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Alpha-Adrenergic Blockers: Mechanism of Action, Blood Pressure Control, and Effects on Lipoprotein Metabolism

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Summary: The sympathetic nervous system plays a major role in the pathogenesis of essential hypertension and is mediated by the α and β receptors. The α receptor is divided into two types, α_1 and α_2, based on response to epinephrine and norepinephrine. α_1-Adrenergic receptors have a high affinity for drugs such as prazosin, doxazosin, and terazosin, which act to reduce blood pressure by selective blockade of the receptor. These agents provide a rational approach to the treatment of hypertension by correcting elevated total peripheral resistance, the fundamental hemodynamic abnormality in essential hypertension. In contrast, early α-adrenergic receptor blockers nonselectively blocked both α_1 and α_2 receptors and were unsuitable as antihypertensive agents because they induced tachycardia and patients developed a tolerance to them rapidly. α_1-Adrenergic blockers also have beneficial effects on plasma lipoproteins, tending to decrease levels of triglycerides and cholesterol and increase levels of high-density lipoprotein (HDL) cholesterol and the HDL cholesterol/total cholesterol ratio. β-Adrenergic blockers, such as propranolol and atenolol, have been shown to have an adverse effect on the lipid profile by tending to increase levels of triglycerides and decrease HDL cholesterol. A number of mechanisms contribute to these effects, in particular, adrenergic modulation of lipoprotein lipase and the triglyceride secretion rate. Doxazosin has been shown to increase the activity of LDL receptors, which may be partly responsible for its beneficial effect on plasma lipids and lipoproteins. Doxazosin is different from other α_1-adrenergic inhibitors in that its maximal hypotensive effect occurs within 5 or 6 hours after administration in acute dosing studies, making first-dose postural hypotension unlikely, and its long half-life provides 24-h blood pressure control with once-daily dosing.

Key words: hypertension, α blockers, β blockers, lipids, doxazosin, prazosin, terazosin

Introduction

The pathogenesis and maintenance of essential hypertension has been associated with a number of factors, but hyperactivity of the sympathetic nervous system plays a major role. A manifestation of this hyperactivity is a generalized increase in total peripheral resistance, the fundamental hemodynamic abnormality in essential hypertension.[1] This abnormality appears even in patients who have no evidence of increased peripheral resistance at rest, but who, on exercise, demonstrate inappropriately high systemic resistance at a given level of increase in cardiac output.[2] Other mechanisms prominent in the development of systemic hypertension include increased vascular sensitivity to catecholamines or to other vasoactive substances, hyperactivity of the renin–angiotensin–aldosterone system, or a reduced level of local or circulating vasodilator substances.[3]

The actions of the sympathetic nervous system are mediated by either of two receptor types, known as α or β. These receptors are defined by their responses to stimulation by catecholamines: α-adrenergic receptor sites respond primarily to epinephrine and norepinephrine and less so to isoproterenol; the converse is true of β-adrenergic receptors.[3] The α-adrenergic receptors are further subdivided into two distinct types: α_1, most of which are located postjunctionally on the vascular smooth muscle cell, and α_2, which are located prejunctionally on the sympathetic nerve ending (Fig. 1).[4] Blockade of the α_1-

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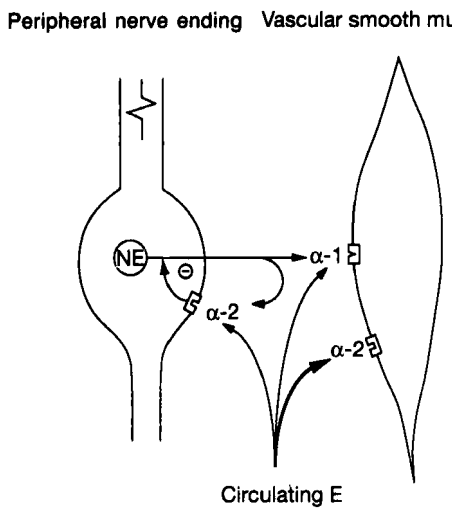

FIG. 1 Schematic representation of the α-adrenergic receptor subtypes on peripheral nerve endings (presynaptic) and vascular smooth muscle (postsynaptic). Contraction of vascular smooth muscle is mediated primarily by α_1 receptors, whereas α_2 receptors located on peripheral nerve endings inhibit norepinephrine (NE) release, thereby providing local feedback control of sympathetic vasoconstriction. Recent data indicate that some vascular postsynaptic receptors are of the α_2 subtype. [Modified from Colucci and Braunwald, *Cardiovasc Clin* 14, 39 (1984)].

adrenergic receptor results in relaxation of vascular smooth muscle and a reduction in blood pressure.

