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Cardiac catecholamine levels and blood pressure after chronic treatment with β-adrenergic blocking agents

The mechanism of the hypotensive effect observed clinically after chronic treatment with β-adrenergic blocking agents is not yet elucidated. Blockade of the sympathetic supply to the heart (Prichard & Gillam, 1966), direct or centrally mediated vasodilatation (Waal, 1966) and a reduction of cardiac output as a result of a decreased heart rate (Frölich, Tarazi & others, 1968) were suggested as possible explanations.

Some hypotensive agents such as reserpine and guanethidine are believed to elicit their effects partially by depleting noradrenaline in the peripheral adrenergic nerve endings. In this study experiments were performed to establish whether chronic treatment with β-adrenergic blocking agents would cause changes in endogenous catecholamine levels in the heart, brain and spleen of normotensive, non-anaesthetized rats, and whether there would be any correlation between these changes and the systolic blood pressure.

Wistar rats (150 g to 175 g) (6 rats for each drug) were injected intraperitoneally daily with 3 mg/kg of propranolol, 5 mg/kg of Kö 592 [1-(3-methylphenoxy)-2-hydroxy-3-isopropylaminopropan] or 10 mg/kg of INPEA [1-(*p*-nitrophenyl)-2-isopropylaminoethanol hydrochloride] for 4 weeks; the dose of each drug was doubled for the subsequent 5 weeks. Concurrently, controls (6 rats) were injected intraperitoneally with 0·5 ml of physiological saline.

Indirect systolic blood pressure was measured weekly (18–20 h after administration of β-adrenergic blocking agents) from the tail of the non-anaesthetized rat by the use of an occluding cuff and a pneumatic pulse transducer connected to an electrosphygmograph, and registered on a Grass polygraph by means of a transducer-monitor coupler (E and M Physiograph Instrumentation, Houston, Texas, U.S.A.). This method was reported to be in good agreement with the direct measurements of blood pressure (Maistrello & Matscher, 1969; Baum & Rowles, 1969).

It was established in preliminary experiments that a single dose of propranolol (6 mg/kg), Kö 592 (10 mg/kg) or INPEA (20 mg/kg) administered intraperitoneally produced on the average a 79, 64 or 74% blockade respectively of the positive chronotropic effects elicited by 1 μg/kg of isoprenaline when the latter was administered intraperitoneally 1 h after β-adrenergic blocking agents. After 18–20 h the blockade was 58, 61 or 63% respectively.

The animals were killed after 9 weeks; the heart, brain and spleen were dissected and placed in liquid nitrogen. Catecholamines were extracted from tissue with acidified n-butanol (Maickel, Cox & others, 1968) and determined by the method of Anton & Sayre (1962). Their amount is expressed in ng/g of tissue and corrected for standard recoveries which ranged from 84 to 92% (average 86%).

Table 1 demonstrates that catecholamine content of the heart was significantly reduced after treatment with propranolol, Kö 592 and INPEA by 51, 32 and 56% respectively. The reduction was significantly greater in INPEA- and propranolol-treated rats than in those treated with Kö 592. Brain catecholamine content was increased by 29% in Kö 592 treated rats, but reduced by 14% in the INPEA treated group. No significant changes were observed after propranolol treatment.

Table 1. *Endogenous catecholamine (CA) content of rat brain, heart and spleen after 9 weeks of treatment with β-adrenergic blocking agents**

Treatment	No. of experiments	Brain CA content ng/g	Brain Weight (g)	Heart CA content ng/g	Heart Weight (g)	Spleen CA content ng/g	Spleen Weight (g)
Control	5	363 ±23·4	1·885 ±0·04	720 ±99·7	1·215 ±0·08	365 ±36·3	1·635 ±0·13
Propranolol	5	370 ±27·5	1·905 ±0·08	350† ±26·6	1·147 ±0·03	367 ±35·2	0·744† ±0·11
Kö 592	6	468† ±17·3	1·959 ±0·03	492† ±38·9	1·122 ±0·03	431† ±18·2	0·858† ±0·01
INPEA	6	311† ±18·5	2·087 ±0·06	316† ±55·1	1·241 ±0·05	643† ±53·0	0·816† ±0·03

* Experimental rats were treated with 3 mg/kg of propranolol, or 5 mg/kg of Kö 592, or 10 mg/kg of INPEA for 4 weeks; the dose of each β-adrenergic blocking agent was doubled for the following 5 weeks. Mean ± s.e. are represented.
† = $P < 0.05$.

