Contribution of cardiovascular reflexes to differences in β-adrenoceptor-mediated responses in essential hypertension

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Summary

1. The responses to stimulation of both cardiac and lymphocyte β-adrenoceptors were studied in 23 normal subjects and 23 with untreated essential hypertension. Lymphocyte cyclic adenosine monophosphate was measured in vitro after incubation with isoprenaline (0.01 μmol/l–10 mmol/l). There were no significant differences between the amount of cyclic adenosine monophosphate generated by lymphocytes in the two groups in the isoprenaline concentration range 0.01 μmol/l–1 mmol/l.

2. In the same subjects we compared cardiac β-adrenoceptor-mediated responses using the change in heart rate after bolus doses of isoprenaline (dose range 0.25–3 μg). In 12 subjects (six normotensive, six hypertensive) we studied the heart rate responses to isoprenaline before and after ‘total’ autonomic block (0.04 mg of atropine/kg and 300 μg of clonidine). The latter permitted assessment of intrinsic cardiac responsiveness after eliminating cardiovascular reflexes.

3. In subjects with reflexes intact the rise in heart rate was significantly greater in normal than in hypertensive subjects at all doses of isoprenaline. Isoprenaline evoked a similar dose-related fall in blood pressure in both groups, which contributed to the reflex drive. After autonomic block the differences in heart rate responses were no longer present.

4. The results indicate that the reduced tachycardia at a given dose of isoprenaline in hypertensive subjects is due to impairment in their baroreceptor–heart rate reflex since this was no longer present after atropine and clonidine.

5. The absence of any intrinsic difference in cardiac β-adrenoceptor responsiveness is in agreement with the results with lymphocytes.

Key words: β-adrenoceptors, autonomic blockade, essential hypertension.

Abbreviations: cyclic AMP, cyclic adenosine monophosphate; MAP, mean arterial pressure.

Introduction

Patients with essential hypertension have been reported to have diminished chronotropic response to isoprenaline compared with that of normotensive control subjects [1–3]. This has been attributed to alteration in β-adrenoceptor responsiveness. However, isoprenaline causes vasodilatation and a fall in blood pressure due to stimulation of β-adrenoceptors in the peripheral vasculature. Apart from its effects on the heart, this fall in blood pressure could contribute reflexly to the increase in heart rate after isoprenaline through the baroreceptor–heart rate reflex. Since this reflex is impaired in essential hypertension [4, 5] some of the observed differences between normotensive and hypertensive subjects in isoprenaline responsiveness may be due to alterations in reflex function rather than to low receptor responsiveness.

β-Adrenoceptor-mediated responses in man can also be studied by measuring the amount of cyclic adenosine monophosphate (cAMP) generated by lymphocytes after incubation with isoprenaline [6]. Clearly reflexes are not involved in the lymphocyte studies. We have compared this method in normotensive and hypertensive subjects with the results of studies of the chronotropic effects of isoprenaline in the same subjects. To investigate the contribution of reflexes to the heart rate effects of isoprenaline we
repeated the studies after combined sympathetic and parasympathetic blockade.

Methods

Twenty-four normal subjects (age 18–54 years, average 25.2 years) and 23 patients with untreated essential hypertension (age 21–65, average 40 years) participated in the study. On the morning of the study 60 ml of venous blood was collected for lymphocyte studies. A brachial artery cannula was inserted for measurement of arterial pressure and heart rate was recorded from the electrocardiogram. Heart rate and blood pressure responses were measured to bolus doses of isoprenaline (0.025–3 μg) as described previously [7, 8]. In six normal subjects and six patients with essential hypertension heart rate and blood pressure responses to the same doses of isoprenaline were determined 30 min after autonomic blockade with clonidine (300 μg) and atropine sulphate (0.04 mg/kg) [9]. This regimen was found to permit assessment of intrinsic cardiac responsiveness after eliminating cardiovascular reflexes, e.g. in six normal subjects heart rate responses were completely eliminated by the above regimen when blood pressure was lowered to 50 mmHg by nitroprusside infusions. Lymphocytes were separated from plasma immediately, incubated for 10 min with concentrations of isoprenaline ranging from 0.01 μmol/l to 10 mmol/l and the change in cyclic AMP was measured [6, 8].

Results

There was no difference in the amount of cyclic AMP generated by lymphocytes from hypertensive and normotensive subjects after incubation with isoprenaline concentrations of 0.01 μmol/l to 1 mmol/l (Fig. 1, bottom panel). Only with isoprenaline at 10 mmol/l, the highest concentration used, was there a significantly greater amount of cyclic AMP produced by lymphocytes from hypertensive subjects (P < 0.05).