The prejunctional α_2-adrenergic receptor is quite different from the α_1-adrenergic receptor and is involved in the maintenance of vascular tone by mediating the release of norepinephrine. When the prejunctional α_2-adrenergic receptor is stimulated by norepinephrine, additional release of norepinephrine is inhibited.[3] Release of norepinephrine may also be reduced by norepinephrine or epinephrine entering the synaptic cleft from the bloodstream.[3] Blockade of the α_2-adrenergic receptor results in an opposite effect; namely increased release of norepinephrine. The prejunctional α_2-adrenergic receptor, therefore, forms part of a feedback loop that maintains sympathetic activity and subsequent vascular tone.

The α-adrenergic receptors also differ in their specificities for antagonist agents. The α_1-adrenergic receptors have a high affinity for drugs such as prazosin, doxazosin, and terazosin, and a low affinity for drugs such as clonidine or yohimbine. The converse is true for α_2-adrenergic receptors: extremely low affinity for prazosin and doxazosin and a high affinity for clonidine or yohimbine.[3]

Sensitivity of Alpha$_1$-Adrenergic Receptor Blocking Agents for Alpha$_1$-Adrenergic Receptors

α-Adrenergic receptor blockers were the first agents to be used as antihypertensive agents. Early examples of these agents are phenoxybenzamine and phentolamine, which are nonselective α-adrenergic receptor blockers. These agents block both the postjunctional receptor on the vascular smooth muscle cell, which is desired to reduce blood pressure, and the prejunctional receptor on the sympathetic nerve ending. The increased levels of norepinephrine resulting from α_2-adrenergic blockade may attenuate the desired postjunctional blockade, thus decreasing the degree of blood pressure reduction. Furthermore, the increase in norepinephrine in the systemic circulation may result in tachycardia and tremulousness.[3] These early agents were clinically unsuitable for use in antihypertensive therapy because of their tendency to induce tachycardia and rapid tolerance buildup.[2]

A different mechanism of action is at work with selective α-adrenergic receptor blockers. These agents selectively block the α_1-adrenergic receptor but do not affect the prejunctional α_2-adrenergic receptors. Consequently, unwanted increased levels of norepinephrine are avoided and thus undesirable cardiac and systemic effects of increased norepinephrine release are circumvented. The use of a selective α-adrenergic receptor blocker makes physiologic and therapeutic sense in the management of hypertension.

The different physiologic effects of selective versus nonselective α blockade in a blood-perfused dog kidney preparation can be seen in Figure 2. In this study,[2] prazosin, injected into the blood supply of a blood-perfused dog kidney preparation, did not increase overflow of norepinephrine when compared with control; phentolamine, however, significantly increased norepinephrine overflow when compared with control ($p<0.001$). Furthermore, prazosin, unlike phentolamine, does not potentiate the effects of sympathetic nerve stimulation. When

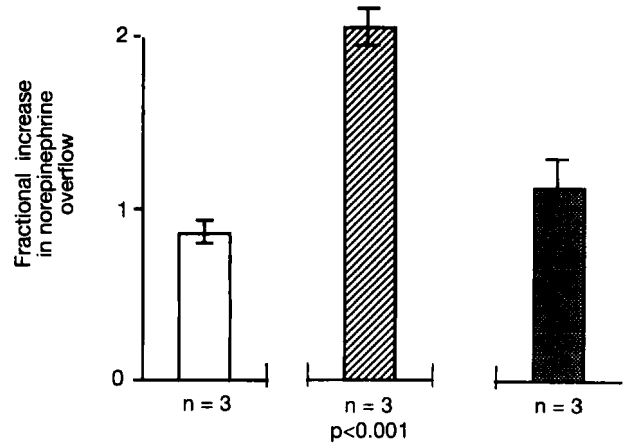

FIG. 2 Effects of phentolamine and prazosin on stimulation-induced norepinephrine overflow in isolated blood-perfused dog kidney. □ Control; ▨ intra-arterial phentolamine 0.5 mg; ■ intra-arterial prazosin 0.5 mg. [Modified from Davey, *Am J Cardiol* 59, 18G (1987), Ref. 2.]

cardiac sympathetic nerves in the dog were stimulated to increase heart rate, prazosin did not potentiate the stimulation, whereas phentolamine increased the effect.[2]

Doxazosin and terazosin have been shown to have a similar α_1-adrenergic receptor selectivity as prazosin. In fact, when the affinity for α_1- and α_2-adrenergic receptors among doxazosin, prazosin, and phentolamine were compared in a rabbit pulmonary artery, doxazosin was shown to have greater selectivity than prazosin for the α_1-adrenergic receptor as opposed to the α_2-adrenergic receptor.[2] At concentrations $> 10^{-6}$ M, prazosin caused an increase in efflux of tritiated norepinephrine. Doxazosin, however, at concentrations $< 10^{-4}$ M had no effect on efflux of norepinephrine (Table I). It is unclear if these differences have any clinical relevance.

