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β-ADRENOCEPTOR BLOCKING DRUGS IN HYPERTENSION

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INTRODUCTION

In spite of considerable differences in their pharmacological properties, all β-adrenoceptor blocking drugs have antihypertensive activity in man. It is therefore generally accepted that the blockade of β-adrenoceptors per se, and not any other unrelated pharmacological effect, is responsible for the effectiveness of these drugs in the treatment of hypertension. Secondary characteristics of β-adrenoceptor blocking drugs such as relative affinity for various β-adrenoceptors, intrinsic sympathomimetic activity, membrane stabilizing action, and ability to enter the central nervous system determine the selection of the β-adrenoceptor blocking drugs in the clinic. The purpose of this review is to compare pharmacological properties of β-adrenoceptor blocking drugs as related to their use in hypertension and to consider the hypotheses on the mechanism of their antihypertensive action.

CLASSIFICATION

The pharmacological classification of β-adrenoceptor blocking drugs proposed by Fitzgerald (1) was based on secondary pharmacological properties of potential significance for clinical use. Subsequently, this classification was modified by Prichard & Boakes (2) who proposed separation of β-adrenoceptor blocking drugs in three divisions: (*a*) drugs without β_1-selectivity, (*b*) cardioselective drugs, and (*c*) drugs with α-adrenoceptor blocking activity. Each division can, in turn, be separated into four groups. Table 1 lists the most commonly used β-adrenoceptor blocking drugs in accordance with the expanded and modified classification of Fitzgerald. The

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"yes" or "no" statements in this table represent relative judgments and refer to therapeutic or slightly higher than therapeutic dose levels of these drugs.

β-Adrenoceptor blocking drugs can also be classified in accordance with their acute hemodynamic effects. Drugs with intrinsic sympathomimetic or α-adrenoceptor blocking effects have vasodilator properties and may even increase cardiac output in acute experiments. This is true not only for labetalol (3) but also for drugs from group 1C: bunitrolol (4, 5) and penbutolol (6).

The classification of β-adrenoceptor blocking drugs in accordance with their physicochemical properties, e.g. their hydrophilicity, is of practical value in relation to the tissue distribution and potential activity on the central nervous system. Day et al (7) studied uptake of β-adrenoceptor blocking drugs in the brain of rats and found that hydrophilic compounds (atenolol and practolol) penetrated the blood-brain barrier poorly. Their brain : blood concentration ratios were 0.054 and 0.18 respectively whereas the corresponding ratios for lipid-soluble compounds (oxprenolol and propranolol) were 3.26 and 8.37.

Of practical clinical significance is the separation of various β-adrenoceptor blocking drugs in accordance with their oral bioavailability. According to Waal-Manning (8), in a series of ten β-adrenoceptor blocking drugs, propranolol and alprenolol had the lowest oral bioavailability.

Table 1 Classification of β-adrenoceptor blocking drugs

Division	Group no.	Drugs	Membrane stabilizing activity	Intrinsic sympathomimetic action
1	1A	Dichloroisoproterenol	Yes	Yes
	1B	Pronethalol	Yes	Yes
		Oxprenolol	Yes	Yes
		Alprenolol	Yes	Yes
	1C	Bunitrolol	Yes	Yes
		Penbutolol	Yes	Yes
	2	Propranolol	Yes	No
	3	Pindolol	No	Yes
	4	Timolol	No	No
		Sotalol	No	No
		Nadolol	No	No
		Bunolol	No	No
2	1	Practolol	No	Yes
	2	Metoprolol	Yes	No
		Tolamolol	Yes	No
	3	Atenolol	No	No
	4	Acebutolol	Yes	Yes
3	1	Labetalol	Yes	No

