β -ADRENOCEPTOR BLOCKADE AND PSYCHIC STRESS IN MAN. A COMPARISON OF THE ACUTE EFFECTS OF LABETALOL, METOPROLOL, PINDOLOL AND PROPRANOLOL ON PLASMA LEVELS OF ADRENALINE AND NORADRENALINE

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1 A random double-blind study was performed in healthy volunteers. The immediate effects of three different β -adrenoceptor blocking agents, metoprolol, pindolol and propranolol, on the plasma concentrations of adrenaline and noradrenaline were compared in a situation of pleasant psychic stimulation during a television-game of tennis. The immediate effects of labetalol in a group of patients with arterial hypertension were studied in a similar experimental situation.

2 During psychic stress the plasma concentration of noradrenaline rose significantly by 85% after placebo, by 95% after labetalol, by 63% after metoprolol and by 55% after propranolol. After pindolol the noradrenaline concentration remained unchanged.

3 During psychic stress the plasma concentration of adrenaline rose significantly by 135% after labetalol, by 110% after metoprolol and by 83% after propranolol. After pindolol and placebo the adrenaline concentration remained unchanged.

4 The present results are taken to indicate that the intrinsic sympathomimetic activity possessed by pindolol prevents the rise in plasma noradrenaline normally seen during psychic stress. It is suggested that β -adrenoceptor blockers with strong intrinsic sympathomimetic effect reduce the release of catecholamines during psychic stress.

Introduction

β -adrenoceptor blocking drugs seem to be equally effective in the management of arterial hypertension despite considerable differences in their pharmacodynamic properties, e.g. intrinsic sympathomimetic activity (ISA), β -adrenoceptor selectivity, membrane stabilizing activity and penetration of the blood-brain barrier (Table 1). It is generally agreed that long-term treatment with β -adrenoceptor blockers such as propranolol and labetalol causes an increase in the plasma concentration of adrenaline and noradrenaline (Christensen *et al.*, 1978, 1979; Carlsen *et al.*, 1980). Therefore it is of interest that Brecht *et al.* (1976), Bonelli *et al.* (1979) and Dominiak & Grobecker (1982) found that the plasma concentrations of catecholamines were reduced after treatment with pindolol, a non-selective β -adrenoceptor blocker with ISA (Table 1). One may ask: Does a β -adrenoceptor blocker with ISA cause a smaller increase in the plasma concentration of catecholamines as compared to β -adrenoceptor blockers without ISA also in situations

with increased activity in the sympathetic nervous system, such as psychic stress during a television game of tennis (Clausen *et al.*, 1978)?

In order to elucidate this we performed a double-blind cross-over study of the immediate effects of metoprolol, pindolol and propranolol on plasma adrenaline and noradrenaline during psychic stress in a group of young healthy subjects (see Table 1). In an attempt to complete this survey we included some of the results from a previous study on the effects of intravenous labetalol during psychic stress in a group of hypertensive patients (see Table 1, Carlsen *et al.*, 1980; Trap-Jensen *et al.*, 1980).

Methods

Seven young healthy male volunteers aged 21 to 30 years, consented to participate in the study. Studies were performed in the morning with the subjects sitting in a comfortable armchair after an overnight

Table 1 Pharmacodynamic properties of some β -adrenoceptor blocking agents

	Non-selective	β_1 -selective	Intrinsic sympathomimetic activity (ISA)	α_1 -receptor blocking properties	Doses (mg/kg body weight)
Labetalol (Trandate®)	+	—	—	+	0.75
Mepindolol (Corindolan®)	+	—	++	—	0.011
Metoprolol (Seloken®)	—	+	—	—	0.13
Pindolol (Visken®)	+	—	+++	—	0.012
Propranolol (Inderal®)	+	—	—	—	0.10

