocking agent, propranolol, or by tetrodotoxin. Therefore, it is concluded that DMI may have either a direct negative chronotropic action or an indirect positive chronotropic one by adrenergic neuronal mechanism.

It is considered that, in the in situ preparation anesthetized with sodium pentobarbital, sympathetic tone always exerts its influence on the SA node.
Thus, DMI produces a marked sinus acceleration by blocking uptake of norepinephrine which is released from sympathetic nerve terminals. In this study, it was tried to evaluate effect of DMI on tyramine action. When only DMI was administered into the sinus node artery, the sinus rate markedly increased over control level. Therefore, in some cases, it was difficult to investigate the correct blocking effect of DMI on chronotropic effects induced by the drug such as tyramine. Previously, it has been reported that tyramine action is not inhibited by tetrodotoxin (Hashimoto and Chiba 1969). Thus, by the use of both tetrodotoxin and DMI, it became easy to observe the blocking of tyramine action. Reserpine is one of the useful key drugs to block tyramine action, but it is impossible to produce its action in a comparatively short period and at the local region. From these reasons, the treatment with both tetrodotoxin and DMI may be a useful pharmacological appliance for excluding indirect effects induced both by nerve excitation and by tyramine action.

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References