Hemodynamic Effects of Alpha$_1$-Adrenergic Receptor Blockers in Hypertensive Patients

Recent studies in humans suggest that postjunctional α_2-adrenergic receptors in resistance vessels significantly contribute to the maintenance of vascular tone resulting in hypertension.[5] Selective α_1-adrenergic receptor blockers, such as prazosin, doxazosin, and terazosin, inhibit adrenergically dependent vascular tone without disrupting overall sympathetic function, thus offering significant clinical advantages over earlier nonspecific agents. Because postjunctional α_1-adrenergic receptors located on arteriolar smooth muscle are the major determinants of sympathetically mediated vascular tone, selective blockade with α_1-adrenergic receptor blockers is a rational approach to lowering blood pressure by correcting elevated total peripheral resistance, the major hemodynamic defect in essential hypertension.[6]

This effect was demonstrated in a study of 14 patients with moderate essential hypertension who received intravenous injection of doxazosin 0.5–1 mg over 3 minutes.[7] Mean resting supine arterial pressure after 1 h was lowered by 8% from baseline at rest supine, by 12% at rest sitting, and by 10% on a bicycle ergometer (at 100 W). Mean total peripheral resistance index was reduced by 5% at rest supine, 9% at rest sitting ($p < 0.01$), and 14% during bicycle ergometric exercise ($p < 0.001$). Heart rate increased by 5%, indicating that only slight reflex tachycardia occurred despite the rapid reduction in blood pressure. Cardiac index remained unchanged at rest and increased by 4% with exercise ($p < 0.05$), primarily as a result of the minor increase in heart rate. The investigators concluded that doxazosin normalizes central hemodynamics, both at rest and during exercise, in hypertensive patients. Doxazosin reduced blood pressure by reducing total peripheral resistance without reducing cardiac output.

In this same study,[7] patients were placed on once-daily oral doxazosin (mean dose 6.5 mg; range 2–16 mg). After one year of treatment, reductions in total peripheral resistance index of 19%, 20%, and 18% were seen at rest supine, at rest sitting, and following bicycle ergometric exercise, respectively. Resting supine cardiac index increased slightly but was unchanged at rest sitting and following bicycle ergometry. Although the doses employed in the acute and chronic phases of the study were not the same, the investigators felt that a similar acute and chronic hemodynamic response was achieved with doxazosin.

TABLE I Effects of antagonists at pre- and postjunctional α_1-adrenergic receptors in superfused strips of rabbit pulmonary artery

	Prejunctional activity EC_{40} pre (nmol)	Postjunctional activity EC_{40} post (nmol)	Selectivity ratio pre/post
Doxazosin	>30,000	50	>600
Prazosin	1,300	4.5	289
Phentolamine	120	1,000	0.12

Abbreviations: EC_{40} pre = concentration producing a 40% increase in overflow to nerve stimulation; EC_{40} post = concentration producing a 40% decrease in the contractile response.
Source: Modified from Davey, *Am J Cardiol* 59, 18G (1987), ref. 2.

Renal Effects of Alpha$_1$-Adrenergic Receptor Blockers in Hypertensive Patients

Since selective α_1-adrenergic receptor blockers do not affect α_2-receptor-mediated negative feedback control of norepinephrine release from sympathetic nerve terminals, these agents effectively lower blood pressure without markedly affecting renal function. This was demonstrated in a clinical study of hypertensive patients who received doxazosin in either stepwise doses of 0.1, 0.3, 1, 3, and 10 μg/kg/min with each infusion lasting 10 minutes or fixed doses of 1 μg/kg/min.[8] A third group served as controls and were infused only with glucose. Only minor changes in renal perfusion and renin secretion were seen in patients receiving doxazosin. The investigators concluded that although α_1-adrenergic receptors in the kidney can influence renal vasoconstriction and inhibition of renin release, the quantitative impact is minor.

