NEW PERSPECTIVES ON α-ADRENERGIC RECEPTORS

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NEW PERSPECTIVES ON α-ADRENERGIC RECEPTORS

In 1980 the authors of more than 200 publications listed α-adrenergic receptors as the central focus of their manuscripts. Why is there great interest in an apparently traditional subject such as this? Three-four years ago α-adrenergic receptors were found to be of two pharmacologically distinct types. One was the classical α-adrenergic receptor which mediates arteriolar constriction and the other served, for some peculiar reason, mostly inhibitory roles in many neuroendocrine functions. However, these functional differences are not the basis for identifying or classifying these two types of receptors. Instead, they are identified according to the selectivity of agonists or antagonists for activation or inhibition of a particular receptor type. Phenylethylamine and methoxamine have a high degree of selectivity for activating α_1 receptors. Prazosin and WB4101 are selective for inhibiting α_1 receptors. Clonidine, tramazoline and the aldomet metabolites are agonists selective for α_2 types of α-receptors. Yohimbine, rauwolscine etc. are selective blockers of α_2 receptors. For reasons to be discussed here this morning there are a number of new selective α_2 blocking agents under development at this time.

A second factor contributing to the interest in α-adrenergic receptors is the development of radioligand binding techniques which permit biochemical studies of these functional units. We use highly radioactive receptor agonists and blockers which quantify binding affinities and count receptor numbers per cell or per mg of membrane

protein. These numbers are deficient or excessive in some disease states and respond to a variety of stimuli which alters the organ response to regulatory hormones.

I would like to introduce the subject of α receptors by describing recent studies of the α_1 selective blocker prazosin and the α_2 selective agonist clonidine in the particularly difficult problem of progression of renal disease in severely hypertensive patients.

Progression of renal disease is the complication of severe hypertension which has not been adequately controlled by use of propranolol, diuretics and minoxidil (1) (appendix I). Patients treated with this regimen have an hypernoradrenergic state and β-blockade resulting in an α-adrenergic dominance. There are two types of α-adrenergic receptors in the kidney, α_1 and α_2, which would be expected to be excessively activated. α_1-Receptors mediate arteriolar constriction. α_2-Receptors are concentrated in the cortex in proximal tubules, the site of increased sodium reabsorption resulting from sympathetic nerve stimulation (vide infra). In recognizing these severe alterations of neuroendocrine functions as well as the known roles of blood pressure per se in morbidity and mortality we have two long-range approaches to this problem of progression of renal disease. One is the study of suppression of, or blockade of the sympathetic nervous system peripherally or secondly to simply further reduce blood pressure in these extremely severely hypertensive patients.

Incidentally, the study of this problem is analogous to other investigations such as familial hypercholesterolemia in that we are dealing with a small group of patients whose disease is genetically determined. The disease is present in an exaggerated form which permits unique types of observations to be made which are frequently applicable to the millions of patients with less severe forms of the disease. Also, this model permits the study of a full range of drug dose-response for individual drugs when combined with other drugs. This is of course not possible in patients with milder hypertension even though these drugs are, in fact used in combination in mild and intermediately hypertensive patients. Thirdly, the natural history of the disease is telescoped in time to such an extent that we can often tell in a much shorter period of time the degree of efficacy of therapeutic interventions. This is particularly true in the fascinating complication of progression of renal disease.

Fifteen of thirty-two severely hypertensive patients with "benign" severe hypertension had progression of renal disease during long term follow-up in our clinic at Parkland. Of these 15 patients, nine progressed to require hemodialysis. Of the other 17 patients with "benign" refractory hypertension none had progression of renal disease or actually improved (1) (appendix I).

Nephrologists in general, are not surprised that renal disease progresses in these patients. Alternatively, they have frequently found a degree of predictability concerning the time interval when dialysis

will be required. Using the simple mathematical manipulation of plotting $\frac{1}{S_{cr}}$ versus time (Figure 1) Mitch et al.(2) have found 1) that the slope of this line is nearly constant with time and characteristic for the individual patient with renal disease and 2) by extending the line for a given patient the date that dialysis will be required can be predicted with a reasonable degree of certainty.

