HYPOTENSIVE ACTIONS OF SEVERAL β-ADRENOCEPTOR BLOCKING AGENTS IN CONSCIOUS NORMOTENSIVE RATS

Kazunobu SUGAWARA, Naoko TAKAMI and Masayori OZAKI

2nd Department of Pharmacology, Nagasaki University School of Medicine, Nagasaki 852, Japan

Accepted September 6, 1978

Since Prichard (1), and Prichard and Gillam (2) reported that pronethalol and propranolol, the β-adrenoceptor blocking agents, possessed antihypertensive action, several other β-adrenoceptor blocking agents have been introduced as antihypertensive drugs. However, the mechanism for the antihypertensive action of these agents is not well understood (3, 4, 5). Indeed it is difficult to demonstrate the antihypertensive effect of β-adrenoceptor blocking agents in some experimental hypertension models such as the spontaneously hypertensive rat, although such models are effective when attempting to manage hypertension in humans (6). In animals, also, effects of these agents on blood pressure differ depending on the dose, route of administration, and whether or not anesthesia is used.

We investigated the effects of β-adrenoceptor blocking agents on blood pressure in conscious normotensive rats and in anesthetized rats by changing the routes of administration (s.c., p.o., i.v. and i.p.) or doses. In the anesthetized rats, i.v. and i.p. administrations of these agents all produced pressor effects. With s.c., p.o. and i.v. administrations to conscious rats, not all β-adrenoceptor blocking agents produced hypotensive effects. Some drugs showed a hypertensive rather than a hypotensive action. On the other hand, the acute hypotensive effect was seen when optimal doses of these agents were given i.p.. In the present study, therefore, we investigated the effects of i.p. administrations of nine β-adrenoceptor blocking agents on blood pressure and heart rate in conscious normotensive rats and compared the hypotensive activities among these agents.

Male Kyoto Wistar strain rats (WKY) weighing 300-350 g were used. In a conscious but slightly restrained state, the systolic blood pressure (SBP) was measured using an electrosphygmomanometer (Narco Biosystem Co.) at 30 minutes, 1, 2, 3, 4, 5, 6 and 24 hours after
a single i.p. administration of a given dose of one of β-adrenoceptor blocking agents. Rats were warmed for 10-15 minutes at 35.2°C before attempting a measurement. Four pressure measurements were recorded for each rat, and the mean was taken as the SBP. The heart rate (HR) was measured by counting the excursions of the SBP tracings.

The β-adrenoceptor blocking agents used were as follows: pindolol (Sandoz), propranolol hydrochloride (I.C.I.), alprenolol hydrochloride (Teikoku Zoki), carteolol hydrochloride (Otsuka), bufetolol hydrochloride (Yoshitomi), timolol maleate (Merck), practolol (Sumitomo), acebutolol hydrochloride (Kanebo) and atenolol hydrochloride (I.C.I.). Agents except pindolol and practolol were dissolved in 0.9% saline. Doses of these agents refer to the salt. Pindolol was dissolved in 0.4% tartaric acid in a concentration of 10 mg/ml and then diluted with saline to the desired concentrations. Practolol was dissolved in an equivalent of dilute hydrochloric acid. Doses of pindolol and practolol refer to the base. Values are expressed by means ± S.E.. Statistical significance of differences between mean values was analyzed using Student's t-test.

The basal SBP of the rats was 125 ± 1 mmHg (110-135 mmHg) and HR was 335 ± 3 beats/min (300-380 beats/min). Though all of the β-adrenoceptor blocking agents examined produced a hypotensive effect in WKY, the effective doses, hypotensive activities and durations varied with each agent. Among these compounds, the most effective was pindolol which produced a marked hypotensive effect in a dose of 0.1 mg/kg (31 ± 9 mmHg) (Fig. 1).

![Fig. 1. Effects of pindolol and propranolol on systolic blood pressure (SBP) and heart rate (HR) in WKY.](image_url) Number of rats used is indicated in parentheses. Vertical bars represent standard error of the mean. Significant difference from control (saline i.p.): *P < 0.05, **P < 0.01, ***P < 0.001.
FIG. 2. Effects of \( \beta \)-adrenoceptor blocking agents on systolic blood pressure (SBP) and heart rate (HR) in WKY.