Clinical Experience with Alpha$_1$-Adrenergic Receptor Blockers in Hypertension

In clinical trials, α_1-adrenergic receptor blockers have been shown to be efficacious antihypertensive agents. Prazosin, doxazosin, and terazosin have been shown to be effective as initial therapy,[9] and in comparison with diuretics[10] and β-adrenergic blockers.[11] In clinical studies

ranging from single-dose administration to long-range studies of more than a year, these agents have been found to be effective antihypertensive agents when given as monotherapy, together with concomitant medications,[12] and in comparison with other antihypertensive agents, such as diuretics, other α_1-adrenergic blockers,[13-16] and β-blockers.[17,18] Table II is a summary of clinical trials comparing doxazosin and other α_1-adrenergic receptor blockers with each other, β-adrenergic blockers, and thiazide diuretics (Table II).[13-17,19-26]

The pharmacodynamic profile of doxazosin in humans differs from that of prazosin in that the maximal hypoten-

TABLE II Summary of double-blind parallel group therapeutic trials comparing different α_1-adrenergic antagonists with each other and with other antihypertensive drugs in patients with mild or moderate essential hypertension

Reference	No. of patients	Dosage (mg/day)	Duration (weeks)	Mean decrease in SBP/DBP		Response rate (%)[a]
				Supine	Standing	
Comparisons with α_1-adrenoceptor antagonists						
Cox *et al.* (1986)[20]	110[b]	D 1-16	9–64	7/9	9/10	60
		P 1-20		6/9	7/10	61
Hayduk and Schneider[14]	55	D 1-16	18	18/15	17/16	73
(1987)		T 1-20		14/14	10/9	64
Torvik and Madsbu[13]	104	D 1-16	52[c]	14/13	11/10	
(1987)		P 1-20		8/9	6/6	
Deger[15] (1986)	174	T 2-20	14	6/7	9/18	
		P 2-20		3/5	8/6	
Comparisons with β-adrenoceptor antagonists						
Baez *et al.* (1986)[21]	12	D 1-16	14	6/9	10/13	
		A 50-100		12/10	8/10	
Cox *et al.*(1986)[20]	312[b]	D 1-16	9–64	5/7	7/8	60
		A 50-100		10/12	9/11	60
	66	D 1-16	9–64	10/13	13/13	60
		M 100-200		23/16	12/14	70
	52	D 1-16	9–64	4/8	7/9	60
		N 40-160		8/10	6/9	54
Frick *et al.* (1986)[22]	143	D 1-16	20–58	7/6	11/8	45
		A 50-100	32	16/12	17/13	50
Frick *et al.* (1987)[23]	91	D 1-16		8/7	11/9	
		A 50-100		13/10	13/10	
Nash *et al.* (1987)[17]	129	D 1-16	16	9/8	11/10	
		A 50-100		13/11	12/12	
Ott *et al.* (1987)[24]	126	D 1-16	28	3/6	9/8	
		A 50-100		20/14	10/9	
Comparisons with thiazide diuretics						
Cox *et al.* (1986)[20]	131[b]	D 1-16	9–64	8/15	13/14	
		H 25-100		13/14	15/14	
Hjortdahl *et al.* (1987)[25]	115	D 1-16	28–32	7/8	13/11[d]	60
		H 25-100		18/10	16/10	51
Trost *et al.* (1987)[26]	106	D 1-16	32	14/12	18/13	
		H 25-100		14/11	17/11	
Luther *et al.* (1989)[16]	194	T 1-10	14	8/11	8/9	
		M 5		15/12	15/9	

[a]Response rate = % with satisfactory response defined as decrease to < 90 mmHg diastolic and a reduction of at least 5 mmHg from baseline or a decrease of ≥ 10 mmHg.

[b]Number of patients treated with other drug only; a similar (unstated) number received doxazosin.

[c]A non-blind comparison.

[d]Effect significantly greater with hydrochlorothiazide for supine systolic pressure only.

Abbreviations: D=doxazosin; P=prazosin; T=terazosin; A=atenolol; M=metoprolol; N=nadolol; H=hydrochlorothiazide; M=methyclothiazide; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Source: Modified from Young and Brogden, *Drugs* 35, 525 (1988), ref. 19.

sive response to a single dose (intravenous or oral) of doxazosin occurs much later (5–6 h) than that of prazosin (0.5–1 h).[27] Thus, doxazosin may be less likely than prazosin to cause symptomatic postural hypotension after the first dose. The short (2.5 h) half-life of prazosin requires multiple daily dosing. The half-lives of doxazosin and terazosin are significantly longer: 10–12 h in single-dose studies. In multiple-dose studies that measured plasma concentrations beyond 24 h, the half-life of doxazosin was 22 h.[28] The pharmacokinetics of doxazosin appear to make the drug suitable for once-daily administration that may achieve 24-h blood pressure control in many hypertensive patients.[28]