— absent

+, ++, +++ presence of particular property: the more + signs, the greater the activity

fast and abstinence from smoking for 12 h. Three praecordial ECG electrodes were fixed to the chest, a sphygmomanometer-cuff was placed on the right upper arm and the tip of an intravenous catheter was placed in the subclavian vein via a median cubital vein. After 20 min rest, basal observations were obtained in duplicate. Subsequently one of the four agents under study, isotonic saline (placebo), metoprolol, pindolol or propranolol, was given intravenously in equipotent doses in a double-blind randomized fashion. Fifteen min later a television-game of tennis was played against one of the staff members, who adjusted his play according to the capability of the subject under study. When stable values for heart rate and blood pressure were reached, blood samples for the determination of plasma concentrations of adrenaline and noradrenaline were collected in duplicate (for experimental details see Carlsen *et al.*, 1980; Trap-Jensen *et al.*, 1980). At least 1 week elapsed between each of the four experimental sessions. The injection volume was in all cases 20 ml. The equipotency of the three different β -adrenoceptor blockers was judged from the reduction in exercise induced tachycardia during upright bicycle exercise (Svendsen *et al.*, 1980).

Seven patients with newly diagnosed and untreated fixed essential hypertension (WHO grade I to II) aged 21 to 52 years receiving labetalol were studied according to a slightly different protocol (For details see Trap-Jensen *et al.*, 1980 and Table 1).

Results

At rest, before administration of the four different

β -adrenoceptor blockers or placebo, the plasma concentration of noradrenaline and adrenaline was not different in the five experimental situations.

Noradrenaline (Figure 1)

During the television-game, the plasma concentration of noradrenaline increased significantly by 85% after placebo, by 55% after propranolol, by 63% after metoprolol and by 95% after labetalol. The plasma concentration of noradrenaline was un-

Figure 1 Changes in the plasma concentration of noradrenaline induced by television-game of tennis after intravenous injection of (1) placebo, 0.9% NaCl, and after equipotent doses of (2) propranolol, prop, (3) metoprolol, M, (4) pindolol, pind (5) labetalol, L (see Table 1). Mean values $\pm$ 1 s.d. are given.

changed after pindolol. The mean values $\pm$ 1 s.d. were 0.18 ± 0.09 ng/ml plasma in the resting state and 0.19 ± 0.08 ng/ml plasma during the television-game after administration of pindolol ($t = 0.8293$).

Adrenaline (Figure 2)

During the television-game the plasma concentration of adrenaline increased by 83% after propranolol, by 110% after metoprolol and by 135% after labetalol. After placebo and pindolol, the plasma concentration of adrenaline remained unchanged. The respective mean values $\pm$ 1 s.d. after placebo and pindolol were 0.03 ± 0.04 ng/ml and 0.07 ± 0.05 ng/ml plasma at rest, and 0.04 ± 0.05 ng/ml and 0.06 ± 0.04 ng/ml plasma during the television-game.

Discussion

Psychic stress is often claimed to cause a marked rise in the plasma concentration of adrenaline and an unchanged or a slight rise in the plasma concentration of noradrenaline. However, most studies on the cardiovascular and hormonal response to psychic stress have been carried out by exposing the subjects to rather unpleasant situations of frustration, anger or fear (Brod, 1963; Bonelli *et al.*, 1979).

We wanted to study the cardiovascular and hormonal response to psychic stress in a situation more pleasant to the subjects under study and thereby approaching situations that are frequently and willingly experienced in normal daily life. During pleasant emotional stimulation we found an increase in the plasma concentration of noradrenaline whereas the

adrenaline concentration remained unchanged after placebo. This suggests that a pleasant emotional stimulation causes an increase in circulating noradrenaline, but not in adrenaline. In contrast an unpleasant emotional stimulation associated with fear or frustration causes an increase in the plasma concentration of adrenaline, but not in noradrenaline.

During psychic stress the increase in the plasma concentration of noradrenaline was practically the same after acute administration of isotonic saline and after propranolol, metoprolol or labetalol. In contrast, the noradrenaline concentration remained unchanged during psychic stress after intravenous administration of pindolol. Thus, pindolol seems to influence the release and/or inactivation (re-uptake) of noradrenaline in a clearly different way than placebo and the three other β -adrenoceptor blockers studied here.

