CARDIOVASCULAR ACTIONS OF OPTICAL ISOMERS OF PROPRANOLOL

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Abstract—Effects of the optical isomers of propranolol on blood pressure in the rat, and in the spinal rat during adrenaline infusion were studied to investigate the mechanism of the pressor action of propranolol. Both isomers of propranolol produced a sustained pressor action in the rat and in the spinal rat infused with adrenaline. The magnitude of the pressor action produced by the d- and l-propranolol was proportional to their β-adrenoceptor blocking activities in the heart as was reported by several investigators. It is concluded that the pressor action of propranolol is due to the blockade of the β-adrenoceptors mediating vasodilation in the skeletal muscle vascular beds.

Propranolol was first described by Black et al. (1) to be a potent β-adrenoceptor blocking agent. Afterwards the agent has been studied most extensively among many β-adrenoceptor blocking agents and has been employed for the treatment of a number of diseases. The l-isomer of propranolol is much more active than the d-isomer in blocking the inotropic, chronotropic and vasodepressor actions of isoproterenol (2, 3). In our previous papers (4, 5), it was shown that propranolol produced a sustained pressor action in the rat, and that this pressor action was probably due to the blockade of the β-adrenoceptors mediating vasodilation in the vascular bed of skeletal muscle. If this view were correct, d-propranolol which has a very low β-adrenoceptor blocking activity, would not produce a sustained pressor action, but l-propranolol, which has a strong β-adrenoceptor blocking activity, would produce a sustained pressor one markedly in the rat.

The present study was undertaken to examine this assumption, and further to investigate the mechanism of the pressor action of propranolol in the rat. The effects of the isomers of propranolol on blood pressure and heart rate in the spinal rat infused with adrenaline were also studied. Effects of the isomers of propranolol in the isolated heart were also examined for their possible contribution to the pressor action.

MATERIALS AND METHODS

Experiments in the anesthetized rat and in the spinal rat

Wistar rats of either sex, weighing between 240 and 320 g were anesthetized with urethane (1.5 g/kg s.c.). Spinal rats were prepared using the same procedure as previously described (4). They were given artificial ventilation with room air at a constant rate and volume immediately after operation. Arterial blood pressure and heart rate were measured...
by the same method as previously described (6). Infusion of adrenaline, diluted in 0.9% saline solution, was given into the left jugular vein at a rate of 5 \( \mu \text{g/kg/min} \) using a motor-driven syringe (KN 202, Natume) set to deliver 0.11 ml/min. Injections of drugs, diluted or dissolved in 0.9% saline, were given into the right jugular vein in a dose volume of 0.2 ml and washed in with 0.05 ml saline. The following drugs were used: d-propranolol hydrochloride (I.C.I.), l-propranolol hydrochloride (I.C.I.) and l-adrenaline hydrochloride. Doses refer to their salts.

**Experiments in isolated rat atria**

Wistar rats of either sex, weighing 220 to 320 g were used. The atrial preparations were made using the same procedure as previously described (7) and experiments were also performed under the same condition as previously described (6). The atrial rate in spontaneously beating atria or the atrial contraction in electrically driven left atrium was measured and recorded using the same method as previously described (7). Drug concentrations were expressed in terms of weight (g) as the salt per ml, referring to the final bath concentrations.

**RESULTS**

**Effects of d- and l-propranolol on blood pressure and heart rate in the rat**

D-Propranolol (0.1 to 1.0 mg/kg) and l-propranolol (0.001 to 1.0 mg/kg) were given i.v. to 83 rats. Both agents produced a sustained pressor action and a decrease in heart rate in all animals. However, the higher doses of d-propranolol (1.0 to 10.0 mg/kg i.v.) caused an initial transient fall, and then a prolonged rise in blood pressure. The minimum doses of d- and l-propranolol producing a sustained pressor action were 30-100 \( \mu \text{g/kg} \) and 0.3-1.0 \( \mu \text{g/kg} \), respectively. At doses less than 0.1 mg/kg of l-propranolol or 10.0 mg/kg of d-isomer, the magnitude of the rise and the decrease in heart rate appeared to be dose dependent (Fig. 1). The rise elicited by l-propranolol (0.1 mg/kg) was almost similar to or slightly larger than that of d-isomer at the dose of 10.0 mg/kg.

**Effects of d- and l-propranolol on blood pressure and heart rate in the spinal rat during adrenaline infusion**

Observations were made in 76 spinal rats. Intravenous infusion of adrenaline (5 \( \mu \text{g/kg/min} \)) produced a moderate rise in blood pressure and a marked increase in heart rate in all rats. When the blood pressure was stabilized, about 15 min after the onset of infusion, d- or l-propranolol was given i.v. Both agents always produced a sustained pressor action and a decrease in heart rate. But minimum doses of d-propranolol producing a sustained pressor action were much larger than those of l-propranolol. The magnitude and duration of the rise caused by these agents appeared to be dose dependent at doses less than 0.1 mg/kg of l-propranolol and 10.0 mg/kg of d-propranolol. The rise elicited by l-propranolol (0.1 mg/kg) was almost similar to that of d-propranolol at the dose of 10.0 mg/kg (Fig. 2).

