Beta-Blockers in the Elderly

Edited by

E. Lang F. Sörgel L. Blaha

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Preface

In conjunction with the Twelfth International Congress of Gerontology, the Carl-Korth Institute for Cardiovascular Research organized an international symposium on "Beta-Blockers in the Elderly." It was the intention of the Scientific Committee that during this symposium we would discuss the specific problems and therapeutic implications arising when elderly people have to be treated with beta-blocking agents. Special emphasis was placed on the side effects and the age-dependent features of beta-blocker therapy.

Beta-blockers have become established in the treatment of both cardiovascular diseases and neuropsychiatric disorders. Their effectiveness in patients suffering from coronary heart disease, hypertension, and hyperkinetic cardiac syndromes has long been proven. The development of new, selectively active beta-blockers has substantially reduced the number of possible side effects, thus enhancing therapeutic safety. Because side effects cannot be eliminated, however, beta-blockers have been introduced only hesitantly into treatment of the elderly.

This book is the first wide-ranging survey of the use of beta-blockers in elderly patients. The articles contained herein – written by pharmacologists, cardiologists, sports physicians, neurologists, psychiatrists, and ophthalmologists – show that advanced age alone does not contraindicate the use of beta-blockers and sympatholytic substances. Also provided are guidelines for examination and determination of indications in the elderly.

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E. Lang, Erlangen

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I. The Pharmacological Basis of β-Blocking Agents

β-Blockers: Theory, Action, and Application to the Elderly

B. Åblad

In 1948, Ahlquist [3] suggested that the adrenergic transmitter noradrenaline and adrenal medullary adrenaline elicit their effects by combining with two kinds of receptors: α and β. More recent studies have shown that β-adrenoceptors are not homogeneous. Lands et al. [18] have suggested a subdivision into β_1 and β_2. Table 1 shows some adrenergic effects and the type of receptor mainly involved in mediating each effect. α-Receptors mediate, for instance, contraction of smooth muscle in blood vessels and uterus, while β_1-receptors mediate cardiac stimulation and other effects such as lipolysis and release of renin. β_2-Receptors mediate smooth muscle

Table 1. Examples of adrenergic target organs, effects, and main types of mediating adrenoceptor

Effector organ	Type of receptor	Adrenergic effect
Heart	β_1	Increased rate
		Increased contractility
		Increased conduction
		Increased exitability
		Increased automaticity
Blood vessels	α	Contraction
	β_2	Dilatation
Bronchi	β_2	Relaxation
Uterus	α	Contraction
	β_2	Relaxation
Skeletal muscle	β_2	Tremor
Kidneys	β_1	Renin release
Fat tissue	β_1	Lipolysis
Skeletal muscle	β_2	Glycogenolysis
	β_2	K^+ transport into cells
Pancreas	α	Inhibition of insulin release
	β_2	Stimulation of insulin release

relaxation in, for instance, blood vessels, bronchi, and uterus, and also mediate various metabolic effects such as release of insulin from the β cells in the pancreas and glycogenolysis in skeletal muscle cells.

More recent work has on the whole confirmed the β_1/β_2 concept of Lands et al. [18]. One modification was introduced by Carlsson et al. [4], who showed that the distribution of β_1 and β_2 is not absolutely organ specific, as Lands suggested. Instead, both β_1 and β_2 are involved in every β-mediated effect, as for example the increase of heart rate. This modification of Lands' concept has been confirmed in several studies, and is also supported by the results of recent radioligand binding assays [20, 21, 22]. Figure 1 demonstrates this further from experiments by Hedberg et al. [15]. Of the β-adrenoceptors in the right atrium, from guinea pig or cat, 20% show β_2 binding properties, and these β_2-receptors contribute in mediating the heart rate increase elicited by β_2-stimulators. However,