This 24-h blood pressure control of doxazosin was demonstrated in a recent study of 40 patients with mild to moderate hypertension who were treated with doxazosin (mean final daily dose in 20 patients of 13.1 mg) or placebo.[29] In the 9th week of double-blind treatment, blood pressure measurements were taken throughout the day during 24-h hospitalization and compared with similar measurements taken during the 2-week placebo run-in period. Inpatient results showed that doxazosin significantly reduced mean standing and supine diastolic blood pressure at most intervals, including 24 h after administration ($p < 0.05$ vs. placebo). For outpatients, mean 24-h postdose reductions from baseline with doxazosin were 12.9/11.9 mmHg for standing systolic/diastolic blood pressure and 9.9/10.0 mmHg for supine blood pressure. Figure 3 shows that the reductions from baseline for standing and supine blood pressure were significantly greater with doxazosin than with placebo ($p=0.002$ and $p=0.001$, respectively). Furthermore, heart rate in both the standing and supine positions was unchanged 24 h after administration of doxazosin.

In a multicenter comparative study of doxazosin and terazosin as once-daily therapy for hypertension, therapeutic success, defined as a decrease in standing diastolic blood pressure to <90 mmHg and a reduction of at least 10 mmHg in standing diastolic blood pressure, was achieved in 19 of 26 (73%) patients receiving doxazosin and in 18 of 28 (64%) patients in the terazosin group.[14] Patients tended to require lower doses of doxazosin than terazosin to achieve therapeutic success. Results are summarized in Table III.

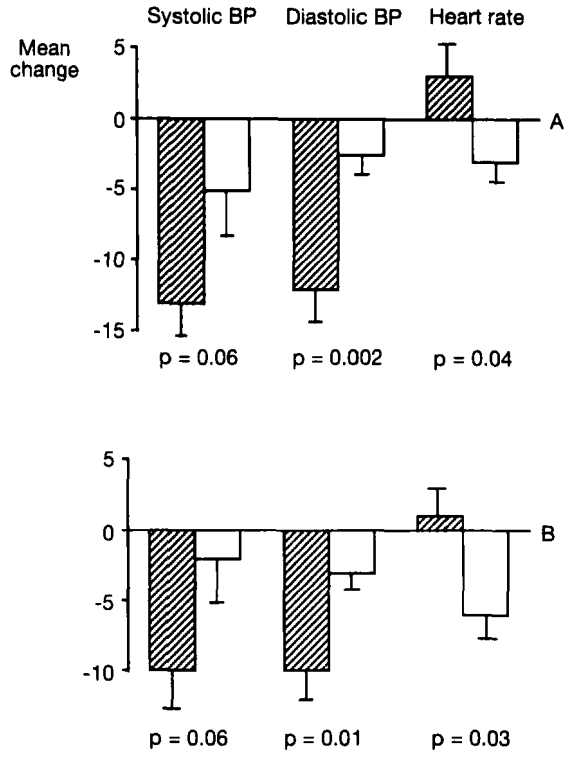

FIG. 3 Outpatient results: Mean 24-h postdose changes (±SEM) in (A) standing and (B) supine blood pressure (mmHg) and heart rate (beats/min) at the end of 9 weeks of treatment with doxazosin (▨) or placebo (□). [Modified from Smyth *et al.*, *Eur J Clin Pharmacol* 34, 613 (1988)]

The Effects of Adrenergic Agents on Plasma Lipoprotein Metabolism

In addition to its contribution to the development of hypertension, the sympathetic nervous system affects lipoprotein metabolism. The adrenergic influence on lipoprotein metabolism may be of primary importance in the development of atherosclerosis and may mediate changes in lipids during long-term treatment with certain antihypertensive agents. β-Adrenergic blockers, such as propranolol, atenolol, and metoprolol, have been shown to increase plasma triglyceride levels and decrease high-density lipoproteins (HDL) without generally affecting low-density lipoproteins (LDL).[30] Labetalol, which is an α- and β-adrenergic blocker, appears to be lipid neutral. Prazosin not only lacks adverse effects on plasma lipids, but has been shown to increase HDL levels, decrease total cholesterol and triglyceride levels, and increase the HDL cholesterol/total cholesterol ratio.[30] Similar beneficial effects have been seen with doxazosin (see section below).

