Anti-hypertensive effect of metoprolol in spontaneously hypertensive rats

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Summary

1. Oral and intravenous administration of metoprolol to adult spontaneously hypertensive rats (SHR) with established hypertension lowered arterial blood pressure within 4 days of treatment.

2. Steady-state plasma concentrations of metoprolol were similar to those of patients during anti-hypertensive treatment with this drug.

3. The neuroeffector function of portal veins of SHR treated orally for 14 days or intravenously for 4 days was not impaired when studied in vitro. This is in contrast to previous findings after long-term treatment.

4. It is concluded that the anti-hypertensive effect of metoprolol in SHR in many respects resembles that observed in patients. It is suggested that impairment of vasomotor nerve control may contribute to the anti-hypertensive effect of β-adrenoceptor antagonists.

Key words: hypertension, metoprolol.

Introduction

Administration of β-adrenoreceptor antagonists causes lowered cardiac output and a reflex increase in arterial resistance. The anti-hypertensive effect in man during long-term treatment is associated with a gradual return of arterial resistance towards pretreatment values. The mechanism of this peripheral effect largely remains to be clarified (Conway, 1975).

It is a matter of debate whether the clinical anti-hypertensive action can be reproduced experimentally in hypertensive animals (Sweet, Scriabine, Wenger, Ludden & Stone, 1975; Conway, Darwin, Hilditch, Loveday & Reeves, 1975). Continuous administration of β-receptor antagonists to growing spontaneously hypertensive rats prevents development of hypertension (Weiss, Lundgren & Folkow, 1974). This was confirmed in our study (Ljung, Åblad, Dahlöf, Henning & Hultberg, 1975) where propranolol and metoprolol, a β₁-receptor selective antagonist (Åblad, Carlsson & Ek, 1973), were added to the drinking water. Furthermore, it was found that vasomotor nerve function was impaired in the isolated portal vein from SHR(1) exposed to the long-term treatment.

The following questions have been examined in the present experiments: (1) is it possible to lower blood pressure in adult SHR with 'established' hypertension by treatment with metoprolol in plasma concentrations comparable with those which prevail during anti-hypertensive treatment in man?; (2) is the development of an anti-hypertensive effect in SHR associated with impairment of vasomotor nerve function?

Methods

Female SHR of the Okamato strain were used. Blood pressure and heart rate were recorded intravenously in unanesthetized animals (Popovic & Popovic, 1960) and in one group by an indirect tail-cuff method (AMS-I. Technilab Instruments Inc.). Neuroeffect control of the portal vein was studied in vitro as previously described (Ljung et al., 1975). Plasma concentrations of metoprolol

(1) Abbreviation: SHR, spontaneously hypertensive rats.
were determined according to the method described by Ervik (1975).

Results

Long-term studies

Long-term oral treatment of adult SHR beginning at the age of 14 months and continuing for 5 months was achieved by administration of metoprolol incorporated into food (approximate daily intake 0.7 mmol/kg). At the end of treatment there was no difference in body weight but blood pressure in the treated group was 152 ± 8 mmHg (mean ± SEM, n = 5) as compared to 189 ± 6 mmHg (n = 5) in the control group. The steady-state plasma concentrations of metoprolol in SHR exposed to this regimen reached a peak of 204 ± 99 nmol/l (70 ± 34 ng/ml, n = 5) and a minimum during late afternoon of 18 ± 8 nmol/l (6 ± 2.8 ng/ml, n = 5). It was estimated from the 24 h plasma concentration profile that more than 20% blockade of neurogenic β-receptor-mediated cardiac responses would occur for 20 h during each 24 h period (Borg, Carlsson, Ek & Johansson, 1975).

Short-term studies

The onset of anti-hypertensive effect has been studied in experiments with intravenous and with oral administration of metoprolol.

A single intravenous dose of metoprolol (15 μmol/kg) did not affect blood pressure. Heart rate was reduced within 15 min and returned to control values within 3 h. The plasma concentration of metoprolol reached an initial peak value of 5.8 nmol/l (2 μg/ml) and the plasma half-life is 36 min in the rat (Borg et al., 1975).