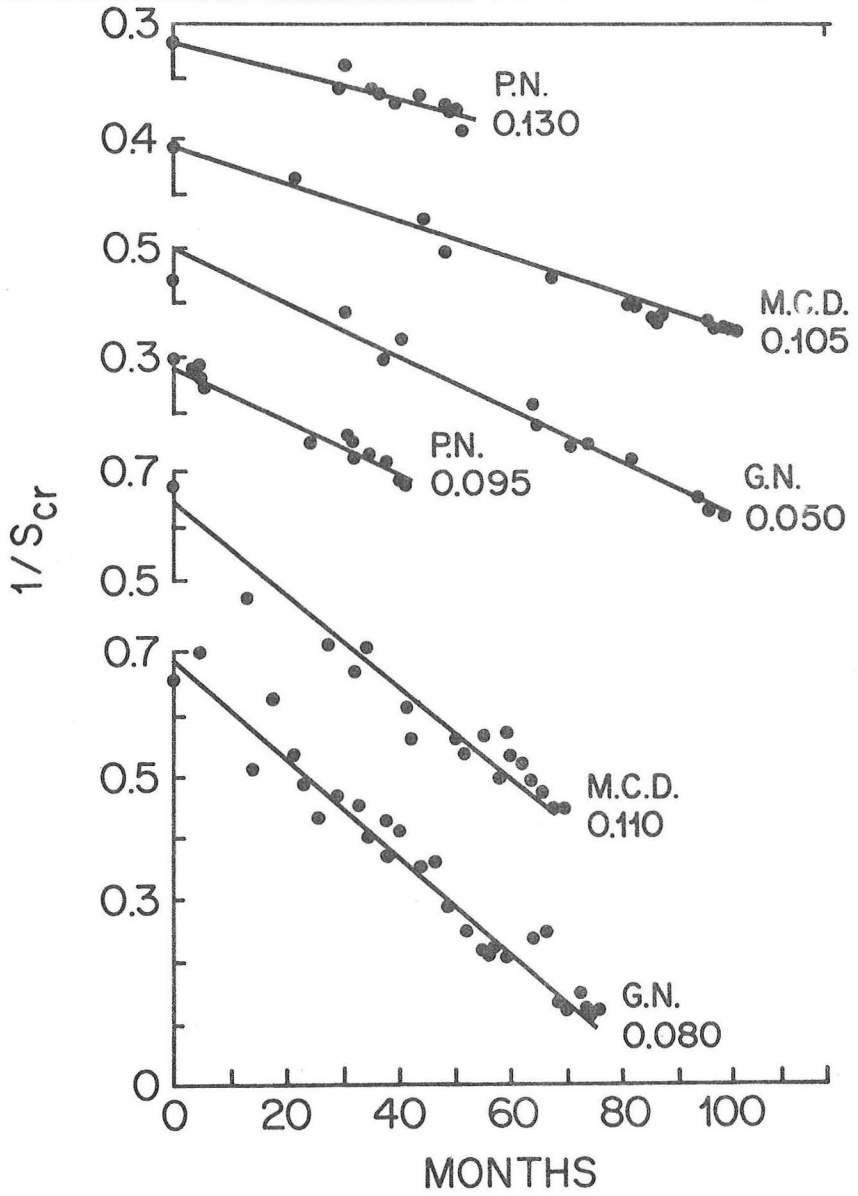

Figure 1. Straight-line pattern of progression of renal disease in individual patients. $1/S_{cr}$-reciprocal of serum creatinine concentration. Numbers below letters are the value of the reciprocal when dialysis was initiated (2).

We have found this technique of Mitch et al. to be particularly useful in monitoring the effect of therapeutic interventions on progression of renal disease in severely hypertensive patients as illustrated in figures 2 and 3.

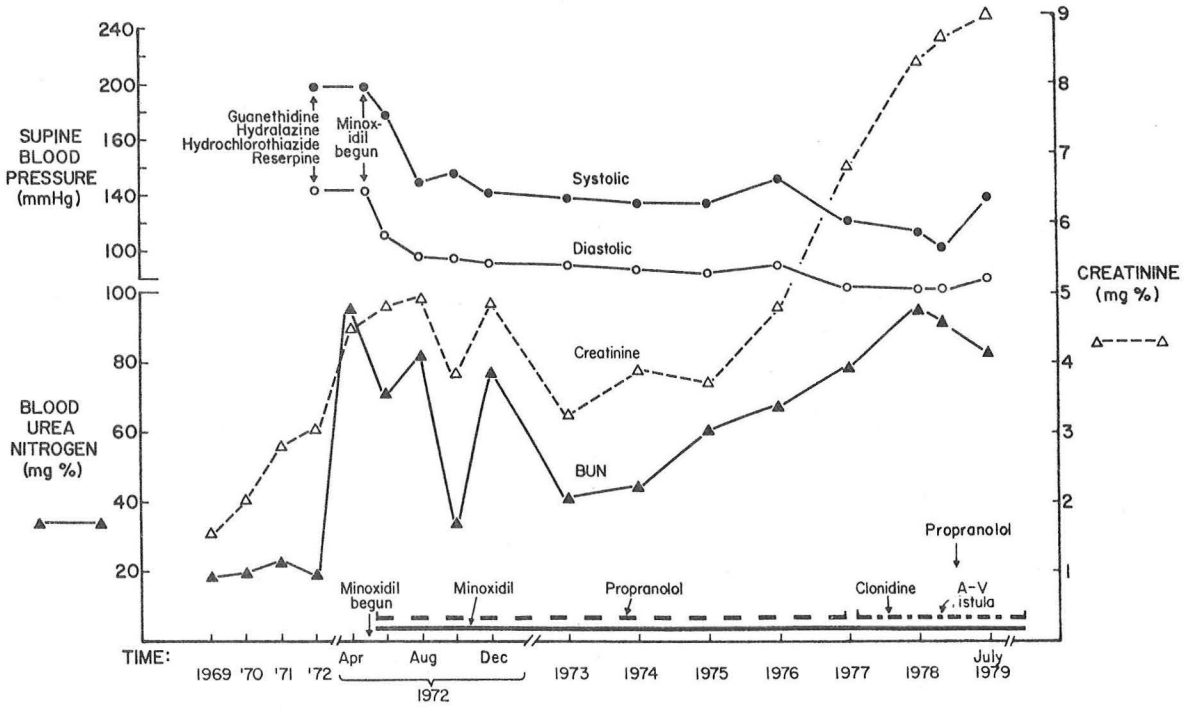

Figure 2. Clinical course of the first patient treated with minoxidil at Parkland Hospital.