THEORIES ON THE MECHANISM OF ANTIHYPERTENSIVE ACTION

Central Mechanisms

The presence of central β-adrenoceptors controlling arterial pressure and heart rate was suggested by Day & Roach (9). According to them, isoproterenol by intracerebroventricular (i.c.v.) administration to cats produced a pressor effect. β-Adrenoceptor blocking drugs, also by i.c.v. route, antagonized pressor effects of isoproterenol and lowered arterial pressure in cats, dogs, rabbits, or rats (10–14). Also by infusion into carotid or vertebral arteries of dogs, propranolol was shown to lower arterial pressure (15). *d*-Propranolol lowered arterial pressure by intracerebroventricular (i.c.v.) administration to cats (16); since this isomer has practically no β-adrenoceptor blocking activity, the central hypotensive effect of propranolol cannot be ascribed solely to the blockade of central β-adrenoceptors. The subsequent studies in rabbits did not confirm the hypotensive activity of *d*-propranolol by the same route (17, 18). Many β-adrenoceptor blocking agents are sufficiently lipophilic to pentrate the blood-brain barrier (19). The presence of β-adrenoceptor blocking drugs in the central nervous system, however, is not a prerequisite for their antihypertensive action. Timolol, which is less lipophilic than propranolol, is found in the central nervous system of rats only in traces (20) but is effective in the treatment of hypertension (21). A decrease in preganglionic sympathetic nerve activity after propranolol (22) was considered as evidence for the central site of antihypertensive action of this drug and of β-adrenoceptor blockade in general. It is conceivable, however, that the sympathetic nerve activity is reduced as a result of reduction of afferent impulses from peripheral receptors, rather than a direct action on central neurons responsible for regulation of the cardiovascular system. It should, therefore, be concluded that although β-adrenoceptor blocking drugs can lower arterial pressure by i.c.v. administration to animals, there is no sufficient evidence for a claim that the central nervous system is the only or the major site of their antihypertensive action.

Cardiac Mechanisms

The early studies with propranolol (23, 24) suggested that a decrease in cardiac output may be directly responsible for the antihypertensive effect of β-adrenoceptor blocking agents. Subsequent observations made this unlikely. Cardiac output is lowered with propranolol immediately, whereas arterial pressure is reduced gradually (25). The propranolol-induced reduction in cardiac output did not correlate well with its antihypertensive effectiveness (26). Also, the doses and blood concentrations of β-adrenoceptor blocking drugs required for blockade of cardiac β-adrenoceptors and a

subsequent decrease in cardiac output are lower than those needed to lower arterial pressure (27). These observations led Tarazi & Dustan (26) to propose the hypothesis of vascular adaptive changes to a prolonged decrease in cardiac output leading to a hypotensive response. This is an attractive hypothesis that was accepted by many investigators. One of the arguments against this hypothesis is the observation that many β-adrenoceptor blocking drugs reduce cardiac output to a considerably lesser degree than propranolol but are equally effective as antihypertensive drugs (28).

The finding that a decrease in cardiac output is not a prerequisite for antihypertensive activity of β-adrenoceptor blocking drugs and that drugs like bunitrolol, penbutolol, and labetalol lower arterial pressure with little or no effect on cardiac output further questions the validity of the adaptation hypothesis of the mechanism of antihypertensive action of β-adrenoceptor blocking drugs. A modification of this hypothesis which takes into account the observation that some β-adrenoceptor blocking drugs do not reduce cardiac output was recently proposed by Philipp et al (29). According to them, it is the blockade of cardiac responses to sympathetic stimulation, rather than the lowering of cardiac output, that initiates the adaptation phenomenon.

Resetting of Baroreceptors

The resetting of baroreceptors as the result of blockade of cardiac β-adrenoceptors by propranolol or other β-adrenoceptor blocking drugs was suggested by Prichard & Gillam (25). According to them, baroreceptors may be gradually conditioned by the reduced cardiac components of pressor responses to regulate the blood pressure at a lower level so that blood pressure falls. This hypothesis is supported by animal studies showing a reduction of carotid sinus reflexes in dogs or cats by propranolol (30, 31). Hypertensive responses to afferent stimulation of peripheral nerves and chemoreceptor stimulation in cats were antagonized by propranolol at 30 to 300 μg/kg (31). It is not clear to what extent the observed effects were due to a local anesthetic or to β-adrenoceptor blocking effects of propranolol. According to Dunlop & Shanks (32), however, propranolol antagonizes pressor effects caused by occlusion of carotid arteries in dogs only by chronic administration. A suggestion of increased sensitivity of baroreceptors during propranolol therapy in man was reported by Hansson, Zweifler, Julius & Hunyor (33). In a more recent study from the same institution (34), no evidence was obtained for any changes in baroreceptor reflex arc sensitivity during therapy with timolol. The involvement of baroreceptors in the mechanism of antihypertensive action of β-adrenoceptor blocking drugs cannot presently be excluded but should be considered unproven.