With a low dose of 0.01 mg/kg, however, pindolol increased rather than reduced the SBP (13±3 mmHg). Propranolol, 1 and 5 mg/kg, also reduced the SBP by 17±4 mmHg and 26±2 mmHg, respectively (Fig. 1). With alprenolol, carteolol, bufetolol, timolol, practolol, acebutolol and atenolol the fall of SBP was also observed, but the hypotensive actions of these drugs were less potent than that of pindolol and propranolol and were not dose-dependent (Fig. 2).

Since doses of \( \beta \)-adrenoceptor blocking agents used for the block of cardiac \( \beta \)-receptor are lower than those which produced a fall in SBP, it is difficult to say that the hypotensive actions of \( \beta \)-adrenoceptor blocking agents were due to the \( \beta \)-blocking activity. Roba et al. (7) reported that the order of the hypotensive potencies of \( \beta \)-adrenoceptor blocking agents has no correlation with their \( \beta \)-adrenoceptor blocking potencies.

The HR was increased with all doses of pindolol, carteolol and practolol and the high dose of alprenolol which possesses an intrinsic sympathomimetic action, and was decreased by bufetolol, timolol, acebutolol, and atenolol (Figs. 1, 2). On the other hand, the HR was not affected by propranolol with the most effective dose and was decreased with a dose which had no effect on the SBP. The decrease in HR produced by the low dose of propranolol may be due to blockade of the sympathetic tone to the heart. The apparent absence of the effect of propranolol at the hypotensive dose on the HR may be due to the increased sympathetic tone initiated by hypotension which might overcome the \( \beta \)-adrenoceptor blocking action of propranolol.

The present findings suggest that the effects of intraperitoneal administration of \( \beta \)-adrenoceptor blocking agents in WKY are similar to those obtained when these agents are used clinically. The mechanism of antihypertensive activity of \( \beta \)-adrenoceptor blocking agents is being studied in our laboratory, using these methods.

REFERENCES

SHORT COMMUNICATIONS  Japan. J. Pharmacol. 29, 138 (1979)


EFFECT OF ALDOSTERONE ON RENAL Na,K-ACTIVATED ADENOSINE-TRIPHOSPHATASE ACTIVITY IN NON-ADRENALECTOMIZED RATS

Fumitake IKEDA, Yasuo IKEDA, Chiyoko INAGAKI
and Shuji TAKAORI

Department of Pharmacology, Faculty of Medicine, Kyoto University,
Sakyo-ku, Kyoto 606, Japan

Accepted September 11, 1978

It has been reported that the activity of Na, K-activated adenosinetriphosphatase (Na,K-ATPase) in the kidney is reduced by adrenalectomy and that the activity is restored by administration of aldosterone (1, 2). However, with the adrenalectomized rats, the restoration of the enzyme by aldosterone has been shown to take much longer time (i.e. 6-24 hr) as compared with the time (1-2 hr) for the maximal effect of aldosterone on the sodium reabsorption (3). We attempted to determine whether or not aldosterone stimulates Na,K-ATPase in correlation with the enhancement of Na reabsorption in non-adrenalectomized rats.

Male Wistar rats weighing 170-250 g were used. Each animal was given water (3 ml p.o.) and pitressin tannate in oil (0.5 U i.m.), and then anesthetized 1 hr later with pentobarbital sodium (30 mg/kg i.p.). Administration of 5% mannitol through the femoral vein was started at a rate of 0.1 ml/min and continued during the experiment. After a 30 min equilibration period, one 30-min urine collection was made and then aldosterone (10 µg per animal) was given i.v. to animals of the experimental group. The control animals were infused with 5% mannitol through the experiment. The bladder was catheterized and sodium and potassium in the urine were determined by flame photometry (Hitachi 205), and the chloride content by a chloridemeter (Hiranuma, Chloride Counter CL-3). To determine the activities of Mg- and Na,K-ATPase, animals were sacrificed and the kidney