Figure 2 shows the quality of blood pressure control and progress of renal disease in one of the first patients treated with minoxidil at Parkland Hospital. He was to be evaluated for bilateral nephrectory in February of 1972 to control his hypertensior and iminent complications thereof. However, during hospitalization he had a stroke, was comatose and therefore no longer a candidate for nephrectomy and chronic hemo-

dialysis. However, with minoxidil and accompanying drugs blood pressure control improved along with CNS function and he did quite well. That is, until seven years later when renal failure occurred and dialysis was required. This progression of renal disease to require hemodialysis occurred in nine other patients (1). When the rising creatinine is plotted as shown in Figure 3 it would appear that, had a catastrophy such as stroke not occurred, dialysis would have been required in approximately 13 months.

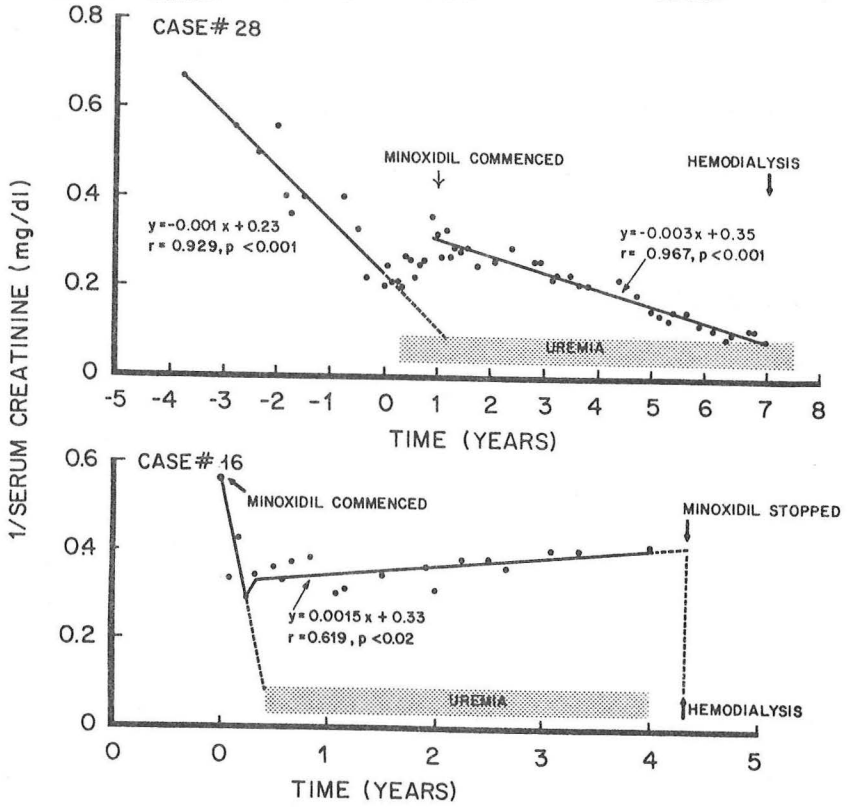

Figure 3. Examples in two patients of using $1/S_{Cr}$ in monitoring the efficacy of pharmacologic interventions on the course of renal disease. Case #28 is an example of the group (appendix I) of "benign" hypertensives whose progression of renal disease was delayed considerably by improved quality of blood pressure control. Case #16 is an example of the malignant hypertensive who has the capacity for recovery of renal function as long as blood pressure control is sustained. A third group (not shown) is the "benign" hypertensives whose renal disease does not progress or, in fact, may improve with blood pressure control.

With the achievement of a better quality of blood pressure control there was modest improvement in renal function for 1-2 years. This temporary improvement was followed by a slow and apparently relentless progression of renal disease. The referees for this manuscript pointed out that blood pressure was "controlled" in this (and other) patient(s) at 90-105 mmHg. While this blood pressure level was considerably lower than the readings during the previous four years it was still not in the range of 65-70 mmHg, the level at which blood pressure as a lethal risk factor approaches zero (3,4). Thus, one might argue that further reduction of blood pressure may provide additional protection to the kidneys and prevent progression of this renal disease. Appropriate studies are required to answer this question but the problem now is how can we acceptably sustain blood pressure in these patients at 65-70 mmHg?

We have done dose-response curves with α-receptor drugs which selectively inhibit or suppress neuroendocrine mechanisms maintaining blood pressure as illustrated in Figure 4. The agents which we have studied are the α_1 receptor blocker prazosin and the α_2 receptor agonist, clonidine.