The amount of noradrenaline released from adrenergic nerve terminals is primarily under control of the central nervous system, which controls the impulse traffic within the sympathetic nervous system. The amount of noradrenaline available for activation of the receptors localized on the cell membranes of the effector organ is regulated by several factors (Figure 3). Most of the noradrenaline released into the synaptic cleft is inactivated by re-uptake by the adrenergic nerve terminals via the amine pump, by noradrenaline metabolizing enzyme systems, e.g. monoamine oxidase- and catechol-o-

Figure 2 Changes in the plasma concentration of adrenaline induced by television-game of tennis after intravenous injections of (1) placebo, 0.9% NaCl, and after equipotent doses of (2) propranolol, prop, (3) metoprolol, M, (4) pindolol, pind, and (5) labetalol, L (see Table 1). Mean values $\pm$ 1 s.d. are given.

Figure 3 Schematic outline of an adrenergic nerve terminal. For full details see the text.

methyltransferase, and extraneuronal uptake. A small amount diffuses over the blood-tissue barrier into the capillary blood corresponding to the measured amount of noradrenaline concentrations.

There is strong evidence for a presynaptic control of the noradrenaline release from the adrenergic nerve terminals (Andersson, 1980). It is assumed that noradrenaline released into the synaptic cleft, triggers a negative feed-back mechanism mediated by the presynaptic α_2 -adrenoceptors (Figure 3). Stimulation of these receptors by α_2 -adrenoceptor agonists will therefore inhibit the local release of noradrenaline. Presynaptic β -adrenoceptors have also been suggested to play a role in a local positive feed-back mechanism for the release of noradrenaline. Blockade of presynaptic β -adrenoceptors is thought to decrease the local release of noradrenaline, whereas stimulations of these receptors e.g. by circulating adrenaline may cause an increase of the local release of noradrenaline, and in the adrenal medulla an increased release of adrenaline from the chromaffine cells (Majewski *et al.*, 1980).

Comparing Figure 1 and Figure 3 it is seen that the unchanged plasma noradrenaline concentration during psychic stress after pindolol may be caused by (1) a central nervous effect including the baroreceptor reflex activity decreasing the frequency of impulses reaching the adrenergic nerve terminals, (2) a stimulation of the capacity of the amine pump, and/or (3) a stimulation of other re-uptake mechanisms and/or (4) a stimulation of the presynaptic α_2 -adrenoceptors, and/or (5) an increased plasma clearance of noradrenaline, i.e. that the noradrenaline clearance depend upon different haemodynamic effects of the different β -adrenoceptor blockers (Svendsen *et al.*, 1981). However, these different haemodynamic actions might be of relevance only at rest supine, whereas it is thought not to be of importance in situations with an increased activity in the sympathetic nervous system (Svendsen *et al.*, 1980). In these situations all β -adrenoceptor-blockers seem

to cause an equal reduction of cardiac output and the regional blood flow to local tissues (Hartling *et al.*, 1981).

This study does not allow us to point out, which of the above mentioned mechanism are the most likely in causing the decreased noradrenaline response to psychic stress after pindolol. However, the chemical structure and/or the intrinsic sympathomimetic activity possessed only by pindolol is undoubtedly causing the reduced catecholamine response to psychic stress after pindolol as compared with the three other β -adrenoceptor blockers studied here.

The most likely effect of ISA is an increased activity in the inactivation of noradrenaline and/or a presynaptic α_2 -adrenoceptor agonist activity. During psychic stress the plasma concentration of adrenaline increased markedly after labetalol, metoprolol and propranolol, but remained unchanged after placebo and pindolol. This is in good agreement with the findings of Bonelli *et al.* (1979) and Brisse *et al.* (1982). These investigators found a significantly reduced catecholamine response to stress after pretreatment with mepindolol and pindolol as compared to propranolol and metoprolol. Both mepindolol and pindolol are non-selective β -adrenoceptor blockers with ISA. Why do β -adrenoceptor blockers with ISA reduce the adrenaline response to psychic stress. An answer to this question will be even more speculative, than those suggested for the reduced noradrenaline response given above. But, whatever the mechanisms be we may conclude, that β -adrenoceptor blockers with strong ISA reduce the catecholamine response to pleasant emotional stimulation.

From a clinical point of view the present results must be regarded as most preliminary. Our findings obtained in young healthy volunteers must be reconfirmed in hypertensive patients during long-term treatment with different β -adrenoceptor blockers with and without ISA before the possible clinical implications of the present results can be validated in every day situations including psychic stress.

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