DIFFERENCES IN THE CARDIAC AND PRESSOR RESPONSES TO PROPRANOLOL OF RATS AND GUINEA PIGS

Junnosuke YAMAMOTO and Atsushi SEKIYA
Department of Pharmacology, Fujita-Gakuen University, School of Medicine, Toyoake, Aichi, Japan

Accepted September 5, 1973

Abstract—Propranolol produces a sustained rise in blood pressure in the rat, but little change in the guinea pig. In order to elucidate this distinct difference, the following experiments were carried out: (a) The pressor effect of propranolol was studied while the vascular tone was changed by infusion of several vasoactive substances in the guinea pig; (b) The effect of propranolol on the isolated atria of rats and guinea pigs was also compared. Propranolol always produced a pressor action during the infusion of adrenergic β-stimulating agents, but not during vasopressin infusion. In spontaneously beating or electrically driven guinea pig atria, propranolol reduced the contractile force to a greater extent than in rat atria. It is concluded that the difference in action of propranolol on the blood pressure of rat and guinea pig may be explained by the following two reasons: (a) the β-adrenoceptive vasodilator tone in skeletal muscle is stronger in the rat than in the guinea pig; (b) the heart of the rat is less sensitive to propranolol than that of the guinea pig.

Many investigators (1-5) reported that propranolol produced a fall in blood pressure in various species of experimental animals. Hypotensive effects of propranolol have been also reported in patients after prolonged oral administration (6-8). Meanwhile we reported in previous papers (9, 10) that propranolol produced a sustained pressor action in the rat. This action may be due to the blockade of the β-adrenoceptive response of peripheral vascular smooth muscle which dominates the maintenance of normotension in the rat.

Such diverse pressor action of propranolol in the rat may be explained as follows: (a) The β-adrenoceptive vasodilator activity maintains the tone in blood vessels of skeletal muscle mediated through the central nervous system more effectively in the rat than in the other species of animals, or (b) the heart of the rat is less sensitive to propranolol than that of other species.

In this experiment, guinea pigs were compared with rats as to the pressor effects of propranolol when the vascular tone was changed by the infusions of various vasoactive substances. The effects of propranolol in the isolated atria of rats and guinea pigs were also compared.

MATERIALS AND METHODS

1. Experiments in guinea pigs

Guinea pigs of both sexes, weighing between 350 and 450 g were anesthetized with urethane (1.5 g/kg s.c.). Arterial blood pressure was measured at the right carotid artery.
with an electronic manometer (Nihon Koden MP-4T). Heart rate and arterial pressure were recorded simultaneously on an ink-writing recorder.

Infusions of vasoactive drugs, dissolved in 0.9% sodium chloride solution, were given at a rate of 0.11 ml/min into the left jugular vein using a motor-driven syringe (Natume). Injections of drugs, diluted or dissolved in 0.9% saline, were made 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: dl-propranolol hydrochloride (Inderal, I.C.I.), l-adrenaline bitartrate (Boasmin, Daiichi), l-noradrenaline bitartrate (Nor-Adrenalin, Sankyo), l-phenylephrine hydrochloride (Neo-Synesin, Kowa), vasopressin (Pitressin, Park-Davis) and dl-isoprenaline sulfate (C.H. Boehringer Sohn).

2. Experiments in isolated atria

Guinea pigs, weighing 350 to 500 g, and rats, weighing 200 to 350 g, were sacrificed by a sharp blow on the head. Hearts were quickly removed and placed in an oxygenated Ringer-Locke solution. The atria were freed from the ventricles by a pair of fine scissors, and then suspended in a water-jacketed bath. The bath contained 50 ml of modified Ringer-Locke solution which was maintained at 32 ± 0.5°C and bubbled with a mixture of 95% oxygen and 5% carbon dioxide. The Ringer-Locke solution had the following composition (grams per liter): NaCl, 7.3; KCl, 0.42; CaCl₂, 0.24; NaHCO₃, 0.21; glucose, 0.2.

The contractile forces were measured by using a semiconductor strain gauge (Shinkoh EN 604) transducer. The amplified input from the transducer was also used to drive a tachograph (Nihon Koden RT-2). This arrangement allowed continuous monitoring of contractile force and rate which were recorded simultaneously on an ink-writing recorder (Nihon Koden WI-130). A resting tension of about 0.5 g was applied.

Isolated left atria driven electrically were also prepared for these experiments. One end of the isolated left atrium was attached to a pair of platinum electrodes. The atria were driven at a rate of 130/min by square-wave pulses of 2 milliseconds duration delivered by a stimulator (Nihon Koden MSE-3). The force of contraction was measured and recorded as previously described. The preparations were allowed to equilibrate in Ringer's solution for almost 60 min before exposing them to propranolol. Propranolol concentrations were expressed in terms of g/ml, referring to the final bath concentrations.