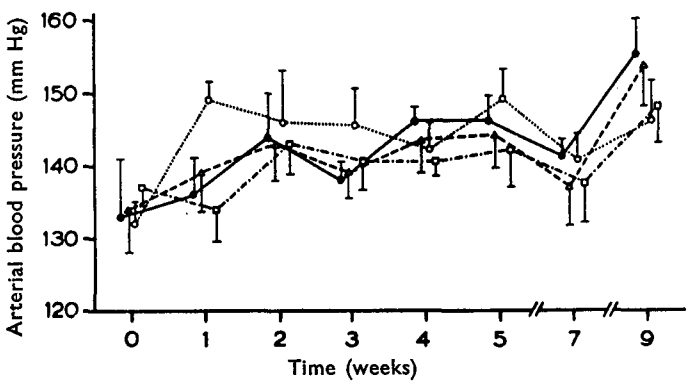

FIG. 1. Systolic blood pressure of non-anaesthetized control rats (○ — ○) and of non-anaesthetized rats treated chronically with 3 mg/kg of propranolol (△ — △), 5 mg/kg of Kö 592 (○ . . . ○) and 10 mg/kg of INPEA (□ — □); for 4 weeks; the dose of each drug was doubled for the subsequent 5 weeks. Records were taken first at weekly then at 2 weekly intervals. Mean ± s.e. of 3–6 rats is shown in each case.

Catecholamine content of the spleen was increased in INPEA and Kö 592 treated rats by 76 and by 18% respectively. No significant changes were observed after propranolol treatment. Surprisingly, the weights of spleens of all treated animals were significantly reduced compared with controls.

Results of blood pressure measurements are reported in Fig. 1.

At the start of experiment ("0" on the abscissa) the average systolic blood pressure of control and experimental groups did not differ significantly, the range being from 132 ± 3 to 137 ± 3 mm Hg. After 9 weeks of chronic treatment the systolic blood pressure was significantly higher than at the start of experiments in all groups of animals except in Kö 592 treated rats; however, there was no statistically significant difference between control and experimental groups or among the experimental groups themselves.

The significant decrease in the content of endogenous cardiac catecholamines observed presently after chronic treatment with propranolol, Kö 592 and INPEA is at variance with previous reports of Westfall (1967a, 1967b) who found no alteration

in the endogenous noradrenaline level in the heart after seven days of daily intraperitoneal administration (2 or 10 mg/kg) of propranolol, Kö 592 or MJ 1999, or 6 h after a single injection (10 or 50 mg/kg) of L(+)- or D(−)-INPEA to normotensive rats. The discrepancies between Westfall's and our results could have been due to differences in the duration of the treatment with β-adrenergic blocking agents. In line with our results a significant decrease in endogenous noradrenaline content was found in the rat heart after chronic treatment daily with pronethalol (10 mg/kg). Westfall's (1967a) findings that chronic treatment with propranolol did not induce changes in endogenous noradrenaline content of spleen are borne out by our own results.

In view of the conflicting reports about the influence of β-adrenergic blocking agents on noradrenaline uptake in *in vivo* and *in vitro* studies (Westfall, 1967b; Iversen, 1965; Foo, Jowett & Strafford, 1968; von Euler & Lishajko, 1968) no conclusion can be reached whether such an action is involved in the reduction we observed in the endogenous noradrenaline content in the heart.

The effect of β-adrenergic blocking agents on the endogenous catecholamine content of brain and spleen was not consistent in the present study, and it would be difficult to speculate on its significance.

No correlation was found between the changes in endogenous catecholamine level in the heart and blood pressure level of experimental animals. In spite of the significantly lower endogenous catecholamine level of the heart, the systolic blood pressure of rats treated chronically with β-adrenergic blocking agents did not significantly differ from control animals. This may indicate that the cardiac catecholamine level was still adequate to maintain the proper cardiovascular homeostasis.

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