Clonidine reverses the vasodilatory drug induced hypernoradrenergic state as shown in Figure 5 (5). Most of the suppression of plasma norepinephrine is achieved at a dose of 0.2 mg Bid. Similarly, most of the additional blood pressure lowering was achieved with this dose of clonidine (Figure 6). While there are α_2 receptors in many peripheral organs (See below) it is believed that the major site of clonidine's

sympathetic suppressant action is in the central nervous system (6).

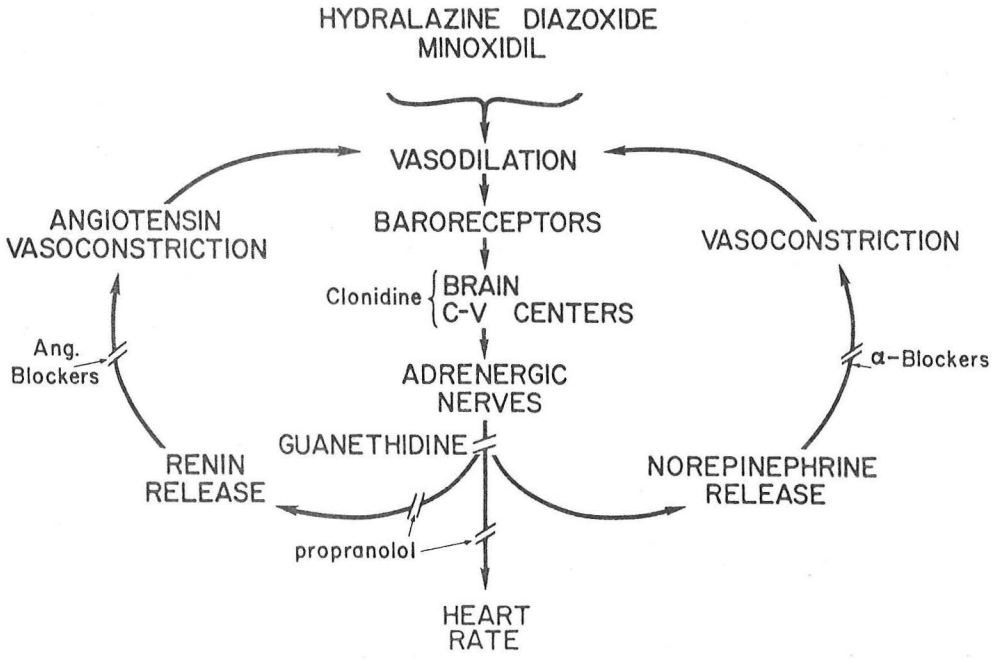

Figure 4. Alteration of neuroendocrine regulatory mechanisms by anti-hypertensive drugs.

