Summary

Effects of $\beta$-blockers on the peripheral sympathetic adrenergic nervous system were studied in atropinized pithed rats under curarized condition using the rise of the diastolic blood pressure produced by stimulation of the spinal nerves as a measure. All the three $\beta_1$-blockers used (practolol, atenolol and metoprolol) and oxprenolol produced an inhibition of the pressure rise, without producing a significant inhibition of the pressor response to close-arterial injection of noradrenaline. Propranolol failed to produce any inhibition. However, the pressor response to intrarterial noradrenaline was significantly potentiated by this compound.

Introduction

In our previous study (1), it was demonstrated that $\beta$-blockers of widely-differing pharmacological properties could induce hypotension in anesthetized rats, if due caution was paid to the state of anesthesia and that the hypotensive effects of $\beta$-blockers such as propranolol, whose blood-brain concentration ratio was reported to be high (1:19)(2), were associated with a decrease in the renal nerve activity (RNA) recorded at the central cut end, while those of atenolol with a low blood-brain concentration ratio of 1:0.2 (2) was related with an increased RNA. Oxprenolol with blood-brain ratio of 1:1 (3) produced variable effects on RNA. These findings suggest that a peripheral mechanism or mechanisms must be taken into consideration to explain the hypotensive effects of certain types of $\beta$-blockers.

Using the pithed rats, an attempt was made in the present study to delineate the effects of several $\beta$-blockers on the peripheral adrenergic nervous system.

Materials and methods

Male Wistar-imamichi rats weighing 240 and 430 g were anesthetized with intraperitoneal thiopental (50-60 mg/kg) and the adrenals were removed bilaterally. Both the right and left carotid arteries were ligated. After intravenous administration of atropine sulfate (1 mg/kg), the artificial respiration was instituted and the animals were pithed according to the method of Shipley and Tilden (4), inserting a stainless steel rod through the orbit, the foramen magnum and down into the spinal column. The rod was then removed and another stainless steel rod was inserted into the vertebral canal. The rod, which was electrically insulated except for the tip 5 mm, was placed in such a position that the bare tip portion reached the height of Th 10-11. By feeding electric current between this electrode and the electrode of similar structure placed at the similar height under the skin of the back, the ventral roots of the spinal nerves were stimulated. Before starting the experiments, 1 mg/kg of d-tubocurarine chloride was injected intravenously to abolish the muscle twitching resulting from the stimulation of the motor fibres in the ventral roots. These procedures are essentially the same as described by Gillespie and Muir (5). Arterial blood pressure was recorded from the femoral artery, and the heart rate was recorded with a cardiotachometer triggered by pressure pulses of arterial blood pressure. Beta-blockers used were: propranolol (ICI Japan), practolol (ICI, Japan), atenolol (ICI, Japan), metoprolol (CIBA-Geigy) and oxprenolol (CIBA-Geigy).

Results

Stimulation of the spinal nerves at Th 10-11 resulted in no change in the heart rate. The diastolic blood pressure rose depending on the rates of stimulation. All the $\beta_1$-selective blockers used (atenolol, metoprolol, and practolol) produced a definite inhibition of the pressure rise, which was more marked at higher stimulation frequencies, as shown in Fig. 1 with practolol. Propranolol did not produce such an inhibition even in doses of 3 mg/kg, although it produced a transient fall of the blood pressure associated with a
decrease in the heart rate. Oxprenolol produced a definite inhibition (Fig. 1). The effects of oxprenolol on the blood pressure were complex. An initial slight rise followed by a fall and the final rise was observed. The heart rate was gradually increased after an initial decrease. Metoprolol produced a decrease in the heart rate and the blood pressure. Practolol increased the heart rate without producing any gross change in the blood pressure, while atenolol was almost without effects.

Close-arterial injection of 2 μg/kg of noradrenaline to the hind quarters resulted in a biphasic rise of the blood pressure. The first one, which was accompanied by no change in the heart rate, was taken to have resulted from the direct action of noradrenaline on the hind-limb vessels, while the second larger one associated with an increase in the heart rate, from the systemic effects. As shown in table 1, there was a tendency for the first phase of the pressor response to noradrenaline to be potentiated after β-blockers, except oxprenolol and the potentiation was significant with propranolol. There was a tendency for the pressor response to be suppressed after oxprenolol.

Discussion

In the present experiment, the stimulation of the spinal nerves was conducted in the pithed rats and in the presence of atropine and d-tubocurarine. Moreover, the adrenals were extirpated bilaterally. Therefore, the response produced by stimulation of the spinal nerves could be explained by stimulation of the efferent sympathetic fibres. Since there occurred no increase in the heart rate when the spinal nerves were stimulated at Th 10-11, the participation of the stimulation of the heart in the observed rise in the diastolic blood pressure may be excluded. All the three β1-selective blockers used and oxprenolol produced an inhibition of the rise of the blood pressure. Since the significant inhibition of the pressor response to close-arterial injection of noradrenaline was not observed with these β-blockers, it may be concluded that these substances exerted inhibitory effects on the peripheral adrenergic system. Thus, the existence of β1-receptor subergying the facilitation of the peripheral adrenergic nervous system activity seems to be substantiated. The most probable candidate may be the much-debated presynaptic β-adrenoceptor. Although propranolol did not produce inhibitory effects on the pressor response to electrical stimulation of the spinal nerve, this may probably be explained by a significant potentiation of the pressor response to noradrenaline produced by this compound. The reason for the potentiation of the pressor response to noradrenaline produced by propranolol is not clear at present. Similar phenomenon was observed in the dog by Burks and Cooper (6), and was explained by enhancement of the α-receptor stimulation by blockade of "silent" α-receptors. The pressor response to noradrenaline tended to be suppressed after oxprenolol. This may probably be due to the weak α1-blocking effect as reported by Hila et al (7).

Thus, in addition to the effects on the central nervous system, β-blockers have action on the peripheral sympathetic nervous system. Both of these two actions may be operative in the hypotensive actions of these compounds.

References

Table 1. Effects of ß-blockers on the pressor response (diastolic) of 2 µg/kg of noradrenaline injected to the hind quarters

<table>
<thead>
<tr>
<th>ß-blockers</th>
<th>doses mg/kg</th>
<th>n</th>
<th>Pressor response before ß-blocker mmHg</th>
<th>Pressor response after ß-blocker mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>3.0</td>
<td>5</td>
<td>35.5 ± 1.5</td>
<td>41.6 ± 3.3*</td>
</tr>
<tr>
<td>Atenolol</td>
<td>3.0</td>
<td>4</td>
<td>34.3 ± 2.3</td>
<td>39.0 ± 5.8</td>
</tr>
<tr>
<td>Practolol</td>
<td>30.0</td>
<td>4</td>
<td>33.3 ± 4.6</td>
<td>39.4 ± 7.4</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>3.0</td>
<td>5</td>
<td>32.7 ± 2.6</td>
<td>29.2 ± 2.9</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3.0</td>
<td>4</td>
<td>27.0 ± 4.2</td>
<td>28.1 ± 4.9</td>
</tr>
</tbody>
</table>

* P < 0.05