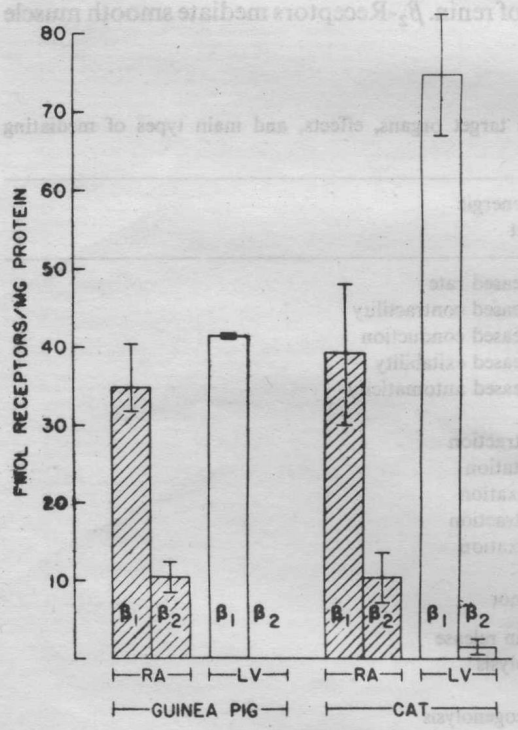

Fig. 1. Densities of β_1- and β_2-adrenoceptors in the right atrium (RA) and left ventricle (LV) of the guinea pig and cat heart, as determined from Hofstee analysis of the inhibition of specific [^{125}I]iodohydroxybenxylpindolol binding by various β_1- and β_2-selective competing ligands. Hedberg [15]

nearly all of the β-receptors in the ventricle are of the β_1 type, and β_1-receptors are of dominating importance in mediating adrenergic heart stimulation.

Further investigation in this field by Carlsson [7] has shown that: (1) there are both β_1- and β_2-receptors in the same organ mediating the same effect; (2) the relative densities of β_1- and β_2-receptors differ from organ to organ, e. g., in heart one finds mainly β_1 and in bronchi and vessels mainly β_2; (3) because noradrenaline is β_1-selective and adrenaline is β_2-selective, the following hypothesis regarding β-receptor mediation may have some relevance: The effects of neuronally released noradrenaline are mainly mediated by β_1-adrenoceptors, whereas the effects of the adrenal medullary hormone, adrenaline, are mainly mediated by β_2-adrenoceptors.

Application to the Elderly

Studies of the effects of β-blockers have usually been carried out on young and middle-aged humans and animals. Before describing these studies, it is important to consider whether these systems change in old age. There are few data available regarding this question, but the acute hemodynamic effects of propranolol in elderly and young healthy human beings have been reported by Conway et al. [9] (Table 2). At supine rest, before propranolol, the elderly had higher arterial pressure, lower cardiac output, and thus higher total peripheral vascular resistance than the younger group. Propranolol caused small reductions in cardiac output, heart rate, and stroke volume in both groups, but arterial pressure was decreased more in the elderly. The left ventricular end diastolic volume was not studied here, but was found to be unchanged after propranolol in a study by Yin et al. [30] in 60–80-year-old resting subjects.

Table 2 also shows the hemodynamics during maximal exercise as observed by Conway et al. [9]. Before propranolol, the elderly reached lower maximal heart rate and cardiac output than the young, but arterial pressure increased more than in the younger group. Propranolol caused a marked reduction of exercise heart rate in both groups. This effect was accompanied by an increase of stroke volume in both groups, so that cardiac output was reduced by only 10%. Systolic and diastolic pressures were decreased somewhat more in the elderly group. β-Blockade leads to reduced systolic rate of ejection from the heart, and this should allow blood to be taken up by a stiffer vascular tree in older subjects, with a resulting smaller rise in arterial pressure.

The results of this study [9] indicate that the healthy old heart deprived of sympathetic activation has a well-maintained inherent ability to contract.

Table 2. Hemodynamic effects of propranolol (0.12 mg/kg IV) in 15 elderly (50–65 years) and 12 young (23–25 years) subjects [9]

	Rest supine				Exercise sitting			
	Elderly		Young		Elderly		Young	
	Before	After	Before	After	Before	After	Before	After
Syst BP/ diast BP (mmHg)	137/73	123[x]/69	108/65	103/66	208/109	185[x]/101[x]	160/91	148[x]/88
CO (liters/min)	5.4	5.0[x]	6.3	5.7	12.5	11.3[x]	15.4	14.0[x]
HR (beats/min)	69	65	73	71	158	121[x]	180	142[x]
SV (ml)	82	76	88	79	80	94	86	99
TPR (dynes/cm/s^{-5})	1411	1476	1032	1123	943	974	598	628