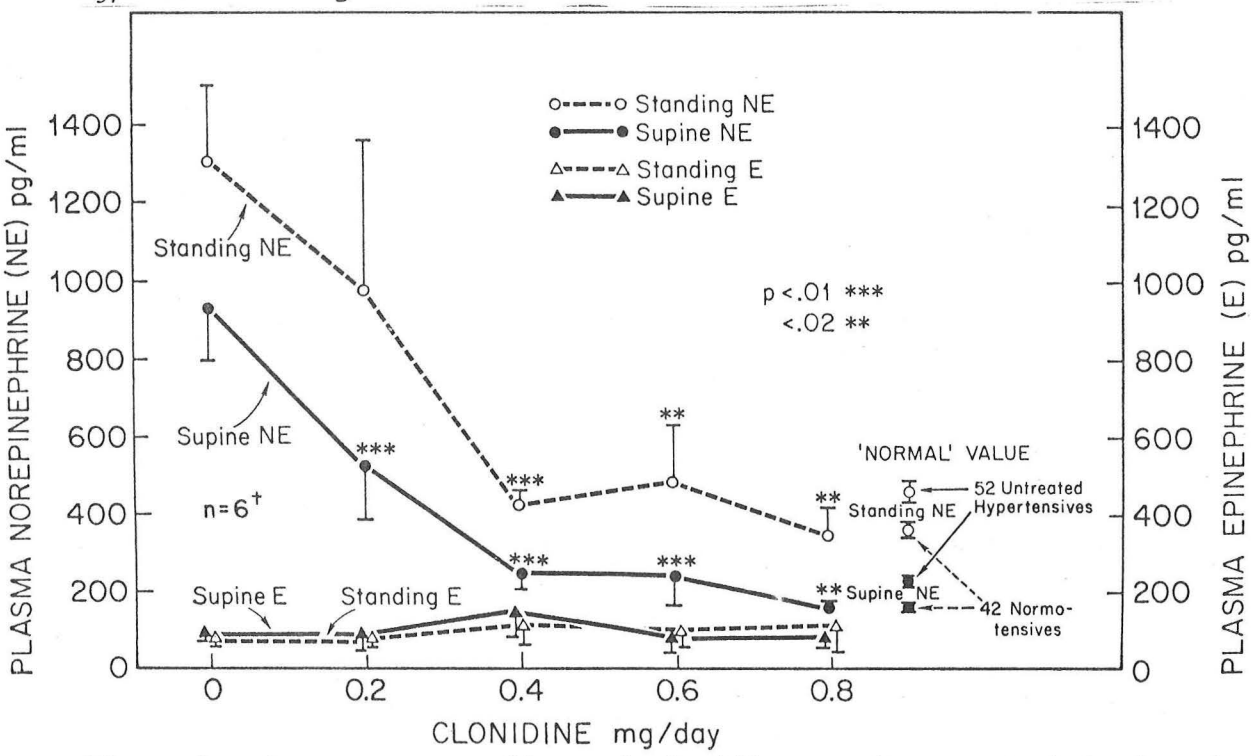

Figure 5. Dose-response effect of clonidine on plasma catecholamines in minoxidil-propranolol-diuretic treated patients (5). Minoxidil dosage was 30-40 mg/day and all drug dosages were maintained constant throughout the study except for clonidine. P values represent paired t comparison with zero cloniidne. †: n=6 at 0 through 0.4 mg, n=5 at o.6 and 0.8 mg.

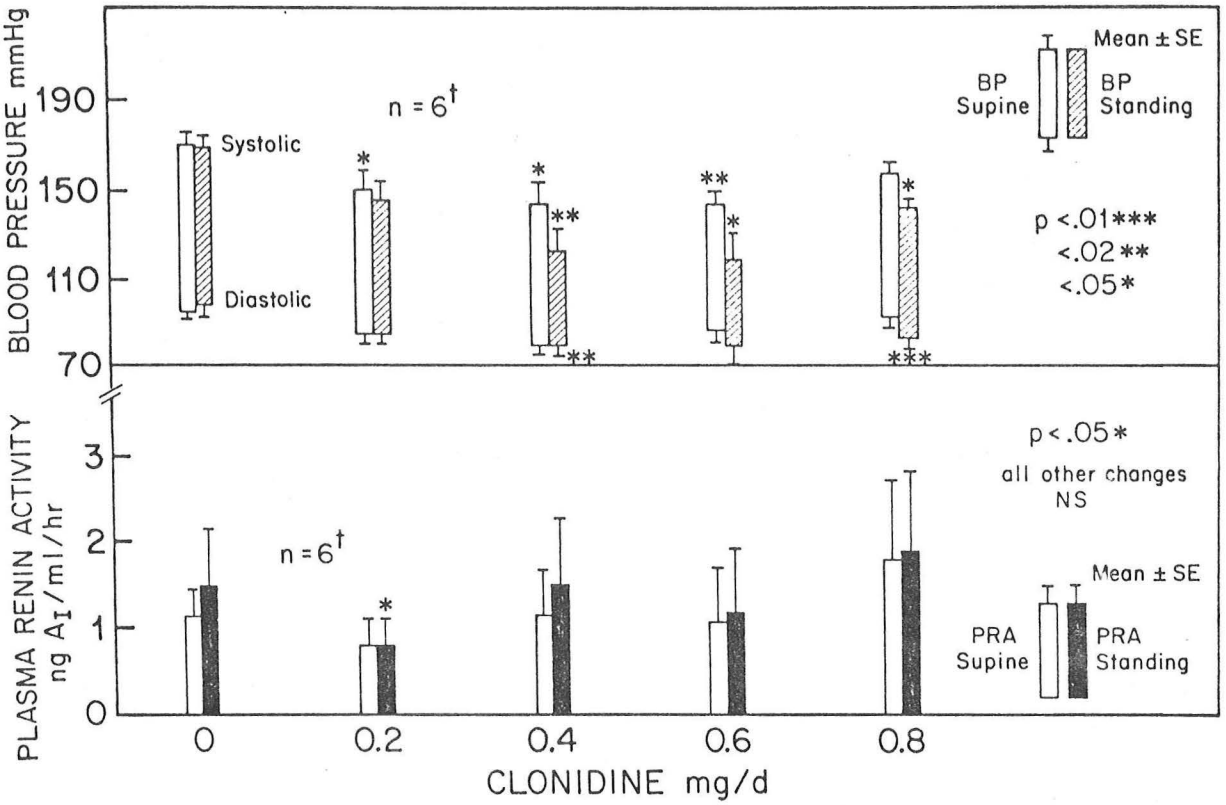

Figure 6. Dose response of clonidine on blood pressure and plasma renin activity in minoxidil-propranolol-diuretic treated patients. Minoxidil dosage was 30-40 mg/day. P values represent paired t comparison with zero clonidine. †: n=6 at o through 0.4 mg, n=5 at 0.6 and 0.8 mg.

The blood pressure lowering action of the α_1 blocker prazosin in this model is similar to and possibly even greater than clonidine (Figure 7). There is further elevation of plasma norepinephrine with prazosin but this effect reaches a plateau at relatively low doses, whereas the blood pressure lowering is greater with higher doses. Why there is a failure to increase plasma norepinephrine with these higher doses in unclear.

Thus, with the addition of these α-receptor agents further lowering of blood pressure occurs in the severely hypertensive patients.