RESULTS

1. Experiments in anesthetized guinea pigs

1. Effect of propranolol on blood pressure and heart rate

Observations were made in 27 guinea pigs. In most cases, propranolol (0.1 mg/kg) produced little change in the blood pressure and a marked decrease in heart rate (Fig. 1, A). But in 4 guinea pigs the drug produced a slightly sustained pressor action. The higher doses of propranolol (more than 1.0 mg/kg) caused a transient and slight fall in blood pressure (Fig. 1, B).
2. Effect of propranolol during adrenaline infusion

Observations were made on 14 guinea pigs. Adrenaline (2 and 5 μg/kg/min), i.v. produced a rise in blood pressure and an increase in heart rate. When the blood pressure was stabilized, about 15 min after the onset of infusion, propranolol (0.001 to 1.0 mg/kg) i.v. was injected. This agent produced a sustained rise in blood pressure and a decrease in heart rate in all guinea pigs (Fig. 2). Propranolol induced a higher rise in blood pressure in guinea pigs infused with adrenaline at a rate of 5 μg/kg/min than at a rate of 2 μg/kg/min (Table 1).

3. Effect of propranolol during noradrenaline infusion

Observations were made on 8 guinea pigs. Noradrenaline infusion (5 and 10 μg/kg/min) produced a marked rise in blood pressure and a slight increase in heart rate. When the blood pressure was stabilized, about 15 min after the onset of infusion, pro-
pranolol (0.1 to 1.0 mg/kg) was injected i.v. The agent always produced a sustained rise in blood pressure (Table 1) and a decrease in heart rate.

4. Effect of propranolol during isoprenaline infusion

In 14 guinea pigs, isoprenaline was infused i.v. at a rate of 0.5 and 1.0 μg/kg/min. It produced little change or a slight fall in blood pressure and a marked increase in heart rate. Propranolol (0.1 to 0.5 mg/kg) was injected i.v. and always produced a slightly sustained rise in blood pressure (Table 1) plus a marked decrease in heart rate.

5. Effect of propranolol during phenylephrine infusion

Observations were made in 8 guinea pigs. Continuous infusion of phenylephrine (15 to 20 μg/kg/min) produced a marked rise in blood pressure and little change in heart rate except an initial transient decrease. When the blood pressure became stable, about 15 min after the onset of infusion, propranolol (0.1 mg/kg) was injected i.v. The drug always produced a slightly sustained rise in blood pressure (Table 1) and a decrease in heart rate.

6. Effect of propranolol during vasopressin infusion

Observations were made in 5 guinea pigs. Vasopressin (0.02 i.u./kg/min) i.v. produced a marked rise in blood pressure and a slight decrease in heart rate. Propranolol (0.1 to 1.0 mg/kg) produced little change in blood pressure (Table 1) and a slight decrease in heart rate.

| Drugs infused               | Number of guinea pigs | Increase in blood pressure (mean ± S.E. mmHg) |
|-----------------------------|-----------------------|-----------------------------------------------|
| None (control)              | 16                    | 0.9±1.4                                       |
| Isoprenaline (0.5 μg/kg/min)| 7                     | 13.7±1.5                                      |
| Adrenaline (2 μg/kg/min)    | 6                     | 17.5±2.4                                      |
| Adrenaline (5 μg/kg/min)    | 7                     | 28.9±3.5                                      |
| Noradrenaline (10 μg/kg/min)| 5                     | 20.4±1.9                                      |
| Phenylephrine (20 μg/kg/min)| 5                     | 9.4±0.8                                       |
| Vasopressin (0.02 i.u./kg/min)| 5                  | 0.4±2.8                                       |

II. Experiments in isolated atria

1. Effect of propranolol on the spontaneously beating atria

The effects of propranolol on rate and force of contraction in rat and guinea pig atria were depicted graphically in Fig. 3 and 4. The results are expressed as the change in percentage from initial value (mean ± S.E.). In 5 control experiments performed under identical conditions but without addition of propranolol, there was little change from initial control levels in inotropic or chronotropic activity of the atrial preparations. Propranolol showed a similar negative chronotropic effect on the rat atria as on the guinea pig atria (Fig. 3). In the presence of 10^-7 g/ml of propranolol, the forces of contraction of rats
and guinea pigs atria showed no significant change. However, the larger doses (more than $3 \times 10^{-7}$ g/ml) of propranolol decreased myocardial contractile forces of both preparations. In rat atria the decrease in contractile force produced by propranolol (more than $3 \times 10^{-7}$ g/ml) was significantly less marked than in guinea pig atria (Fig. 4).

