CARDIOVASCULAR ACTION OF PROPRANOLOL IN RATS UNDER VARIOUS ANESTHETIC PROCEDURES

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Abstract—We previously reported that the pressor action of propranolol was observed in the rat anesthetized with urethane. In the present study, rats, anesthetized with pentobarbitone or ether, treated with curare or unanesthetized, were used to investigate the influence of anesthetics on the blood pressure response to propranolol. Propranolol always produced a pressor response under these experimental conditions as well as urethane anesthesia. But under pentobarbitone anesthesia, the magnitude of the pressor action was significantly lower than that obtained under the other experimental conditions. It is concluded that the choice of urethane as the anesthetic does not create a situation irrelevant to that found with other anesthetics and that the cardiovascular responses of rat to propranolol are unique when compared to other species.

Propranolol, a sympathetic β-blocking agent, is considered to produce a fall in blood pressure both in humans and in experimental animals. On the other hand, in our previous papers (1, 2) it was shown that propranolol produced a sustained pressor action in the rat under urethane anesthesia, and that this action was considered to be due to the blockade of β-receptor vascular tone in the peripheral vessels. Dasgupta (3) and Regoli (4) also reported that this drug produced a pressor response in rats anesthetized with urethane. This difference in action of propranolol on blood pressure of rats and other species of animals may be explained by the following two reasons as we have mentioned previously (5): (a) the β-adrenoceptive vasodilator tone was so strong that a passive vasoconstriction induced by the blockade of β-receptors with propranolol was marked in rats; (b) the depressant effect of propranolol on the heart was relatively small in rats.

However, Barrett (6) suggested, from his study on the effect of propranolol on the heart rate in rats, that the influence of anesthetics on the cardiovascular system is not negligible and urethane is not suitable for these experiments as the anesthetic. He also suggests that the cardiovascular responses of the rat to propranolol were not different from those of other animals.

The present experiments were performed under pentobarbitone or ether anesthesia and also in the curare-immobilized or unanesthetized rats to investigate the influence of anesthetics on the cardiovascular responses to propranolol.

MATERIALS AND METHODS

Wistar rats of both sexes, weighing between 200 and 380 g were anesthetized with urethane (1.5 g/kg s.c.), pentobarbitone (35 mg/kg i.p.) or ether (by endotracheal insuffla-
In some experiments, rats were fixed on their back after light ether anesthesia and then curare (0.3 to 0.5 mg/kg s.c.) was injected to immobilize them under artificial ventilation. In other experiments, rats were fixed on their back after light ether anesthesia and then the operation was carried out under local anesthesia with 2% procaine.

Arterial blood pressure was measured from the right carotid artery with an electronic manometer (MPU-0.5 290, SAN-EI). The right jugular vein was cannulated for i.v. injection of drugs. Heart rate was measured with a pulse rate tachometer (Type 2130, SAN-EI). Blood pressure and heart rate were recorded simultaneously on an ink-writing recorder.

Propranolol hydrochloride (Inderal, I.C.I.) was diluted in 0.9% saline and injected in a volume of 0.2 ml/animal, followed by 0.05 ml of saline solution.

RESULTS

Effect of propranolol on blood pressure and heart rate in unanesthetized rats

Observations were made in 21 rats. Propranolol (0.1 to 0.5 mg/kg i.v.) produced a sustained pressor action and a decrease in heart rate in all rats (Fig. 1). The magnitude and duration of the rise appeared to be dose dependent.

