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Reduction in sympathetic nervous activity as a mechanism for hypotensive effect of propranolol

THE β-adrenoceptor antagonist propranolol is an effective antihypertensive drug in man[1] but it is not known how the fall in blood pressure is produced[2]. There is a decrease in plasma renin activity[3] and in cardiac output immediately on starting propranolol therapy but neither of these effects can explain fully the hypotensive action of the drug which is delayed in onset and associated with a reduction in peripheral vascular resistance[4]. It has been suggested that the fall in blood pressure after propranolol results from blockade of β-like adrenoceptors within the central nervous system[5]. Thus, intracerebroventricular injection of propranolol lowers blood pressure in conscious cats[5] and rabbits[6], an effect which is specific for the β-blocking (—) isomer of the drug[7]. The effective concentration of propranolol achieved in the hypothalamus by this route of administration is within the range predicted for hypertensive patients after chronic oral therapy[8]. We now present direct evidence that propranolol diminishes sympathetic nerve activity in the rabbit and that this central effect contributes to the hypotensive action of the drug.

Electrodes were implanted in the greater splanchnic nerve of rabbits weighing 3–4 kg (ref. 9). After a recovery period of at least 4 d a catheter was inserted under local anaesthesia into the central artery of an ear and used for measurement of blood pressure. Another catheter was inserted into the marginal vein of the other ear for administration of drugs. Each conscious unrestrained animal was placed in an individual cage and left undisturbed for 1 h. Integrated splanchnic nerve activity and arterial pressure were then recorded continuously for a 3-h period. The first hour served for control observations. After these, intravenous infusion of one of four solutions was begun and continued at a rate of 3 ml h^{-1} for the remaining 2 h. The solutions used were saline, (±)-propranolol, (+)-propranolol and sodium nitroprusside, sufficient of each drug being dissolved in saline to enable an infusion rate of 1 mg kg^{-1} h^{-1}. Each treatment was given to eight animals. Splanchnic nerve activity during each hour was summed by planimetry of the record, and the values during the infusion hours expressed as a percentage of that during the pretreatment hour. The systolic and diastolic arterial pressure traces were treated similarly except that the results were expressed in terms of mean arterial pressure, calculated as diastolic pressure plus one third of the pulse pressure.

Table 1 Effect of intravenous (+)- and (±)-propranolol, sodium nitroprusside and saline on mean arterial pressure (MAP) and splanchnic nerve activity (SNA) in conscious rabbits

Infusion	No. of animals	First hour MAP	First hour SNA	Second hour MAP	Second hour SNA
Saline	8	97±2	111±5	99±3	104±16
(+)-Propranolol	8	101±2	122±17	99±4	132±24
(±)-Propranolol	8	94±3	68±11*	87±2†	52±9*
Sodium nitroprusside	8	74±1†	178±30*	73±2†	199±38*

Values are the mean ±s.e.m. of the average during one hour expressed as a percentage of the average during the hour pretreatment. Significant differences from saline control group: $*P < 0.05$; $†P < 0.01$ (Student's unpaired t test).

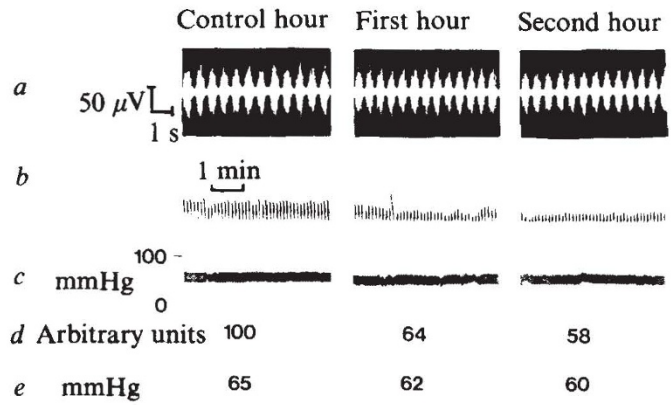

Fig. 1 Effect of (±)-propranolol infusion (1 mg kg^{-1} h^{-1} intravenously) on sympathetic nerve activity and arterial pressure in a conscious rabbit. *a*, Splanchnic nerve discharges as original oscilloscope records and as integrated activity over 6-s periods (*b*); *c*, arterial pressure (each record was taken at the end of the time period indicated); *d*, mean values of integrated splanchnic nerve activity per hour and of mean blood pressure measured over the complete hour by planimetry (*e*).

Table 1 shows the effect of the four treatments on splanchnic nerve activity and mean arterial pressure. Neither saline nor (+)-propranolol, the non-β-blocking isomer of propranolol, altered these parameters significantly. Sodium nitroprusside, a vasodilator drug which relaxes vascular smooth muscle[10], reduced arterial pressure. An increase in preganglionic sympathetic nerve activity accompanied the fall in blood pressure, indicating that the preparation is sensitive enough to detect reflex changes which are the expected response to a peripherally mediated hypotension.

By contrast, a different pattern of response was seen with (±)-propranolol which decreased both blood pressure and splanchnic nerve discharges. Figure 1 shows the original record of such an experiment, illustrating the parallel fall in preganglionic sympathetic nerve activity and blood pressure during (±)-propranolol infusion.

As sympathetic nerve activity was recorded from a preganglionic nerve, the site of the sympatho-inhibitory action of propranolol must be in the central nervous system. The only other possible explanation—that the drug increases the sensitivity of the arterial baroreceptors—seems very unlikely. Therefore, we suggest that blockade of central β-adrenoceptors brings about a reduction in sympathetic nervous tone and that this action could explain the antihypertensive effect of propranolol.

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