Abbreviations: CO, cardiac output; HR, heart rate; SV, stroke volume; TPR, total peripheral resistance

The cardiac response to exercise in the elderly is not dependent upon a greater sympathetic drive to the heart than in the young. Comparisons at equal work load in the Conway study indicate instead that the exercise response in the elderly subjects involved less activation of cardiac sympathetic nervous activity. This may, in part, be due to a reduced responsiveness to β-adrenoceptor stimulation in the elderly. As evidence of this, Fig. 2 shows the contractility response to noradrenaline in isolated trabecular muscles from the left ventricle of young and old rats. The response to β-stimulation was significantly reduced in the old muscle, and this was ascribed to be an impaired ability of noradrenaline to transport calcium to the contractile element [19].

A reduced responsiveness to β-adrenoceptor activation in the elderly has also been ascribed to a reduction of the density of β-adrenoceptors. Figure 3 shows that the β-adrenoceptor density in human lymphocytes is reduced with age and the 80-year-old has three times less receptors than the 20-year-old [24]. The characteristic properties of the receptors to bind to agonists and antagonists are not changed with age, however. It is at present not known whether the β-adrenoceptor density in the heart is also reduced with advancing age.

We certainly need to learn much more about age-dependent changes of β-adrenoceptor functions. To judge from the data available now, it

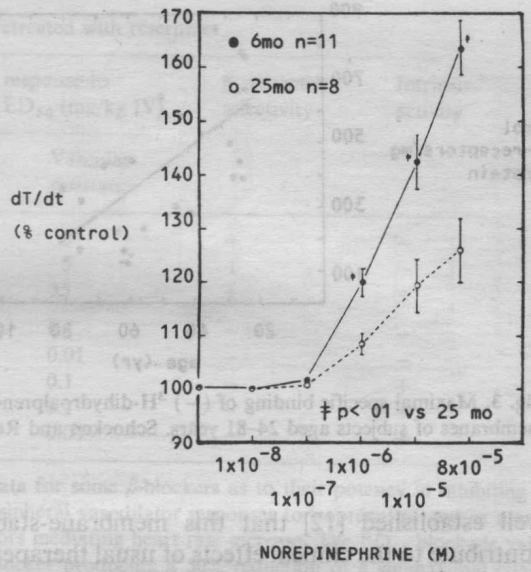

Fig. 2. Inotropic response to noradrenaline in isolated left ventricular trabeculase carnae from adult and old rats. Lakatta et al. [19]

appears that the function of β-adrenergic systems in general are qualitatively the same in the elderly subject as in the young, but there are evidently quantitative changes with age. It is, therefore, likely that data on the pharmacodynamic properties of β-blockers obtained in studies on younger and middle-aged animals and humans are at least of qualitative relevance for elderly humans.

Pharmacological Properties of β-Adrenoceptor Antagonists

Some factors of importance for the characterization of the pharmacological properties of a β-blocker include: pharmacodynamic properties such as β_1- and/or β_2-affinity, intrinsic sympathomimetic activity, and nonspecific effects. The clinical effect pattern of one β-blocker can differ from that of another, and this is mainly due to different β_1/β_2 affinities. Differences as regards intrinsic β-sympathomimetic activity may be a contributory factor, but the clinical significance of this factor is still incompletely investigated.

The most discussed nonspecific effect of β-blockers is a membrane-stabilizing action, which may cause a direct cardiodepression. It is now

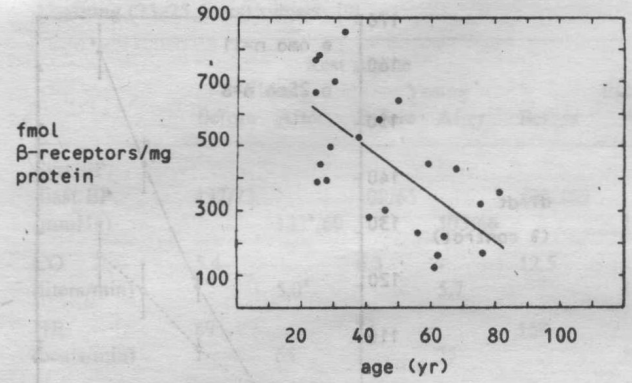

Fig. 3. Maximal specific binding of (−) ^{3}H-dihydroalprenolol to crude mononuclear cell membranes of subjects aged 24–81 years. Schocken and Roth [24]

well established [12] that this membrane-stabilizing action does not contribute to the clinical effects of usual therapeutic doses of all currently registered β-blockers.