A number of mechanisms have been proposed to explain the influence of adrenergic antagonists on lipid metabolism.[31] The first involves adrenergic modulation of lipoprotein lipase, a key enzyme involved in the breakdown of triglycerides into free fatty acids, via constriction of the precapillary sphincter tone in microcirculatory vessels. Blockade of the α-adrenergic pathway leads to increased capillary flow and greater availability of lipoprotein lipase, which ultimately results in decreased plasma levels of triglycerides and triglyceride-rich lipoproteins. In contrast, β-adrenergic blockers (e.g., propranolol) inhibit lipoprotein lipase activity, leading to reduced clearance of triglycerides (Fig. 4).[32] Prazosin has been shown to increase lipoprotein lipase activity in hyper-

TABLE III Doxazosin compared with terazosin: patient response by dose

	Doxazosin (n=26)		Terazosin (n=28)		
Final dosage (mg daily)	Patients considered therapy successes no. (cumulative %)	Patients controlled no. (cumulative %)	Final dosage (mg daily)	Patients considered therapy successes no. (cumulative %)	Patients controlled no. (cumulative %)
1	4 (21)	4 (24)	1	2 (11)	2 (13)
2	11 (79)	9 (77)	2	4 (33)	4 (36)
4	3 (95)	3 (94)	5	8 (77)	8 (88)
8	1 (100)	1 (100)	10	3 (94)	1 (94)
16	0	0	20	1 (100)	1 (100)
Total response	19/26 (73)	17/26 (65)		18/28 (64)	16/28 (57)
Dose summary					
Mean	2.4	2.5		5.6	5.0
Median	2	2		5	5

Source: Modified from Hayduk and Schneider, *Am J Cardiol* 59, 95G (1987), Ref. 14.

tensive patients.[33] In a study of 15 patients with hypertension, terazosin was shown to have no adverse effects on lipid metabolism.[34]

Effect on VLDL and HDL Metabolism

Adrenergic mechanisms affect several factors that influence synthesis and secretion of very low-density lipoproteins (VLDL), including stimulation of synthesis by the uptake of chylomicron remnants, plasma free fatty acids, glucose metabolites, and norepinephrine. Additional factors include inhibition via hormonal manipulation by epinephrine, insulin, and glucagon.[31] Studies in humans show that during periods of hypoglycemic stress, production of VLDL and triglycerides is reduced.[35] The extent to which the triglyceride levels are reduced correlates with urinary epinephrine release but not norepinephrine. This suggests that β-adrenergic receptors decrease the production of VLDL, which agrees with the increase in VLDL levels seen with propranolol, a β-adrenergic blocker.[29] This was demonstrated in a study in which rats received prazosin, propranolol, or no treatment (control).[36] Hepatic triglyceride secretion rate in rats receiving prazosin was lower than in control rats and those treated with propranolol. Triglyceride secretion rate correlated with plasma triglyceride concentration. These data also suggest a direct effect of α- or β-adrenergic blockers on the triglyceride secretion rate in the liver.

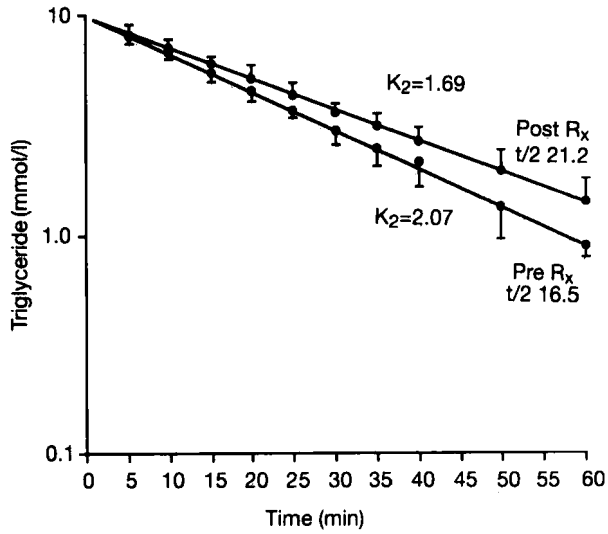

FIG. 4 Intralipid clearance levels for 25 patients before and after 3 months of therapy with a β-blocking agent. (*$p<0.05$; **$p<0.01$) [Modified from Day *et al. Am J Med* 74, 94 (1984)]