**Effects of d- and l-propranolol on the isolated rat atria**

Effects of d- and l-propranolol at concentrations \( 10^{-7}, 3 \times 10^{-7}, 10^{-6}, 3 \times 10^{-6} \) and
$5 \times 10^{-6}$ g/ml on the rate of spontaneously beating rat atria and on the contractile force of electrically driven atria are shown in Figs. 3 and 4. In each 6 control experiments performed under identical conditions but without addition of $\beta$-adrenoceptor blocking agents, there was little change from initial control levels in inotropic or chronotropic activity of the atrial

![FIG. 1. Effects of d- and l-propranolol on blood pressure (B.P.) and heart rate (H.R.) in the anesthetized rat. Each point represents mean ± S.E. of 6 experiments.](image1)

![FIG. 2. Effects of d- and l-propranolol on blood pressure (B.P.) and heart rate (H.R.) in the spinal rat infused with adrenaline. Each point represents mean ± S.E. of 6 experiments.](image2)

![FIG. 3. Changes in heart rate of spontaneously beating rat atria induced by d- and l-propranolol 30 min after administration. Each point represents mean ± S.E. of 7 experiments. *Significantly different from d-propranolol ($p < 0.01$).](image3)

![FIG. 4. Changes in contractile force of electrically driven rat left atrium induced by d- and l-propranolol 30 min after administration. Each point represents mean ± S.E. of 7 experiments.](image4)
preparations. Both isomers of propranolol depressed the atrial rate at concentrations lower than $10^{-6}$ g/ml in a concentration-dependent manner. But at concentrations higher than $3 \times 10^{-6}$ g/ml the l-isomer depressed the atrial rate to a significantly greater extent than did the d-isomer. The d- and l-propranolol reduced the contractile force of electrically driven left atria in a concentration-dependent manner, and there was no or little difference between the depression induced by l-propranolol and that induced by the d-isomer.

**DISCUSSION**

In the present study, both isomers of propranolol produced a sustained rise in blood pressure in the rat. But the magnitude of the pressor action induced by d-propranolol was much smaller than that induced by the same dose of l-propranolol. The minimum dose of d-propranolol required to produce a pressor action was approximately one hundred times that of the l-isomer.

Howe and Shanks (2) and Barrett and Cullum (3) reported that d-propranolol had less than one hundredth the potency of l-propranolol in blocking the positive inotropic and chronotropic responses to isoproterenol. Therefore, the magnitude of the pressor action caused by propranolol is considered to be directly proportional to the $\beta$-adrenoceptor blocking activity of the drug and the minimum dose of the isomers required to cause the pressor action is considered to be inversely proportional to $\beta$-adrenoceptor blocking activity of the drug. Thus, the present observation supports our previous view that the pressor action of propranolol in the rat is due to the blockade of $\beta$-adrenoceptors mediating vasodilation in skeletal muscle (4, 5). The results reported by Nakao et al. (8) that the pressor effects of the l-isomers of propranolol and YB-2 on arterial pressure were greater than those of the d-isomers in both normal and hypertensive rats, appear to be in favour of this suggestion.

From the experiments in isolated rat atria, both isomers of propranolol were found to have similar negative chronotropic and inotropic responses at lower concentrations. However, the negative chronotropic action produced by a large concentration of the l-isomer was greater than that obtained with the d-isomer. This finding suggests that the cardiac depression produced by a large concentration of propranolol seems to be due not only to the nonspecific property of the agent, such as local anesthetic action, but also to the specific $\beta$-blocking action. Thus, the magnitude of the pressor action induced by larger doses of propranolol is considered to be unrelated to their $\beta$-blocking activities because of their marked cardiac depression.

In this study, the following results were also obtained. Both isomers of propranolol produced a sustained pressor action in the spinal rat in which vasodilation mediated through $\beta$-adrenoceptors was produced by adrenaline infusion. The magnitude of the pressor action was dose-dependent and was also considered to be related to the $\beta$-blocking activity of the agents as observed in the anesthetized rat. But the rise elicited by each dose of $\beta$-adrenoceptor blocking agent in the spinal rat infused with adrenaline was less scattering than that obtained in the anesthetized rat. Therefore, it is more valid to compare the
β-adrenoceptor blocking activity of a β-adrenoceptor blocking agent using the magnitude of the rise elicited by β-adrenoceptor blocking agents, or the minimum dose of the agents required to cause a pressor action in the spinal rat infused with a given dose of adrenaline than using data obtained in the rat, because there is almost a constant activation of adrenoceptors in the heart and peripheral vascular beds and little reflex mechanism in the spinal rat infused with a given dose of adrenaline.

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REFERENCES