EFFECT OF PROPRANOLOL ON SOME MECHANISMS REGULATING CARDIAC OUTPUT

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In acute experiments on anesthetized cats propranolol reduced the venous return to the heart while increasing the capacity of the systemic venous circulation. Myocardial β-adrenoreceptor blockade is not the only cause of this effect.

KEY WORDS: cardiac output; venous return; propranolol.

One of the principal mechanisms of the hypotensive action of propranolol is a decrease in cardiac output [4, 5, 8]. Most workers agree that this effect is due to negative chrono- and inotropic influence of the drug through myocardial β-adrenoreceptor blockade [7, 10]. Meanwhile, the action of propranolol on the capacity of the systemic circulation has virtually never been studied despite the fact that changes in it play a leading role in heterometric regulation of cardiac output [1-3].

The object of this investigation was to study this problem.

EXPERIMENTAL METHOD

Experiments were carried out on 25 anesthetized (chloralose 50 mg/kg and urethane 500 mg/kg) cats which were curarized and artificially ventilated.

In the experiments of series I changes in the blood flow in the ascending part of the arch of the aorta (the cardiac output – CO), measured by means of an electromagnetic flowmeter, the arterial pressure (AP) and, in some experiments, the pressure in the right atrium (the central venous pressure – CVP) were recorded during electrical stimulation of the hypothalamus in the region of the ventromedial nucleus (100 Hz, 3 msec, 8-10 V, 10 sec).

In the experiments of series II the same parameters were recorded under conditions of partial stabilization of the venous return to the heart along the system of the superior or inferior vena cava by means of a constant delivery pump. At the same time the volume of blood flowing into the extracorporeal reservoir was measured [11].

Propranolol was injected intravenously in doses of 0.2-1 mg/kg. The effect of the drug on the capacity of the systemic circulation was judged from the difference in the time of onset of changes in the venous return to the reservoir and in the aortic blood flow.

EXPERIMENTAL RESULTS

In these experiments the original values were: AP = 107 ± 4 mm Hg, CO = 270 ± 30 ml/min, the cardiac frequency (CF) = 164 ± 7 beats/min, and CVP = 1.5 ± 1 mm Hg. Electrical stimulation of the ventromedial hypothalamic nucleus caused AP to rise on average by 55 ± 8%. The pressor response was accompanied by varied changes in CO at a time of maximal elevation of AP. In 11 experiments the maximal rise in AP corresponded to a fall in CO by 35 ± 9%, in eight experiments a rise of 31.6%, whereas in six cases CO remained unchanged.

Intravenous injection of propranolol in a dose of 0.2 mg/kg led to a decrease in the original CF by 30 ± 3% and in CO by 16 ± 3%. The original AP was reduced by 21 ± 4%. After administration of propranolol in a dose of 1 mg/kg the degree of reduction of CF and CO was increased to 40 ± 3 and 20 ± 5%, respectively, and of AP to 25 ± 4%. In four experiments in which AP fell by more than 25% a significant decrease in the total

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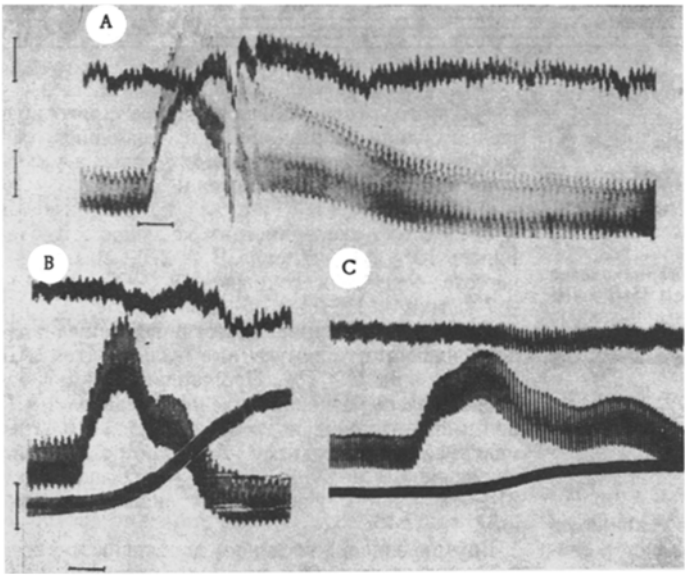

Fig. 1. Effect of propranolol, in a dose of 1 mg/kg, on changes in CO, AP, and venous return along superior vena cava to reservoir caused by electrical stimulation of hypothalamus. In A from top to bottom: CO (calibration 100 ml/min), AP (calibration 15 mm Hg); marker of stimulation, 10 sec. In B and C from top to bottom: CO, AP, volume of blood in reservoir (calibration 5 ml); marker of stimulation 10 sec. A) Initial responses; B) with partial stabilization of venous return to the heart before injection of propranolol; C) responses after injection of propranolol, 1 mg/kg.

peripheral vascular resistance of 21 ± 4% was observed. The hypotensive effect of propranolol was thus due not only to a fall in CO, but also to a reduction of the peripheral vascular resistance which, according to some investigations [6, 9], is associated with the central action of propranolol. Changes in CVP under the influence of propranolol were not significant. In some experiments only a slight tendency for CVP to rise was observed.