Renin Release

The effectiveness of propranolol in the treatment of hypertension was linked to its suppression of plasma renin activity and of aldosterone secretion (35, 36). Propranolol was claimed to be uniformly effective in patients with high but not low plasma renin activity (PRA). On the basis of these differential effects of propranolol, a renin profiling of patients was proposed (37). Patients with low plasma renin activity were thought to benefit more from diuretics while propranolol was recommended for treatment of patients with elevated plasma renin activity. Subsequently, another system was proposed (38) in which all patients, except the elderly or those with heart failure, bradycardia, or asthma, are treated with propranolol alone. Only in nonresponders would diuretic therapy be superimposed and in some patients, propranolol subsequently discontinued.

Other investigators failed to confirm clinical correlation between plasma renin activity and antihypertensive effectiveness of propranolol (39–43). Amery et al (43) found that antihypertensive and cardiac β-adrenoceptor blocking effects of propranolol and atenolol were correlated; both increasing in parallel fashion with the increase in the dose of β-adrenoceptor blocking drugs, while no such correlation was found between antihypertensive and plasma renin activity–lowering effects of the two drugs.

Additional evidence suggesting that the lowering of plasma renin activity is not the major mechanism of antihypertensive action of β-adrenoceptor blocking drugs includes the observation that relatively low doses of propranolol are required to reduce plasma renin activity as compared to those needed to lower arterial pressure (44) and findings that pindolol when given acutely reduces arterial pressure but elevates plasma renin activity (42). It should be concluded that overwhelming evidence suggests that lowering of plasma renin activity does not represent the only, or even the major, mechanism of antihypertensive action of β-adrenoceptor blocking drugs. The possibility cannot be excluded, however, that lowering of plasma renin activity and of aldosterone secretion may play a contributory role in the mechanism of antihypertensive action of β-adrenoceptor blocking drugs in some hypertensive patients.

Presynaptic Inhibition of Sympathetic Transmission

β-Adrenoceptor antagonists were shown to reduce responses of the isolated vas deferens and isolated rabbit ear artery preparations to field stimulation without affecting the responses to exogenous norepinephrine. It was suggested that β-adrenoceptor antagonists may have guanethidine-like properties at the sympathetic nerve endings (45–48). The effects of propranolol differed, however, in some respects from guanethidine; the effect was more

evident at lower frequency stimulation, was not complete, and was reversed at higher doses of propranolol (49, 50). The reduction of norepinephrine release by propranolol was shown in isolated guinea pig atria with sympathetic nerves and led to a proposal for the existence of a positive feedback mechanism for release of norepinephrine, which is triggered through activation of presynaptic β-adrenoceptors (51). The presynaptic mechanism mediated by β-adrenoceptors is thought to be activated by low concentrations of the transmitter and to lead to an increase of norepinephrine release per stimulus. This is in contrast to presynaptic α-receptor mechanism which is activated by high concentrations of the transmitter and leads to the inhibition of norepinephrine release. The existence of presynaptic β-adrenoceptors that control norepinephrine release in human omental arteries and veins was demonstrated by Stjärne & Brundin (52). These receptors appear to be primarily stimulated by β_2- and not β_1-adrenergic agonists and were, therefore, claimed to belong to the β_2 subgroup of adrenoceptors (53). The distribution of presynaptic β-adrenoceptors appears to vary with species and organs involved. The evidence for presynaptic effects of β-adrenoceptor blocking agents was reviewed by Weinstock (54). More recently (55), isoproterenol was shown to augment norepinephrine release from rat superior cervical ganglia grown in organ cultures; this effect was blocked by propranolol and a β_2-adrenoceptor blocking agent, butoxamine. The concept of peripheral control of adrenergic tone by β-adrenoceptor blocking agents through an action at presynaptic β-adrenoceptors is attractive, but conclusive demonstration of its importance in the mechanism of antihypertensive action of β-adrenoceptor blocking agents is not yet available.