However, it is not to the 65-75 mmHg range required to exclude blood pressure as a risk factor in the progression of renal disease in these patients. We are now doing similar studies using captopril to block angiotensin II production, expecting to achieve substantive additional blood pressure control. Possibly diuretic and other drug requirements will decrease to the extent of simplifying the drug regimens required in these patients.

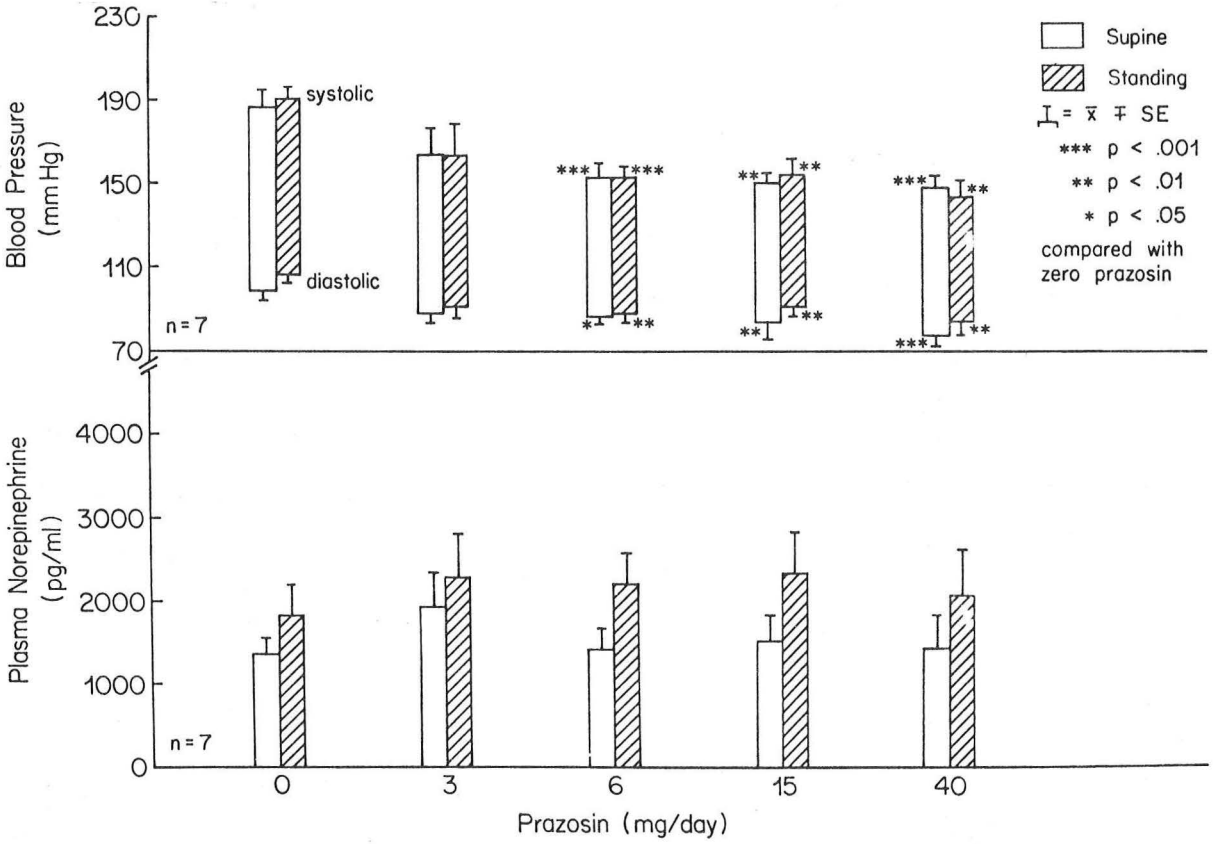

Figure 7. Dose-response of the α_1 blocker prazosin on supine and standing blood pressure and plasma norepinephrine in six minoxidil-propranolol-diuretic treated hypertensive patients.

Let me return for a moment to the "Benign" severely hypertensive patients. Those patients who had progression of renal disease during

chronic minoxidil-propranolol-diuretic therapy had higher plasma norepinephrine levels (7) than the patients whose renal disease improved or remained constant (Figure 8). Whether this norepinephrine is contributing to progression of renal disease in this select and complicated group of patients or whether it is the result of the disease process is unclear. At this time it is identified only as a risk-factor in progression of renal disease in this exclusive subset of hypertensive patients. Plasma renin activity was lower in these patients suggesting that the renin-angiotensin system is not contributing to the progression of renal disease.