A similar study was performed comparing the effects of doxazosin and propranolol on lipoprotein lipases and plasma lipids in rats.[37] In rats fed a normal diet, doxazosin increased heart lipoprotein lipase activity by 14%, while propranolol decreased it by 20% ($p<0.05$ compared with the doxazosin group). In rats fed a cholesterol-rich diet, doxazosin still increased heart lipoprotein lipase activity by 5%, adipose tissue lipase by 14%, and hepatic lipase by 13% (Fig. 5). Propranolol decreased all three parameters by 12%, 20%, and 9% respectively. The difference between the two treatment groups reached statistical significance for heart and hepatic lipase ($p<0.05$). Although neither agent had an effect on total plasma cholesterol or triglyceride content in the cholesterol-fed rats, the doxazosin group had significant-

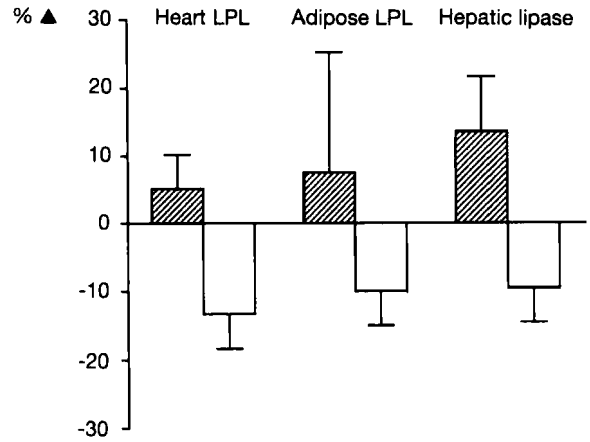

FIG. 5 Percentage change in heart and adipose tissue lipoprotein lipase and hepatic lipase activity in cholesterol-fed rats during treatment with doxazosin (▨) and propranolol (□). Mean ±SEM lipase activities per heart, left fat pad, or liver are expressed as a percentage of a mean control value. Control values were: heart lipoprotein lipase 899 mU, n=5; adipose tissue lipoprotein lipase 180 mU, n=5; hepatic lipase 3120 mU, n=15. [Modified from Jansen and Baggen, *J Cardiovasc Pharmacol* 10 (suppl 9), S16 (1985), Ref. 37.]

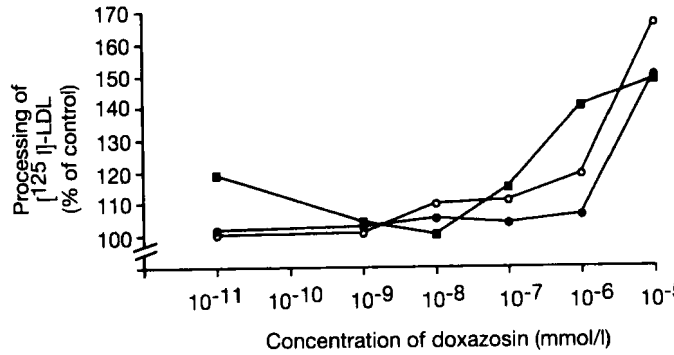

FIG. 6 Effect of different concentrations of doxazosin on the processing of [^{125}I]low-density lipoprotein (l-LDL) by cultured skin fibroblasts. Fibroblasts were cultured in a monolayer in medium with 10% fetal calf serum. Different concentrations of doxazosin were added before 24 h of incubation at 37°C. Values for association of [^{125}I]LDL at 4°C (—■—), association of [^{125}I]LDL at 37°C (—○—), and degradation of [^{125}I]LDL (—●—) were obtained as described in the Materials and Methods section in reference 35. The values (mean of 3 parallels) are expressed as % of the values obtained with control medium. [Modified from Leren, *Acta Pharmacol Toxicol* 56, 269 (1985), Ref. 38.]

ly increased HDL cholesterol levels (+24%) when compared with controls and the propranolol group ($p<0.05$).

The same mechanism that decreased triglyceride secretion in this study may also explain the increase seen in HDL cholesterol levels. The decrease in hepatic lipase activity was partially reversed by doxazosin, and since hepatic lipase may play a role in uptake of HDL cholesterol by the liver, this action may be enhanced by the α_1 inhibition induced by doxazosin and not by β-adrenergic inhibition. The investigators concluded that doxazosin may produce changes in lipids and lipoproteins that are favorable to more efficient cholesterol transport to the liver and out of the body. They noted that this interpretation needed scientific confirmation and that whether these effects were mediated by adrenergic receptors or hormones is still unknown.[37]