![Fig. 1. Rat, 300 g, operated on under local anesthesia with 2% procaine. Records of arterial blood pressure (B.P.) and heart rate (H.R.). Response to the intravenous injection of propranolol (PP).](image)

<table>
<thead>
<tr>
<th>Anesthetic or treatment</th>
<th>Propranolol (mg/kg)</th>
<th>Blood pressure (mean ± S.E., mmHg) Before</th>
<th>After</th>
<th>Change</th>
<th>Heart rate (beats min⁻¹ ± S.E.) Before</th>
<th>After</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>No general anesthetic</td>
<td>0.1 (&lt;15) *</td>
<td>130.9 ± 5.2</td>
<td>145.7 ± 5.7</td>
<td>14.8 ± 2.4</td>
<td>471 ± 14</td>
<td>392 ± 16</td>
<td>89 ± 7</td>
</tr>
<tr>
<td></td>
<td>0.5 (&lt;15)</td>
<td>135.1 ± 4.8</td>
<td>156.3 ± 5.2</td>
<td>21.2 ± 1.3</td>
<td>456 ± 10</td>
<td>360 ± 7</td>
<td>96 ± 8</td>
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<td>Curare</td>
<td>0.1 (&lt;15)</td>
<td>135.5 ± 4.4</td>
<td>148.8 ± 4.8</td>
<td>13.3 ± 1.2</td>
<td>417 ± 15</td>
<td>343 ± 12</td>
<td>74 ± 6</td>
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<td></td>
<td>0.5 (&lt;10)</td>
<td>132.6 ± 5.4</td>
<td>151.4 ± 5.2</td>
<td>18.8 ± 2.1</td>
<td>416 ± 18</td>
<td>329 ± 15</td>
<td>86 ± 6</td>
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<tr>
<td>Urethane</td>
<td>0.1 (&lt;22)</td>
<td>101.5 ± 5.4</td>
<td>115.6 ± 5.3</td>
<td>14.1 ± 1.5</td>
<td>382 ± 13</td>
<td>337 ± 10</td>
<td>45 ± 5</td>
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<td></td>
<td>0.5 (&lt;16)</td>
<td>100.2 ± 4.9</td>
<td>120.3 ± 3.6</td>
<td>20.1 ± 1.9</td>
<td>372 ± 13</td>
<td>319 ± 10</td>
<td>53 ± 7</td>
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<td>Pentobarbitalne</td>
<td>0.1 (&lt;25)</td>
<td>117.8 ± 4.3</td>
<td>122.4 ± 4.2</td>
<td>4.6 ± 1.3</td>
<td>398 ± 10</td>
<td>351 ± 8</td>
<td>46 ± 14</td>
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<td>0.5 (&lt;14)</td>
<td>117.9 ± 3.8</td>
<td>126.6 ± 2.9</td>
<td>8.8 ± 1.9</td>
<td>409 ± 8</td>
<td>359 ± 10</td>
<td>51 ± 8</td>
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<tr>
<td>Ether</td>
<td>0.1 (&lt;13)</td>
<td>109.5 ± 3.7</td>
<td>126.0 ± 3.1</td>
<td>16.5 ± 2.5</td>
<td>401 ± 13</td>
<td>354 ± 12</td>
<td>48 ± 5</td>
</tr>
<tr>
<td></td>
<td>0.5 (&lt;11)</td>
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<td>132.5 ± 5.4</td>
<td>22.4 ± 2.8</td>
<td>411 ± 13</td>
<td>352 ± 8</td>
<td>59 ± 8</td>
</tr>
</tbody>
</table>

*: Numbers in parentheses indicate the number of experiments.
Effect of propranolol in rats treated with curare

In 25 rats, curare (0.3 to 0.5 mg/kg) was injected s.c. under artificial ventilation. Propranolol (0.1 to 0.5 mg/kg i.v.) produced a sustained rise in blood pressure and a decrease in heart rate in all rats (Fig. 2). This rise in blood pressure and the decrease in heart rate were similar to those obtained in unanesthetized rats (Table 1).

Effect of propranolol under urethane anesthesia

Observations were made in 41 rats. Propranolol (0.1 to 0.5 mg/kg i.v.) produced a sustained pressor action and a decrease in heart rate in all rats except one. This rise in blood pressure was similar to that obtained in unanesthetized rats and in rats treated with curare. But the decrease in heart rate was significantly lower than that obtained in curare-treated or unanesthetized rats (Table 1).

