Cardiovascular effects of chronic infusion of propranolol in the conscious spontaneously hypertensive rat

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The mechanism of antihypertensive action of the β-adrenoceptor blocking agent propranolol is still largely unknown. A major reason for this lack of understanding is the absence of a consistent effect of propranolol in animal models of human essential hypertension (Levy 1976). The spontaneously hypertensive (SH) rat is a commonly used model for studying pathogenic mechanisms and therapy of essential hypertension. A number of conflicting reports have appeared on the effects of propranolol in this species. Some authors reported that propranolol has no significant effects on blood pressure in SH rats or even causes a small rise (Forman & Mulrow 1974; Numao & Iriuchijima 1974; Levy 1976), whereas others found a hypotensive action (Vavra et al 1973; Garvey & Ram 1975; Sweet et al 1976). Close comparison of the results of these studies is hampered by differences in experimental conditions, such as the use of anaesthetics, the method of pressure measurement, the dosage used and the schedule of drug administration.

We recently described a technique for chronic controlled delivery of propranolol in the conscious unrestrained rat (Struyker-Boudier & Smits 1978). In the present experiments this technique was used in SH rats with a chronic intra-aortic catheter to allow long-term direct measurement of arterial blood pressure.

Male SH rats (Centraal Proefdierenbedrijf T.N.O., Zeist, the Netherlands), 3–4 months old, 250 (10) g (mean with s.d.) were used. Under ether anaesthesia a PE-10 catheter was inserted into the abdominal aorta just below the left renal artery according to the method described by Browning et al (1970). The distal end of this catheter had been previously heatmolded to a PE-50 catheter which was exteriorized at the back of the rats between the shoulder blades. This catheter system was filled daily with a fresh heparinized (250 U ml^{-1}) 0·9% NaCl (saline) solution. Mean arterial blood pressure (MAP) was measured daily for 1 h between 12·00 and 15·00 h in experimental cages in which the rats were allowed to move freely. Heart rate (HR) was determined from a biotachometer triggered with the blood pressure signal. MAP and HR on the first and second day after surgery were used as baseline values. If MAP was higher than 125 mm Hg and if MAP and HR values for the 2 consecutive days did not deviate by more than 10%, an ALZET osmotic minipump (batch AR-C507, ALZA Corporation, Palo Alto, Cal., U.S.A.) was implanted. An osmotic minipump consists of a 0·17 ml collapsible reservoir that releases its contents continuously at a rate of 0·63 ± 0·01 μl h^{-1} for the batch used in this study, by a driving force exerted by the swelling of the osmotic substance surrounding the reservoir (further details: Theeuwes & Yum 1976; Struyker-Boudier & Smits 1978). This release rate remains constant for at least 6 days and produces a steady-state distribution of propranolol in the SH rat within 1 day (Struyker-Boudier & Smits 1978). In this study control animals (N = 8) received minipumps filled with saline, whereas in 2 other groups (N = 8 each) minipumps were implanted containing (±)-propranolol hydrochloride in concentrations corresponding to a daily release of 1 or 5 mg kg^{-1}.

MAP and HRP were measured on 5 days following minipump implantation. Animals were then killed and blood was taken for the determination of plasma concentrations of propranolol by t.l.c. according to Garceau et al (1978). Results are given as mean values ± s.e., unless stated otherwise. Differences were compared by Student's *t*-test for unpaired values. Mean values for MAP on the day of implantation of the minipumps ranged from 128–166 mm Hg, whereas HR ranged from 366–455 b min^{-1}. There were no statistically significant differences in MAP or HR for each of the groups on this day. Chronic subcutaneous infusion of saline produced only minor changes in HR (Fig. 1 upper part). 1 mg kg^{-1} day^{-1} propranolol also caused