Decrease in Enzymatic Activity in the Sympathetic Ganglia

β-Adrenoceptor blocking drugs by chronic administration to rabbits were shown to reduce tyrosine hydroxylase and dopamine-β-hydroxylase activities in superior cervical ganglia (56). Propranolol, but not its *d*-isomer, was effective at 4 mg/kg s.c. twice daily for 6 or 24 days. Significant inhibition of both enzymes was also obtained with metoprolol, acebutolol, and practolol. It is presently unclear whether a decrease in the activity of these enzymes is the result of a direct inhibitory action of β-adrenoceptor blocking drugs on the enzymes or a consequence of reduction in preganglionic nerve activity caused by central β-adrenoceptor blockade. Decentralization of superior cervical ganglia was, in the same report, shown to reduce the activity of both enzymes. Whatever the mechanism, the reduced activity of the two enzymes in the superior cervical ganglia can be expected to reduce the availability of the neurotransmitter for release. The reduced availability of the neurotransmitter after treatment with β-adrenoceptor blocking drugs was suggested by experiments with isolated portal veins of spontaneously

hypertensive rats. Chronic treatment with metoprolol or propranolol was shown to reduce the contractile responses to field stimulation in these preparations (57). It is therefore likely that reduction in the tyrosine hydroxylase and dopamine-β-hydroxylase activities in the peripheral sympathetic nervous system contributes to the antihypertensive effectiveness of the β-adrenoceptor blocking drugs but does not necessarily represent an initial mechanism of action.

Restoration of Vascular Relaxant Activity

It was proposed by Amer (58) that chronic β-adrenoceptor blockade may enhance the responsiveness of adenyl cyclase–relaxation complex to known mediators of vasodilatation, e.g. histamine, PGE_2. Enhanced relaxation of vascular smooth muscle would be expected to counterbalance adrenergic vasoconstriction and lead to normalization of arterial pressure. This hypothesis was based on the assumptions that vascular β-adrenoceptors are coupled in one subunit with receptors for other vasoactive substances and that in hypertension, catecholamines reduce the sensitivity of the whole receptor subunit through continuous interaction with their receptors. The blockade of β-adrenoceptor would therefore be expected to enhance the responsiveness of other receptors to various endogenous vasodilators. This hypothesis was developed as a result of an original experimental observation showing that in various forms of chronic hypertension in rats, the sensitivity of β-adrenoceptors to stimulation by agonists is reduced (59, 60). This hypothesis deserves careful consideration by other investigators. Unfortunately, it is based on too many assumptions; this makes its experimental verification and general acceptance in the near future unlikely.

SIDE EFFECTS AND HEMODYNAMIC PROPERTIES

The clinical use of β-adrenoceptor blocking drugs in hypertension was the subject of numerous recent reviews (8, 61–66) and symposia (67–71). The advantages of β-adrenoceptor blocking drugs include effectiveness in the majority of hypertensive patients, relative freedom from side effects, particularly from postural and exercise hypotension, disturbances in electrolyte balance, as well as conceivable long-term benefits in reducing the incidence of ischemic heart disease. Their disadvantages are their side effects which are either related to β-adrenoceptor blockade, e. g. bradycardia, bronchospasms, or unrelated to their β-adrenoceptor blocking action and possessed only by some drugs of this class.

The side effects and contraindications for β-adrenoceptor blocking drugs were reviewed by Lydtin (72). The most severe side effects of β-adrenoceptor blockade include heart failure, bronchospasm and A-V conduction

defects. The reported incidence of side effects with β-adrenoceptor blocking drugs varies considerably from one report to the other and with individual drugs. In a series of 390 patients on propranolol, Zacharias (73) reported 14.4% incidence of dose-limiting side effects and 9.7% of prohibitive side effects leading to withdrawal of the drug. Fatigue, bronchospasm, cold extremities, and "vivid" dreams were among commonly reported side effects. Comparing the incidence of side effects of atenolol with those of propranolol, Zacharias et al (74) concluded that the incidence of dose-limiting side effects with atenolol is identical with that for propranolol while the incidence of prohibitive side effects is lower (2.2 vs 9.7%). In general, the side effects with β-adrenoceptor blocking drugs are clearly lower than with other antihypertensive drugs (75) but still represent a limiting factor in their widespread use in the treatment of hypertension.

The occasional development or worsening of heart failure in patients receiving β-adrenoceptor blocking drugs is generally attributed to myocardial depressant action of these drugs. β-Adrenoceptor blocking drugs depress myocardial contractility by two different mechanisms. The first mechanism is a consequence of their therapeutic action—decrease in sympathetic control of myocardial function. The second mechanism is a direct myocardial depressant effect, prominent with drugs known to have membrane stabilizing effects, e.g. propranolol (76–78) and negligible with drugs with little or no membrane stabilizing activity, e.g. timolol (79), sotalol (80), or nadolol (81). The direct myocardial depressant action of propranolol is not seen in dogs unless the dose of propranolol exceeds 1–2 mg/kg i.v. (82). This is still of some concern clinically since propranolol is occasionally used at daily oral doses up to 640 mg (83–86). The mechanism of direct negative inotropic action of propranolol is likely to involve inhibition of microsomal uptake and binding of Ca^{2+} as demonstrated for canine cardiac microsomes (87) or sarcolemma of rat heart (88). Inhibition of sarcolemmal Ca^{2+}- and Mg^{2+}-ATPase activities may also explain the direct cardiac depressant activity of propranolol (88). The acute hemodynamic effects of β-adrenoceptor blocking agents vary considerably between drugs of various groups and are dependent on their secondary effects.