Furthermore, differences in the clinical effect patterns of β-blockers may be due to variations concerning pharmacokinetic properties (cf. chapter by Estler, this volume).

Table 3 shows results obtained with some β-blockers in the anesthetized cat pretreated with reserpine. The intravenous dose of blocker required to inhibit the mainly β_1-mediated heart rate response to isoprenaline is shown, along with the dose inhibiting the mainly β_2-mediated peripheral vasodilator response to isoprenaline. Compounds like propranolol, timolol, alprenolol, oxprenolol, and pindolol are relatively nonselective as regards β_1 and β_2 inhibition. Metoprolol, atenolol and practolol are β_1-selective and inhibit the cardiac response in a lower dose than required for blockade of the vasodilator response to isoprenaline. Metoprolol and atenolol are equally β_1-selective. Within each group there are compounds with various degree of β-mimetic intrinsic activity on the heart. Of these compounds, propranolol and metoprolol will mainly be discussed here. Both compounds are devoid of β-mimetic intrinsic activity, but metoprolol differs from propranolol in being a β_1-selective blocker.

The doses of these drugs used in treatment of hypertension, angina pectoris, and cardiac arrhythmias indicate that the therapeutic effects of these blockers are mainly due to inhibition of β_1-mediated effects [2].

A discussion on some aspects of β_1-blockade is pertinent here. Figure 4 shows data by Sannerstedt and co-workers [2] on the hemodynamic effects of metoprolol in six middle-aged patients after one oral dose and after

Table 3. Anesthetized cat pretreated with reserpine

Substance	Inhibition of response to isoprenaline, ED_{50} (mg/kg IV)		β_1-receptor selectivity	Intrinsic activity
	Heart rate	Vascular resistance		
Metoprolol	0.3	5	+	−
Atenolol	0.3	5	+	−
Practolol	0.5	35	+	+
Propranolol	0.1	0.1	−	−
Timolol	0.01	0.01	−	−
Alprenolol	0.1	0.1	−	+
Oxprenolol	0.1	0.1	−	+
Pindolol	0.005	0.005	−	+

Approximate comparative data for some β-blockers as to their potency in inhibiting the cardiac chronotropic and peripheral vasodilator responses to isoprenaline and as regards intrinsic activity on β-receptors mediating heart rate increase. The ED_{50} blockade values indicate the dose of the β-blocker producing a 50% reduction of a submaximal control response to isoprenaline. The intrinsic activity is expressed as the maximal chronotropic response of a compound in relation to that of isoprenaline. For details of the experimental technique, see Åblad et al. (1)

3–5 weeks' treatment. These results show that the first dose reduced cardiac output by 15% because of cardiac β-blockade. This effect was accompanied by an increase of the total peripheral resistance, probably elicited through the baroceptor reflex. As a result, there was an acute reduction of the systolic pressure, but no change of the diastolic pressure. Continued metoprolol treatment for 3–5 weeks caused no further reduction of cardiac output, but the diastolic pressure was decreased due to return of the initially raised peripheral vascular resistance. Similar results with propranolol have been published earlier by Tarazi and Dustan [25] and Hansson et al. [14].

These findings suggest that the antihypertensive effect of a β-blocker embraces: (1) a rapid component, which includes inhibition of β-adrenoceptor-mediated increase of heart rate and contractility, and (2) a slower component, operating to relax resistant vessels. The mechanism of this gradually appearing effect is not known.

Figure 5 shows another long-term effect of β_1-blockade in hypertension [13]. Here 15-month-old hypertensive female rats (Okamoto strain) were treated with metoprolol for 6 months. The control animals had a significant progression of left ventricular hypertrophy. Metoprolol,