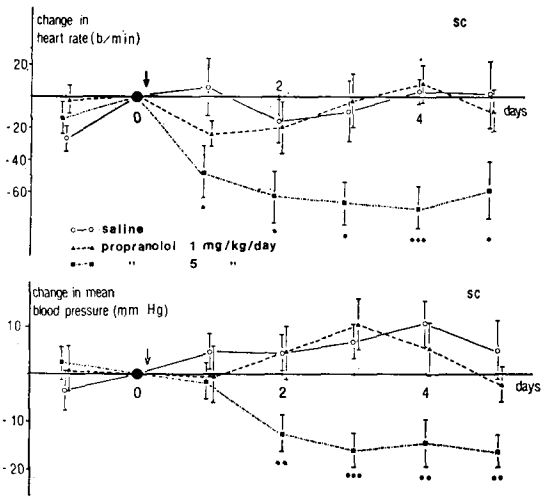

FIG. 1. Effects of chronic subcutaneous (sc) infusion of saline, 1 and 5 mg kg^{-1} day^{-1} propranolol on heart rate (upper part) and mean arterial blood pressure (lower part) in conscious unrestrained SH rats. $^{\cdot}P < 0·05$, $^{\cdot\cdot}P < 0·01$, $^{\cdot\cdot\cdot}P < 0·001$ compared with saline-treated animals.

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very little change in HR, except for the first day after the start of the infusion when a small and not significant bradycardia was observed. In contrast, after the start of a 5 mg kg^{-1} day^{-1} infusion a significant ($P < 0.05$) fall in HR (47 ± 15 b min^{-1}) was observed already on the first day. The degree of bradycardia even increased with a maximum fall of 68 ± 13 b min^{-1} on day 4. The effects of saline and propranolol infusion on MAP are given in Fig. 1 (lower part). Saline caused a slight increase in MAP with a maximum of 10 ± 4 mm Hg on the fourth day. 1 mg kg^{-1} day^{-1} propranolol infusions led to similar small changes in MAP. However, during infusion with 5 mg kg^{-1} day^{-1} a significant ($P < 0.01$) drop in blood pressure of 13 ± 3 mm Hg was observed on day 2. MAP remained significantly below control values throughout the rest of the experimental period.

Plasma concentrations of propranolol at the end of the 5-day infusion period were 99 ± 25 ng ml^{-1} in animals receiving 5 mg kg^{-1} day^{-1} and 22 ± 10 ng ml^{-1} for animals infused with 1 mg kg^{-1} day^{-1}. The latter value is similar to the plasma value of 39 ± 12 ng ml^{-1} reported earlier when [^{3}]propranolol was infused at 1 mg kg^{-1} day^{-1} (Struyker-Boudier & Smits 1978).

Our results indicate that continuous subcutaneous infusion of propranolol in the conscious unrestrained SH rat causes a drop in blood pressure and heart rate. This effect can be observed during a daily dose of 5 mg kg^{-1} day^{-1} producing a mean steady-state plasma propranolol concentration of about 100 ng ml^{-1}. Despite wide variations in plasma concentrations after oral propranolol in hypertensive patients, Esler et al (1977) have shown that plateau concentrations at a similar value (100 ng ml^{-1}) are associated with a similar hypotensive response. The dose used in this study may be supra-maximal and further investigation is required to establish the presence of a similar variability in response as seen in man.

In a previous study we showed that subcutaneous infusion of propranolol with osmotic minipumps leads to a steady-state distribution of this drug within 1 day (Struyker-Boudier & Smits 1978). This rapidity can be expected on the basis of the short plasma elimination half-life of approximately 1 h for propranolol in the SH rat (Forman & Mulrow 1974; Smits & Struyker-Boudier 1979). If the cardiovascular effects induced by propranolol follow its pharmacokinetic behaviour, a steady-state effect should also occur within 1 day. Our results show that this seems to be the case for propranolol-induced bradycardia, whereas the antihypertensive effect was observed after a delay of 1–2 days. A similar discrepancy has been reported in hypertensive patients, where long-term administration of propranolol also leads to an immediate bradycardia, whereas the blood pressure lowering effect can only be observed after a delay of several days (Tarazi & Dustan 1972; Hansson 1973). We recently proposed that this delay may be related to an early baroreceptor reflex-mediated increase of total peripheral resistance during the first hours to days after the administration of a cardiac output reducing agent such as propranolol (Struyker-Boudier et al 1979).

Whereas a few authors have been able to show a blood pressure lowering effect of propranolol in SH rats (Vavra et al 1973; Garvey & Ram 1975; Sweet et al 1976), others were not able to confirm this observation. However, the latter either used blood pressure recording techniques in which they were forced to restrain the animals (Forman & Mulrow 1974; Levy 1976) or only measured short-term cardiovascular changes (Numao & Iriuchijima 1974). Our data show that a blood pressure lowering effect similar to that in hypertensive patients may be obtained if propranolol is delivered chronically to the conscious unrestrained SH rat using osmotic minipumps.

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