Effect on LDL Receptors

The lipoprotein most clearly identified with the development of atherosclerosis is the LDL particle. Levels of LDL are controlled by the number and activity of LDL receptors located on liver and other tissue cells and by the rate of endogenous LDL synthesis. LDL is primarily derived by catabolism of VLDL. Mechanisms by which adrenergic antagonists affect production of VLDL may also be responsible for changes in LDL levels.[31] Data from a study with doxazosin suggest that blockade of the α-adrenergic pathway can promote or increase clearance of LDL.[38] In this study, the effect of doxazosin on LDL receptor activity was studied in cultured skin fibroblasts at confluence. Figure 6 shows that at concentrations of 10^{-6} to 10^{-5} M, doxazosin increased processing of [^{125}I]LDL. Doxazosin (10^{-5} M) significantly increased the LDL receptor activity determined as association or degradation of [^{125}I]LDL at 37°C. After incubation with doxazosin, the two LDL receptor indices increased by 57% (association) and 45% (degradation). A slight increase in LDL receptors independent of the processing of [^{125}I]LDL was seen. The mechanism underlying the increase in LDL receptor activity is unknown.

Since doxazosin increases LDL receptor activity, it would be expected that the drug would reduce LDL and total cholesterol levels. In one study, 20 weeks of antihypertensive therapy with doxazosin in 42 patients with mild to moderate essential hypertension resulted in significant decreases in total plasma cholesterol (8.9%) and LDL cholesterol (16.9%) over pretreatment values ($p<0.01$).[39]

Effect of α_1-Adrenergic Blockers on Plasma Lipoproteins

Other studies show that a consistent pattern has emerged in the effect of α_1-adrenergic blockers on lipoproteins in clinical trials.[13,17,18,22-26,40] Doxazosin therapy is associated with reductions in levels of triglycerides and total cholesterol and with increases in the levels of HDL cholesterol and the HDL cholesterol/total cholesterol ratio. A total of 746 patients with evaluable lipid data at

TABLE IV Overall comparative effect of doxazosin versus placebo in double-blind titration studies, mean baselines,[a] and changes with treatment for serum lipids

Treatment	Number of patients	Total triglycerides		Total cholesterol		HDL cholesterol		HDL/Total cholesterol	
		Baseline	Percent change	Baseline	Percent change	Baseline	Percent change	Baseline	Percent change
Doxazosin	142	119.1	−9.1	224.01	−1.2	51.0	7.6	0.228	8.9
Placebo	155	119.8	−3.0	221.2	0.6	50.3	4.8	0.228	4.1
Significance		$p<0.05$		$p<0.05$		NS		$p<0.05$	

[a]Baseline calculated as a geometric mean; percent change derived from geometric mean of final/baseline. Significant difference between treatments from ANOVA on changes in logarithms of values. NS=not significant.
Source: Data on file, Pfizer, Inc., New York, Ref. 27.

baseline and the end of treatment has been included in controlled studies.[27] Of these 746 patients, 142 were treated with doxazosin in placebo-controlled studies. Table IV shows favorable trends for doxazosin relative to placebo for all four lipid parameters. Significant reductions in total triglycerides and total cholesterol levels ($p<0.05$) and a significant increase in the HDL cholesterol/total cholesterol ratio ($p<0.05$) were seen. HDL cholesterol levels tended to increase, but this trend did not reach statistical significance. As mentioned above, a possible mechanism for these favorable changes in blood lipids may be increased LDL receptor activity induced by doxazosin. Similar trends were seen in a comparative study of terazosin with the diuretic methychlothiazide.[16] Patients randomized to terazosin experienced a 5% drop in LDL plus VLDL after 14 weeks of therapy while there was a 7% increase in patients receiving the diuretic. HDL was unchanged in the terazosin group and down 1.3% in the methychlothiazide group. Total cholesterol, triglycerides, and total cholesterol/HDL ratio also decreased in the terazosin group.

Conclusions

Although blockade of α-adrenergic receptors has long been an approach to lowering blood pressure, it was only with the introduction of selective α_1-adrenergic receptor blockers that this mechanism could be clinically utilized. Selective blockade of postjunctional α_1-adrenergic receptors results in inhibition of postjunctional α_1-receptor-mediated vasoconstriction without affecting the α_2-receptor-mediated negative feedback control of norepinephrine release from sympathetic nerve terminals. α_1-Adrenergic receptor blockers are effective in reducing blood pressure without reflex tachycardia or other adverse effects on the sympathetic nervous system. These agents act hemodynamically by reducing elevated total peripheral resistance, the fundamental hemodynamic abnormality in essential hypertension. Adrenergic mechanisms that act upon plasma lipoprotein metabolism favor α_1-adrenergic blockers, which, contrary to β-adrenergic blockers, do not adversely affect the lipid profile and may even induce beneficial changes in blood lipids.

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