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REDUCED ADRENAL AMINE SYNTHESIS IN SPONTANEOUSLY HYPERTENSIVE RATS AFTER LONG-TERM TREATMENT WITH PROPRANOLOL

B. ÅBLAD, O. ALMGREN, A. CARLSSON, M. HENNING, J. JONASSON & B. LJUNG

Research Laboratories, AB Hässle, Mölndal & Department of Pharmacology, University of Göteborg, Göteborg, Sweden

Male spontaneously hypertensive rats were either fed a diet containing 3 mg/g of (±)-propranolol, giving a mean daily intake of 178 ± 4.2 mg/kg, or a control diet from 7 weeks of age for 6 months. Three days after cessation of propranolol-treatment, the arterial blood pressure of the treated group was about 10% lower than that of the control group. Adrenal dopamine content and tyrosine hydroxylase activity were reduced to 76% and 71% of the control values, respectively. The results indicate that propranolol causes a reduced sympathetic discharge through its central action, although blockade of β-adrenoceptor-mediated local regulatory mechanisms cannot be excluded.

Introduction The mechanism of the antihypertensive action of β-adrenoceptor-blocking drugs is still a matter of debate. Several investigations point to an involvement of the central nervous system. A hypotensive response has been recorded after intracerebroventricular administration of propranolol to conscious cats (Day & Roach, 1974) or conscious rabbits (Reid, Lewis, Myers & Dollery, 1974; Myers, Lewis, Reid & Dollery, 1975). Reduced splanchnic discharge after intravenous administration of propranolol to conscious rabbits has also been reported (Lewis & Häeusler, 1975).

The present study was undertaken to investigate certain peripheral effects pointing to decreased sympathetic activity following long-term treatment of spontaneously hypertensive rats of the Okamoto strain (SHR) with propranolol.

Methods Male SHR were treated from 7 weeks of age, for a period of 6 months, with (±)-propranolol administered in pelleted food, an ordinary rat diet with an admixture of (±)-propranolol 3 mg/gram. The daily intake of the drug averaged 178 ± 4.2 mg/kg with a somewhat lower value towards the end of the study. Control SHR of the same age received a similar diet without propranolol, and were otherwise treated identically.

At the end of the six months' treatment period the propranolol diet was replaced with the control diet. Under pentobarbitone (75 mg/kg i.v.) anaesthesia, a polyethylene catheter was inserted into one carotid artery and passed out through the skin of the neck for blood pressure recording in the unrestrained animal in the morning of the third day after cessation of the drug; the animals were killed and the adrenals immediately taken out, weighed and frozen on dry ice for later analysis. The adrenals of one side (alternating) were used for analysis of noradrenaline, adrenaline and dopamine (Bertler, Carlsson & Rosengren, 1958; Atack & Magnusson, 1970; Atack, 1973) and the other for *in vitro* determination of tyrosine hydroxylase activity (TH), according to Nagatsu, Levitt & Udenfriend (1964).

Results The weight of rats in the treated group was slightly lower both at the start of the study (185 ± 5.8 g, $n=10$) and at the end (299 ± 7.7 g, $n=10$) compared with the control group (219 ± 3.7 g, $n=9$ and 344 ± 9.4 g, $n=9$, respectively). However, there was no difference in growth rate (i.e. percentage increase per week) between the two groups. Thus, propranolol did not seem to retard growth in the treated group.

The parameters studied are presented in Table 1. Blood pressure was approximately 10% lower in the treated group ($P<0.05$). This antihypertensive effect was paralleled by a reduction in adrenal dopamine (76% of control value, $P<0.01$). Neither the weight of the adrenals nor their content of noradrenaline or adrenaline was significantly affected. No apparent behavioural changes (i.e. in motility, irritability, aggressiveness) were observed in the treated group compared with controls.

Discussion The lower blood pressure of propranolol-treated SHR was accompanied by a reduction in adrenal dopamine content and TH activity, reflecting lowered catecholamine synthesis in adrenal medullary cells (see e.g. Mueller, Thoenen & Axelrod, 1969; Snider & Carlsson, 1972). A similar effect was recently described by Chubb & Raine (1976) in sympathetic ganglia of rabbits after 3–6 days treated with (±)-propranolol, 4 mg/kg subcutaneously twice daily. The most obvious explanation for lowered catecholamine synthetic activity of adrenal medullary or sympathetic ganglion cells would be reduced impulse frequency in the sympathetic system (see e.g.

Thoenen, Mueller & Axelrod, 1969; Carlsson & Lindqvist, 1974). Such an interpretation of the data is supported by the finding of Lewis & Häeusler (1975) of reduced splanchnic discharge in the conscious rabbit after intravenous propranolol administration.

It is unlikely that the results of the present study are due to the membrane-stabilizing action of propranolol, since preliminary data from this laboratory indicate that the β_1-selective antagonist metoprolol, which is devoid of membrane stabilizing properties, also reduces adrenal dopamine and TH activity in SHR after long-term oral treatment in doses which lower blood pressure. The involvement of β-adrenoceptor-mediated local regulatory mechanisms in sympathetic neurones and adrenal medullary cells cannot be excluded at present. A presynaptic β-adrenoceptor, mediating a weak positive feed-back regulation of noradrenaline release from sympathetic nerve terminals has been described (see e.g. Dahlöf, Åblad, Borg, Ek & Waldeck, 1975). Theoretically, blockade of this adrenoceptor should result in a reduced rate of amine synthesis. In addition, a weak β-adrenoceptor-mediated induction of TH in rat superior cervical ganglia has been postulated (Hanbauer & Costa, 1975). However, as these local regulatory mechanisms seem to be of a low potential it is questionable if they suffice to explain the present results. A centrally-mediated reduction of the sympathetic outflow seems at present to be a more probable explanation for the decreased catecholamine synthetic activity of the adrenal medulla after long-term propranolol treatment and the same mechanism may, at least in part, contribute to the antihypertensive action of β-adrenoceptor blocking drugs.

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Table 1 Mean arterial blood pressure, heart rate, adrenal weight and noradrenaline (NA), adrenaline (Ad), dopamine and tyrosine hydroxylase activity (TH) 3 days after cessation of chronic propranolol treatment (6 months) of spontaneously hypertensive rats

	Control (n=9)	*Propranolol (n=10)*	*Significance (Mann-Whitney)*
Mean arterial blood pressure (mmHg)	160±4.3	146±5.3	$P<0.05$
Heart rate (beats/min)	386±16	348±16	NS
Adrenal weight (mg/gland)	27±1.1 ($n=18$)	25±0.5 ($n=20$)	NS
Adrenal NA (μg/gland)	5.97±0.517	5.42±0.421	NS
Adrenal Ad (μg/gland)	13.58±1.139	13.35±0.793	NS
Adrenal dopamine (ng/gland)	464±36.3	352±16.8	$P<0.01$
Adrenal TH (nmol/gland)	19.54±1.926	13.81±1.007	$P<0.01$

The Mann-Whitney U-test was used for statistical comparisons.

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