After administration of propranolol in doses of under 1 mg/kg the amplitude of the pressor response to electrical stimulation of the hypothalamus fell a little. In eight experiments in which CO increased initially, this increase was reduced by 71 ± 10%. However, in cases when hypothalamic stimulation led to a decrease in CO, propranolol could reverse these changes and produce an increase in CO. This reversal of the responses was most characteristic in experiments in which a considerable decrease in the original value of AP (by more than 25%) took place after administration of propranolol.

In the experiments of series II the character of responses of the venous return to the heart (the volume draining into the reservoir) to electrical stimulation of the hypothalamus, causing an increase, decrease, or no change in CO, and the effect of propranolol on changes in the capacity of the systemic circulation were studied.

When the venous return to the heart was partially stabilized hypothalamic stimulation evoked pressor responses which, compared with responses observed with a natural venous return, were lower in amplitude (Fig. 1A, B). Meanwhile, the increase in CO was reduced in experiments in which it was initially increased, and the degree of lowering of CO was increased when it was lower initially. Hypothalamic stimulation causing an increase, decrease, or no change in CO at a time of maximal rise of AP also led in all cases to an increase in the blood flow along the venae cavae (as shown by the return flow into the reservoir) on average by 11 ± 4 ml. The latent period of this response was 9 ± 3 sec. The beginning of the increase in the venous return in most cases preceded the maximal rise of AP or coincided with it (Fig. 1B).

Intravenous injection of propranolol in doses of 0.2 and 1 mg/kg under conditions of partial stabilization of the venous return to the heart was accompanied by changes in CF, AP, CO, and CVP similar to those ob-

served in the experiments of series I. At the same time there was a marked decrease in the velocity of the blood flow along the venae cavae. The venous blood flow was reduced after injection of propranolol in doses of 0.2 and 1 mg/kg by 11 ± 1.1 and 17 ± 1.7%, respectively. The velocity of the venous blood flow was reduced in all cases before the fall in CO (more than 10 sec earlier; $P < 0.001$). Under these conditions electrical stimulation of the hypothalamus caused a much smaller increase in the venous blood flow (Fig. 1B, C). The amplitude of the increase in the venous return was reduced by 68 ± 8 and 85 ± 13% depending on the dose of the drug. The changes in CO caused by hypothalamic stimulation were reduced or disappeared completely (Fig. 1C).

The experiments thus showed that propranolol causes an increase in the capacity of the systemic circulation and a decrease in the venous return to the heart, before any change in CO. This suggests that one of the factors responsible for the decrease in CO after administration of propranolol is a reduction in the blood flow to the right ventricle. Propranolol also has an inhibitory effect on changes in the venous blood flow in response to hypothalamic stimulation.

LITERATURE CITED

1. N. M. Amosov, V. A. Lishchuk, S. A. Patskina, et al., Self-Regulation of the Heart [in Russian], Kiev (1969).
2. A. Guyton, Physiology of the Circulation. Minute Volume of the Heart and Its Regulation [in Russian], Moscow (1969).
3. L. I. Osadchii, The Work of the Heart and Vascular Tone [in Russian], Leningrad (1975).
4. F. E. Ostapyuk and M. B. Beganova, Klin. Med., No. 6, 57 (1974).
5. Z. M. Booker, A. Hyde, A. Fletcher, et al., Circ. Res., 41, 179 (1977).
6. M. D. Day and A. G. Roach, in: Central Action of Drugs in Blood Pressure Regulation (Proceedings of an International Symposium), Tunbridge Wells, England (1975), pp. 215-224.
7. M. Esler, A. Zweifler, O. Randall, et al., Clin. Pharmacol. Ther., 22, 299 (1977).
8. L. Hanson, Acta Med. Scand., Suppl. 606, 49 (1977).
9. P. J. Lewis, in: Central Action of Drugs in Blood Pressure Regulation (Proceedings of an International Symposium), Tunbridge Wells, England (1975), pp. 206-214.
10. P. Lund-Johansen, Acta Med. Scand., 201, Suppl. 603, 1 (1977).
11. W. J. Rashkind, D. H. Lewis, J. B. Henderson, et al., Am. J. Physiol., 175, 415 (1953).