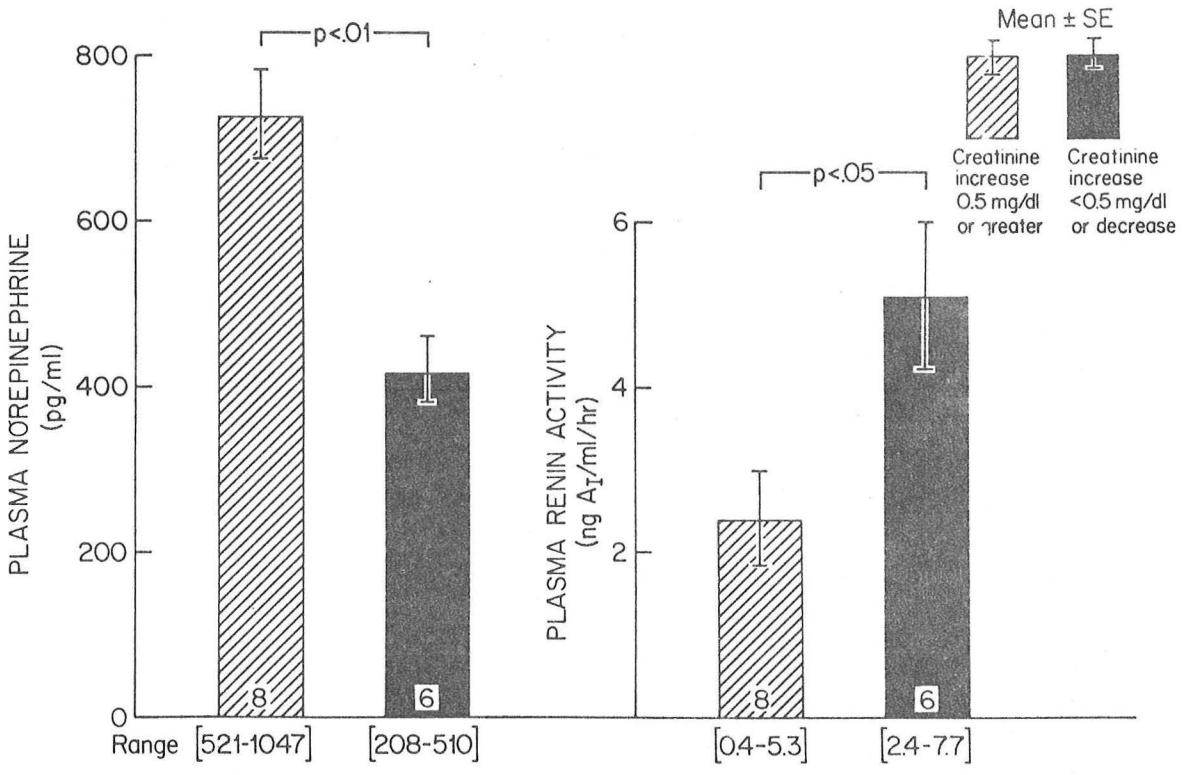

Figure 8. Plasma norepinephrine (on left) and plasma renin activity (on right) in minoxidil-propranolol treated patients whose renal disease progressed (lined bars) and those whose renal disease did not progress (solid over bars) in a 2-7 year interval. The number in the bars is the number of patients in each group (7).

About the same time that we found NE to be a renal risk factor in these patients we discovered that α-adrenergic receptors were increased in the kidneys of an animal model of essential hypertension, the spontaneously hypertensive rat (Figure 9).