2. **Effect of propranolol on the electrically driven atrium**

The effects of propranolol on contractile force of electrically driven rat and guinea pig atrium are depicted in Fig. 5. Propranolol produced a negative inotropic action in rat and guinea pig preparations. The negative inotropic action of propranolol (more than $3 \times 10^{-7}$ g/ml) on rat atrium was significantly less marked than on guinea pig atrium.
DISCUSSION

It was found in our previous experiment (9) that propranolol produced pressor action in the rat. In this study propranolol produced little change in blood pressure in most guinea pigs and with higher doses (more than 1.0 mg/kg) produced a slight initial fall in blood pressure. However, even in the guinea pig, propranolol produced a pressor action during infusions of isoprenaline, adrenaline and noradrenaline, but not during vasopressin infusion. These observations suggest that the β-adrenoceptive vasodilator tone is lower in the guinea pig than in the rat. This condition induced by the infusion of β-stimulating agents in the guinea pig may be similar to that of the rat with a strong β-receptor tone in the peripheral vascular beds.

A sustained rise in blood pressure was obtained with propranolol given during phenylephrine infusion in the guinea pig. Phenylephrine has been considered to directly affect adrenergic α-receptors only. Recently, however, phenylephrine has been shown to stimulate β-receptors in heart (11-13) and tracheal smooth muscle (14). In a previous paper, (10) we also reported that phenylephrine stimulated β-receptors in skeletal muscle vascular beds and heart of the rat. On the basis of these facts, the evidence that propranolol produces a pressor action in the guinea pig during phenylephrine infusion indicates that phenylephrine probably stimulates not only α-receptors, but also β-receptors in peripheral vessels.

In isolated rat atria, propranolol reduced the heart rate to the same extent as observed in guinea pig atria, however, this agent reduced atrial contractile force to a greater extent in isolated guinea pig atria than it did in rat atria. These findings suggest that propranolol reduces cardiac output to a greater extent in the guinea pig than in the rat, and that the cardiac depression caused by propranolol may overcome the peripheral vasoconstriction by the drug in the guinea pig. Frohlich et al. (8) reported that the depressor action caused by oral administration of propranolol to humans probably was due to the decrease in cardiac output. The cardiac depression observed in this experiment is presumably due to the nonspecific action of propranolol, such as local anesthetic action, but not to the β-blocking action of this agent.

The finding that the sustained pressor action of propranolol was observed only in the rat, can be explained by the following two reasons: (a) in the rat, the β-receptor tone in the vascular bed of skeletal muscle, maintained by the direct sympathetic discharges from the central nervous system, is stronger than that in the guinea pig; (b) the cardiac depression caused by propranolol is weaker than that of guinea pig.

REFERENCES

1) SHANKS, R.G.: Br. J. Pharmacol. Chemother. 26, 322 (1966)
2) OLIVARES, G.J., SMITH, N.T. AND ARONOW, L.: Br. J. Pharmacol. Chemother. 30, 240 (1967)
3) FLACKE, J.W., OSGOOD, P.F. AND BENDIXEN, H.H.: J. Pharmacol. exp. Ther. 158, 519 (1967)
4) SINGH, K.P. AND MAHAWAR, M.M.: Arch. int. Pharmacodyn. Ther. 171, 58 (1968)
5) MAZURKIEWICZ, I.M.: Arch. int. Pharmacodyn. Thér. 171, 136 (1968)
6) PRICHARD, B.N.C. AND GILLAM, P.M.S.: Br. med. J. 2, 725 (1964)
7) PRICHARD, B.N.C. AND GILLAM, P.M.S.: Am. J. Cardiol. 18, 387 (1966)  
8) FROHLICH, E.D., TARAZI, R.C., DUSTAN, H.P. AND PAGE, I.H.: Circulation 37, 417 (1968)  
9) YAMAMOTO, J. AND SEKIYA, A.: Arch. int. Pharmacodyn. Thér. 179, 372 (1969)  
10) YAMAMOTO, J. AND SEKIYA, A.: Arch. int. Pharmacodyn. Thér. 198, 347 (1972)  
11) GOVIER, W.C.: J. Pharmacol. exp. Ther. 159, 82 (1968)  
12) KRELL, R.D. AND PAIL, P.N.: J. Pharmacol. exp. Ther. 170, 262 (1969)  
13) YOO, C.S. AND LEE, W.C.: J. Pharmacol. exp. Ther. 172, 274 (1970)  
14) CHAHLE, L.A. AND O’DONNEL, S.R.: Br. J. Pharmacol. Chemother. 37, 41 (1969)