The hemodynamic effects of propranolol in hypertension were reviewed by Tarazi & Dustan (26). In the initial stage of therapy with propranolol, the drug consistently lowered cardiac output and increased peripheral vascular resistance without fall in arterial pressure. With continuous therapy, the cardiac output remained lowered while peripheral vascular resistance returned to control or even below control levels. Brundin et al (89) demonstrated that the acute hemodynamic effects of propranolol administered intravenously are largely abolished by chronic administration of the same drug. These authors administered propranolol, 0.2 mg/kg i.v., to 14 male

patients with moderate essential hypertension and measured various hemodynamic parameters. In 8 of these patients, an identical hemodynamic study was repeated after 2–9 months of oral therapy with propranolol. The first intravenous injection of propranolol produced a significant reduction in oxygen uptake, heart rate, cardiac output, stroke volume and increased systemic and pulmonary vascular resistance. After long-term therapy with propranolol (160–640 mg/day) and a 3-day drug-free interval, propranolol (0.2 mg/kg i.v.) had no significant effect on the same hemodynamic parameters. Only after exercise was there still an increase in ventricular filling pressure. The authors explained their findings with physiological adaptation to acute reduction of heart rate and cardiac output which led to less frequent and weaker stimuli to the baroreceptors and reduction of the afferent discharge frequency in the depressor nerves. With chronic propranolol therapy, a physiological adaptation is thought to occur and to persist even when the drug is metabolized and excreted.

β-Adrenoceptor blocking agents of group 4 of the first division have acute hemodynamic effects in some respects similar to those of propranolol. They lower cardiac output and heart rate and elevate peripheral vascular resistance. In a recent hemodynamic study with timolol in man, the left ventricular ejection rate was first reduced but returned to control level in spite of continuous administration of the drug, whereas propranolol is known to maintain reduced left ventricular ejection rate (90). The reduction in cardiac output following chronic treatment with timolol was seen in most studies (90–92) but not by Franciosa et al (93), who found that after 5 weeks of continuous therapy with timolol cardiac output returned to control levels.

The β-adrenoceptor blocking drugs with intrinsic sympathomimetic activity have a lesser tendency to decrease cardiac output or elevate peripheral vascular resistance. The hemodynamic effects of alprenolol and propranolol were compared at single i.v. doses in hypertensive patients. Both drugs reduced arterial pressure and heart rate. Alprenolol had a less depresssant effect on cardiac output than propranolol and unlike propranolol, did not increase systemic vascular resistance (94). Also, practolol by single intravenous administration had little effect on the cardiac index in resting volunteers (95). Pindolol, even by long-term oral therapy, decreased peripheral vascular resistance in patients with essential hypertension (96).

A cardioselective β-adrenoceptor blocking agent, metoprolol, considered to be free of intrinsic sympathomimetic action, tended to reduce peripheral vascular resistance by chronic administration (97). Another cardioselective agent, atenolol, after one year of therapy reduced arterial pressure, heart rate, and cardiac output and increased stroke volume while peripheral vascular resistance remained unchanged (98, 99).

β-Adrenoceptor blocking agents with intrinsic sympathomimetic activity and vasodilator action (bunitrolol and penbutolol) have little or no effect on cardiac output in acute experiments. Bunitrolol (100–102) reduced peripheral vascular resistance in animals and man. Also, in patients with coronary artery disease, bunitrolol did not decrease cardiac output (103, 104). Penbutolol was found to have vasodilator activity probably not mediated by intrinsic sympathomimetic stimulation (6) and was active as an antihypertensive agent in man (105).

