RELEVANCE OF SELECTIVITY AND NON-SELECTIVITY IN β -ADRENOCEPTOR BLOCKING DRUGS

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1 The heart rate responses to increasing doses of isoprenaline ($n = 6$) (during infusion with atropine 0.5 mg/min i.v.) and noradrenaline ($n = 5$), (during infusion with phentolamine 160 mg/h i.v.) were recorded before and after the intravenous administration of propranolol (15 mg) or metoprolol (15 mg).

2 In the doses used, metoprolol was less potent than propranolol in antagonizing isoprenaline-induced tachycardia, during atropine infusion.

3 In volunteers treated with phentolamine both metoprolol and propranolol produced similar inhibition of noradrenaline-induced tachycardia, indicating comparable β_1 -adrenoceptor blockade in the doses used.

4 The fact that the shift of the dose-response curve of isoprenaline-induced tachycardia was smaller after metoprolol than after propranolol supports the hypothesis that β_2 -adrenoceptors are present in the heart.

Introduction

In a comparative study in healthy volunteers on the β -adrenoceptor blocking activity of three β -adrenoceptor blocking drugs with intrinsic sympathomimetic activity we found that exercise-induced tachycardia was reduced to about the same extent by pindolol 2 mg i.v. (–18%), mepindolol 0.5 mg i.v. (–15%) and practolol 100 mg i.v. (–13%). The dose-response curve for the increase in heart rate during isoprenaline infusions, however, showed a marked shift to the right after pindolol and mepindolol, but only a very small shift after practolol. This difference was attributed to the fact that practolol, having less effect on peripheral β_2 -adrenoceptors, would only block the isoprenaline effect on heart rate, but not the reduction in peripheral resistance, which, in turn, by reducing vagal tone, leads to an increase in heart rate (Bonelli, 1977).

Ablad *et al.* (1975) however, demonstrated in animals that there are not only β_1 -adrenoceptors in the heart but also some β_2 -adrenoceptors which are also able to mediate an increase in heart rate and contractility. This prompted the question whether the smaller reduction of isoprenaline-induced tachycardia by practolol in comparison to pindolol and mepindolol could not, at least in part, also be due to the fact, that a relatively β_1 -adrenoceptor selective drug, when given in selective doses, blocks only β_1 -adrenoceptor mediated increases in heart rate, but not those due to stimulation of β_2 -adrenoceptors.

Lands *et al.* (1967) showed that the relative affinities of various sympathomimetic amines for the two types of β -adrenoceptor differ. Whereas isoprenaline stimulates both β_1 - and β_2 -adrenoceptors, noradrenaline has an almost exclusive affinity for the β_1 -adrenoceptor and adrenaline has a greater relative affinity for the β_2 -adrenoceptor. Noradrenaline infusions, in the presence of an α -adrenoceptor blocking drug, should therefore permit specific stimulation of β_1 -adrenoceptors on the heart. Comparison with the effects of isoprenaline may determine if β_2 -adrenoceptors play an important part in the positive chronotropic effect. This was the aim of the study presented here.

Methods

In the first experiment, the effect of the cardio-selective β -adrenoceptor antagonist metoprolol (15 mg i.v.) and the non-selective antagonist propranolol (15 mg i.v.) in inhibiting the heart rate response to increasing doses of i.v. isoprenaline was investigated in six healthy male volunteers aged between 25 and 30 years. To eliminate as far as possible the vagal reflexes a continuous infusion of atropine 0.5 mg/min was given. This dose of atropine was chosen because in preliminary experiments it was found to produce a relatively consistent increase in

heart rate of 35–40 beats/min (see also Innes & Nickerson, 1970).

In the second experiment, in five male volunteers aged 25–30 years, the effects of increasing doses of i.v. noradrenaline on heart rate were studied before and after metoprolol 15 mg i.v. or propranolol 15 mg i.v. The subjects were simultaneously treated with phentolamine 160 mg/h i.v. This dose was chosen because in preliminary experiments it was found to inhibit almost completely the blood pressure response to noradrenaline 320 µg/min (see also Nickerson, 1970).

Results

In the presence of atropine, the shift to the right of the dose-response curve to isoprenaline-induced tachycardia was more marked after propranolol than after metoprolol (Figure 1).

The shift to the right of the dose-response curves to noradrenaline-induced tachycardia, in the presence of phentolamine, however, was similar after metoprolol and propranolol (Figure 2).

Discussion

The fact that the shift to the right of the dose-response curve of noradrenaline-induced tachycardia was similar after metoprolol and after propranolol indicates that equipotent cardiac β -adrenoceptor blocking doses of the two drugs were used. The fact, that the shift of the dose-response curve of isoprenaline-induced tachycardia was smaller after metoprolol than after propranolol supports the hypothesis that β_2 -adrenoceptors are present in the heart. β_1 -adrenoceptor antagonists, given in selective doses, block only β_1 -adrenoceptors leaving any β_2 -adrenoceptors in the heart free to be stimulated by isoprenaline and endogenous catecholamines.

The present study indicates that the smaller shift of the isoprenaline dose-response curves observed after

Figure 1 Dose-response-curves for the heart-rate (HR) during an isoprenaline infusion after propranolol (15 mg i.v., —) and metoprolol (15 mg i.v.,). Mean $\pm$ s.e. mean, $n = 6$.

Figure 2 Dose-response-curves for the heart-rate (HR) during a noradrenaline infusion after propranolol (15 mg i.v., —) and metoprolol (15 mg i.v.,). Mean $\pm$ s.e. mean, $n = 5$.

relatively β_1 -selective adrenoceptor blocking drugs is at least partly due to the existence of chronotropic β_2 -adrenoceptors in the heart. Cardiac β -adrenoceptor blockade which can be reached by a hypothetical absolutely β_1 -adrenoceptor selective drug is therefore smaller than after non-selective drugs. Because in the higher doses used in clinical practice the relatively cardioselective drugs lose their selectivity, this fact is probably of no great clinical relevance, but still favours the use of non-selective drugs especially in situations where adrenaline, which stimulates both, β_1 and β_2 -adrenoceptors of the heart, is involved.

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