Effect of propranolol under ether anesthesia

Observations were made in 23 rats. Propranolol (0.1 to 0.5 mg/kg i.v.) produced a sustained pressor action and a decrease in heart rate in all rats (Fig. 3). The rise in blood pressure was slightly greater than that obtained in rats anesthetized with urethane and in unanesthetized rats, but the differences were not significant. The decrease in heart rate was significantly lower than that obtained in curare-treated or unanesthetized rats (Table 1).

Effect of propranolol under pentobarbital anesthesia

Observations were made in 39 rats. In most cases propranolol (0.1 to 0.5 mg/kg i.v.)
produced a slightly sustained rise in blood pressure and decrease in heart rate. In 7 rats, however, propranolol produced a slight fall in blood pressure and no change occurred in 3 rats. Fig. 4 shows two examples of the changes induced by propranolol on the blood pressure and heart rate of rats anesthetized with pentobarbitone. The rise in blood pressure was significantly lower than that obtained in unanesthetized or curare-treated rats and in rats anesthetized with urethane or ether. The decrease in heart rate was significantly lower than that obtained in curare-treated or unanesthetized rats, but was similar to that obtained under urethane anesthesia (Table 1).

DISCUSSION

In the present study, propranolol produced a pressor action of similar magnitude in ether anesthetized rats and in curare-treated or unanesthetized rats. Under pentobarbitone anesthesia this drug, in most cases, produced a smaller rise in blood pressure than under the other experimental conditions.

Barrett (6) pointed out that urethane is not suitable as an anesthetic for experiments to observe the action of autonomic blocking drugs, because this anesthetic raises the autonomic activity to an artificially high level. However, in guinea pigs (5) and rabbits (7), the pressor action of propranolol was difficult to observe even under urethane anesthesia, whereas the action could be observed in rats under other experimental conditions. These results suggest that urethane is not specific as the anesthetic and the cardiovascular responses of the rat are different from those of other animals.

In general, the depressant action of anesthetics on the autonomic function has been often demonstrated experimentally. It is well known, above all, that barbiturates have a strong ganglionic blocking action (8). For this reason, it may be expected that bar-
biturates depress β-adrenoceptive vasodilator tone in the peripheral vessels, thus making it difficult to observe the pressor response derived from the blockade of peripheral β-receptor vascular tone with propranolol.

Therefore, pentobarbitone anesthesia may not be suitable for such an experiment. Barrett (6) used pentobarbitone in the large dose of 55 mg/kg while in our experiments a dose of 35 mg/kg was sufficient to achieve anesthesia in rats. It is reasonable to suppose that the depression of autonomic activity is lower in the latter case. Thus, it is possible to conclude that the pressor action of propranolol in rats is not the artificial results derived from anesthesia, but as we have emphasized, this action is unique in the rat.

There are several reports (9–11) that ether anesthesia produces sympathoadrenal stimulation. In the present study, there was little evidence that ether caused such an effect on the sympathetic nervous system, because initial level of heart rate and blood pressure before propranolol was significantly higher in unanesthetized rats than in anesthetized ones. This fact suggests that the sympathetic activity to the heart and peripheral vascular beds may be expected to be raised to a high level by the various stimuli derived from unanesthetized and restricted conditions. With regard to these facts, Tabei et al. (12) showed, using a tail plethysmographic technique, that propranolol and pronethalol caused a pressor action in conscious hypertensive rats.

The degree of decrease in heart rate by propranolol was significantly smaller in rats anesthetized with pentobarbitone as well as with urethane or ether than in curare-treated or unanesthetized rats. A possible explanation for this finding is that these anesthetics may to some extent depress the sympathetic tone to the heart. Another explanation could be that the sympathetic activity to the heart in unanesthetized rats was raised to an artificially high level by the various stimuli derived from unanesthetized and fixed conditions.

REFERENCES

9) BHATIA, B.B. AND BURN, J.H.: J. Physiol. 78, 257 (1933)