In the same subjects studied with reflexes intact, bolus doses of isoprenaline caused a dose-related increase in heart rate although the increases after successive doses above 1.5 μg were small. The rise in heart rate was significantly greater in normal than in hypertensive subjects at all doses of isoprenaline (Fig. 1, top panel). For example, after 1.5 μg of isoprenaline heart rate rose by 21.2 ± 1.2 in the former and by 16.1 ± 1.1 beats/min in the latter (P < 0.01). This difference could not be accounted for by the difference in average age between the two groups as it was present in subjects when those aged 20–30 years (19 normal, six hypertensive) were considered separately (P < 0.05).

Isoprenaline evoked a transient dose-related fall in mean arterial pressure in all subjects from the average resting values of 85 and 115 mmHg in normal and hypertensive subjects respectively. The fall occurred at the time of maximum heart rate and was followed by a rise in systolic and pulse pressure. The magnitude of the fall in blood pressure at each dose was not significantly different between the various groups.

In 12 subjects (six normotensive, six hypertensive) we studied the heart rate responses before and after autonomic blockade with clonidine and atropine. In these subjects there was also a smaller rise in heart rate at each dose of isoprenaline in hypertensive subjects than in normals before autonomic blockade. After autonomic blockade resting heart rate increased, e.g. in normals from 69.1 ± 4 to 88.6 ± 3.8 beats/min (P < 0.01). Heart rate was higher at each dose of isoprenaline after autonomic blockade, but the increase in heart rate above resting values at any given dose was less (Fig. 1, top panel). The difference in heart rate responses between normotensive and hypertensive subjects observed when reflexes were intact was no longer present after autonomic blockade (Fig. 1, top panel).

Blood pressure fell more at each dose of isoprenaline after autonomic blockade than before and there was a tendency for the absolute fall to be slightly greater in hypertensive subjects although the differences were not significant (Fig. 1, middle panel).

Discussion

This study confirms previous findings that heart rate responses to isoprenaline are lower in patients with essential hypertension than in normal subjects [1–3]. This difference was not present after autonomic blockade, however, suggesting that the reduced tachycardia at a given dose of isoprenaline in hypertensive subjects is due to impairment in their cardiovascular reflexes [4, 5] and not an intrinsic difference in cardiac β-adrenoceptor responsiveness. The absence of difference in intrinsic responsiveness is in agreement with the lymphocyte data for incubation of isoprenaline at concentrations between 0.01 μmol/l and 1 mmol/l. The difference in cyclic AMP generated after incubation with isoprenaline at 10 mmol/l is unexplained, but this concentration is very high and unlikely to be of relevance during cardiac stimulation of β-receptors under physiological conditions.
Examination of the isoprenaline–heart rate dose–response curves (Fig. 1) reveals that commonly used indices of isoprenaline responsiveness, which are obtained from the dose at which a given absolute change in heart rate occurs (e.g. EC\textsubscript{25}, dose of isoprenaline required to increase heart rate by 25 beats/min) \cite{1-3} are markedly influenced by the efficiency of cardiovascular reflexes. Such indices are therefore applicable only to studies of alteration in β-adrenoceptor responsiveness within subjects where reflexes can reasonably be expected to exert a constant effect.

Indices obtained from the whole dose–response relationship were influenced much less by autonomic blockade in the present study, e.g. the dose at which half-maximal effects occurred was 0.65 µg before and 0.7 µg after autonomic blockade in normal subjects. However, the difference in heart rate response range between groups, from resting to maximum, was entirely due to a difference in reflex properties.

Our use of the combination of atropine and clonidine to achieve autonomic blockade in the present study deserves comment. We have previously combined these drugs with pro-
pranolol and phentolamine [9] to achieve total sympathetic and parasympathetic block. The present regimen was found to achieve a similar degree of block of sympathetic components of postural and Valsalva reflexes and was highly efficient in our normal subjects in inhibiting the tachycardia associated with reduction in blood pressure by non-adrenergic means with nitroprusside. The level at which clonidine inhibited the sympathetic system in these studies is not clear, but it is likely that there was a combination of central and peripheral presynaptic inhibition at these doses [10]. Clonidine alone was used to inhibit sympathetic activity as it does not affect cardiac β-adrenoceptors [11].

In conclusion, the present study suggests that there is no difference in intrinsic cardiac β-adrenoceptor responsiveness between normal subjects and patients with essential hypertension. The previously reported differences in isoprenaline responsiveness could be explained by alterations in cardiovascular reflexes in hypertension. Further studies are required to determine whether other factors which alter isoprenaline responsiveness, such as age [3], are also due to changes in reflexes, or in β-adrenoceptors themselves.

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References