In SHR given metoprolol 15 μmol/kg intravenously twice daily, the blood pressure did not differ significantly from the pretreatment values or from blood pressure of control SHR receiving injections of sodium chloride solution, until after injection on the third day of treatment. Before administration in the morning of the fourth day, blood pressure of the treated group was 140 ± 6 mmHg (n = 5), which was on average 28 mmHg below pretreatment values (168 ± 2 mmHg, n = 5) and 18 mmHg below the control SHR (157 ± 9 mmHg, n = 5). These differences were statistically significant.

The rats were killed on the fourth day and their portal veins were studied in vitro. In all respects, responses to exogenous noradrenaline and to transmural sympathetic nerve stimulation were the same in portal veins from the control group as in those from the treated group of SHR.

Blood pressure and heart rate were determined with an indirect tail-cuff method in one series of experiments. After control values had been obtained over 3 days, metoprolol was administered in the food (see above). On the fourth day of treatment, blood pressure was again significantly lower than before treatment and this reduction remained during the following week of treatment. On day 11 the mean blood pressure of the treated group was 157 ± 3 mmHg (n = 6) and of the control group 184 ± 6 (n = 6). Catheters for intra-arterial measurements were then implanted and blood pressure was determined on day 13 of treatment. These values tended to be lower (147 ± 4, n = 6 and 176 ± 5 mmHg, n = 6) than those obtained with the indirect method.

Isolated portal veins from the treated and control SHR were studied on day 14 of treatment. No apparent differences were found in vitro in the neuroeffector control of the tissues from the two groups.

Discussion

It seems clear from the present results that metoprolol not only prevents development of hypertension in SHR (Weiss et al., 1974; Ljung et al., 1975) but also lowers blood pressure in established hypertension. As in man, one single dose of the β-receptor antagonist lowered heart rate in SHR without affecting blood pressure, but a clear-cut anti-hypertensive effect was obtained after repeated drug administration for a few days. Quantitatively the metoprolol-induced reduction in blood pressure corresponded to that seen in hypertensive patients. The effect persisted during 5 months' therapy in rats exposed to metoprolol in plasma concentrations corresponding to those seen in patients under anti-hypertensive treatment (Bengtsson, Johnsson & Regårdh, 1975). The daily oral dose of metoprol given to rats had to be about 20 times higher than that used in man to achieve comparable plasma concentrations. This reflects the short half-life and low bioavailability of metoprolol in the rat (Borg et al., 1975).

Repeated intravenous administration of metoprol resulted in a gradually developing anti-hypertensive effect in spite of the fact that significant
cardiac β-receptor blockade occurred only during a minor part of each 24 h period. This finding has several interesting implications, one of which is the importance of sustained cardiac β-receptor blockade for the anti-hypertensive effect.

In our previous study (Ljung et al., 1975) long-term treatment of young SHR led to reduced responses of the portal vein to vasomotor nerve stimulation within the low-frequency field. Since the α-receptor sensitivity to noradrenaline was not altered, the results strongly indicated that the amount of transmitter released per impulse was decreased. The present findings of unaffected neuroeffector control of portal veins studied in vitro on days 4 and 14 of metoprolol treatment, that is, at the very onset of hypotensive effect, indicate that such gross impairment of vasomotor nerve function does not cause the anti-hypertensive response. Rather it seems possible that a reduction in the amount of transmitter released per impulse may be a secondary change in the vasoconstrictor neuron due to prolonged suppression of adrenergic nerve function. The primary effect might be a reduced rate of discharge due to an action within the central nervous system (Lewis & Haeusler, 1975) or prolonged blockade of the prejunctional β₁-receptor-mediated positive feedback mechanism governing adrenergic transmitter release (Dahlöf, Åblad, Borg, Ek & Waldeck, 1975; Adler-Graschinsky & Langer, 1975). It is suggested as a working hypothesis that an effect on vasomotor nerve control contributes to the anti-hypertensive effect of metoprolol.

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References