Labetalol is the first drug with clearly manifested β- as well as α-adrenoceptor blocking properties (3). The interaction of other β-adrenoceptor blocking drugs with vascular α-adrenoceptors, however, was reported (106, 107) and blockade of α-adrenoceptors is likely to be responsible for acute vasodilator activity of some β-adrenoceptor blocking drugs. Pharmacological evaluation of another α- + β-adrenoceptor blocking agent (RMI 81,968) was recently described (108). A concern was expressed that the postural hypotension related to α-adrenoceptor blocking action of labetalol may severely limit its clinical use (109). Most of the clinical studies suggest, however, that this concern was not justified; the drug is well tolerated and the orthostatic effect is mild. Cardiac output is unchanged after 7–10 days therapy with labetalol; mean arterial pressure, heart rate, and peripheral vascular resistance are significantly reduced (110). Also, by single intravenous dose, the acute hypotensive effect of labetalol in man was not accompanied by any significant changes in cardiac output (111). In hypertensive patients in an upright position, labetalol may decrease heart rate, stroke volume, cardiac output, and peripheral vascular resistance (112). The hemodynamic effects of labetalol were compared with those of hydralazine and propranolol combination and found to be particularly attractive in the management of acute hypertensive crisis (113, 114).

The clinical indications for β-adrenoceptor blocking drugs in the treatment of hypertension vary considerably from country to country. According to Waal-Manning (8) 60% of patients attending Dunedin Hypertension Clinic are being treated with β-adrenoceptor blocking drugs, which are the drugs of choice for most hypertensive patients free from heart failure or asthma. In the USA, experience is largely limited to propranolol which is used primarily in patients in which the goal level of arterial pressure has not been reached with a thiazide diuretic after 2–3 weeks of therapy (64). In some patients β-adrenoceptor blocking agents may not be sufficiently effective alone; additional use of diuretics and/or vasodilators will be required. Such combination therapy is rapidly gaining acceptance in the treatment of moderate or severe hypertension.

CONCLUSIONS

In spite of numerous hypotheses discussed above, the mechanism of antihypertensive action of β-adrenoceptor blocking drugs should still be considered largely unknown. The common denominator in most of the discussed hypotheses is the reduction in sympathetic tone induced by β-adrenoceptor blockade. There is less agreement on the site of action leading to a decrease in the sympathetic tone. Neither the central effect on catecholaminergic neurons nor the peripheral effect on presynaptic β-adrenoceptors at sympathetic nerve endings, nor an indirect effect through afferent pathways, can be excluded as possible sites of antihypertensive action of β-adrenoceptor blocking drugs. It is also conceivable that more than one site of action is involved and the multiplicity of the mechanisms is responsible for a gradual development of an antihypertensive effect free from orthostatic hypotension.

The future developments in the field of β-adrenoceptor blocking drugs will undoubtedly lead to drugs acting selectively on a subgroup or subgroups of various β-adrenoceptors. Relatively selective β-adrenoceptor blocking drugs with a lesser tendency to produce bronchospasm, e.g. metoprolol or atenolol, are already available. Absolute specificity for β_1-adrenoceptors will be achieved with new drugs if medical need will justify such development. The subdivision of β_1-adrenoceptors into those mediating positive chronotropic and inotropic effects is presently controversial. If there is even a slight structural difference in the receptors mediating these two effects, drugs that block preferentially positive chronotropic effects of sympathetic stimulation with little or no effect on positive inotropism will be developed. Mepindolol may represent a step in this direction (115). If the negative dromotropic action of β-adrenoceptor blocking drugs is mediated by still another subgroup of β-adrenoceptors, drugs free of the negative dromotropic action are likely to be found. Further elucidation of the nature of β-adrenoceptors controlling renin release may lead to selective drugs which would lower plasma renin activity without general β-adrenoceptor blockade. The decrease in cardiac output or heart rate is no longer considered the sine qua non of β-adrenoceptor blockade. β-Adrenoceptor blocking drugs that reduce peripheral vascular resistance, do not affect cardiac output, and have little or no effect on resting heart rate are already available and may prove to be useful not only in the therapy of hypertension but also in the treatment of myocardial infarction. The existence of presynaptic β_2-adrenoceptors at the sympathetic nerve endings was demonstrated in man; their physiological significance in the control of the transmitter release and of arterial pressure remains to be proven. Development of specific inhibitors

of these receptors may lead to β-adrenoceptor blocking drugs with a novel pharmacological profile. The future developments of new β-adrenoceptor blocking drugs are likely to reflect our ability to differentiate among various subgroups of β-adrenoceptors and to select those subgroups whose selective inhibition would produce the greatest therapeutic benefits.

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