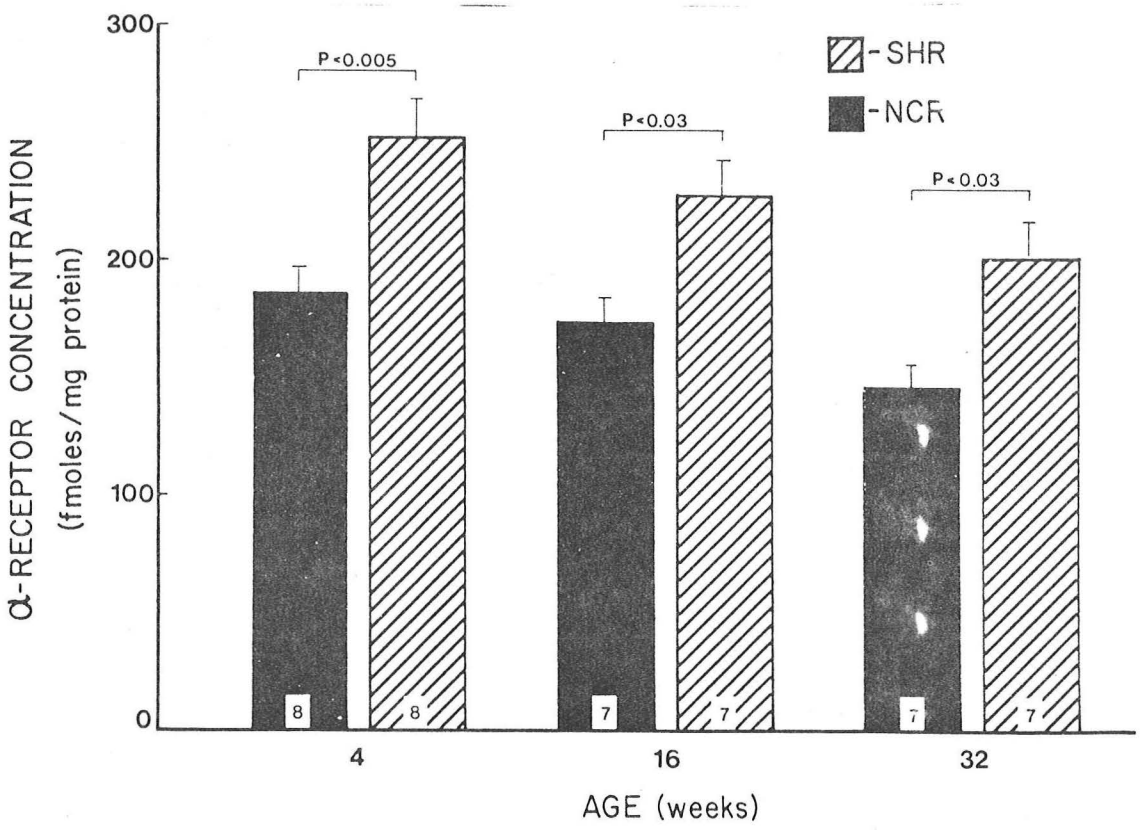

Figure 9. Total α-adrenergic receptor concentration in a membrane fraction from kidneys of SH and normotensive WKY rats determined by [^{3}H]-dihydroergocryptine binding (8).

High plasma norepinephrine levels at 4 and 16 weeks of age were coupled with this increase in total α-adrenergic receptors. Techniques at that time did not permit classification of α-adrenergic receptors into α_1 and α_2 but within the last three months we developed a technique for measuring α_2 receptors. There is an increase in both α_1 and α_2 receptors but the predominant increase is in the α_2 receptors (Figure 10).

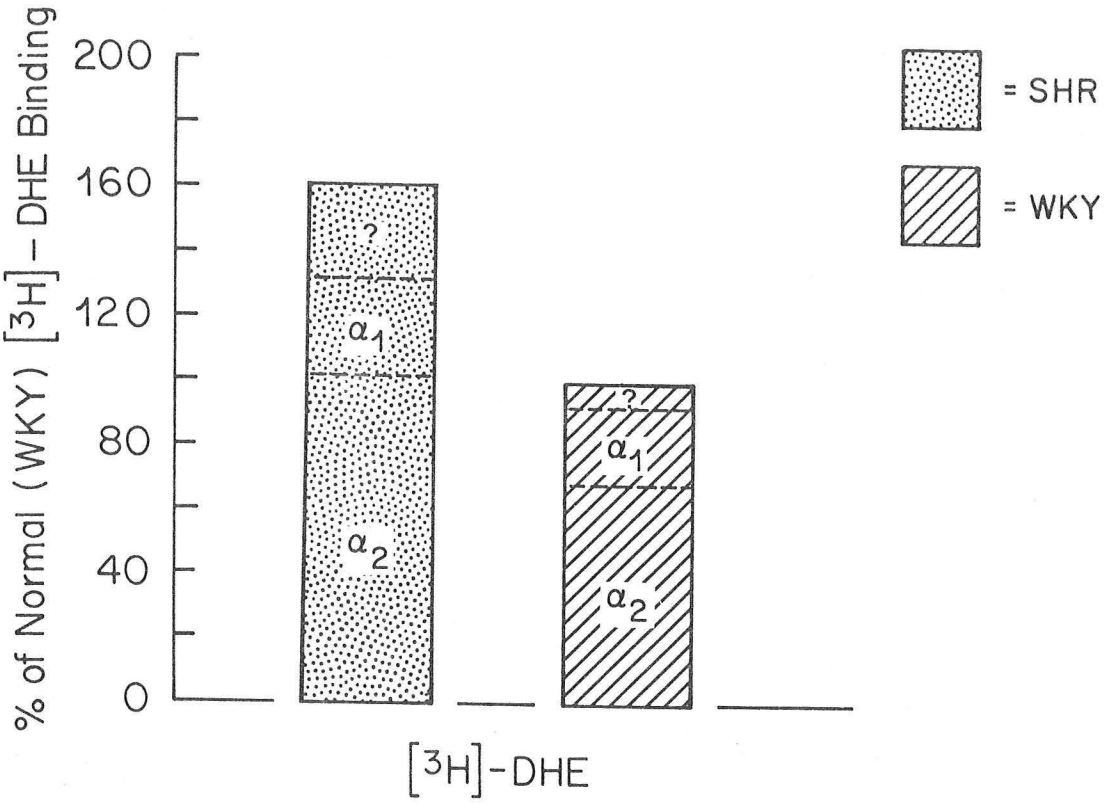

Figure 10. Total (top of columns) and α_1 and α_2 adrenergic receptors in a membrane fraction from kidneys of SH and WKY (normotensive) rats expressed in percent of normal.

Where are these α_1 and α_2 receptors in kidneys and what do they do? α_1 adrenergic receptors are located on plasma membranes of arterioles and mediate vasoconstriction (11). When the capacity (affinities) of α-adrenergic agonists or antagonists to displace [^{3}H]-prazosin from renal plasma membrane α-adrenergic receptors is plotted against their capacities to either induce (agonists) or block (antagonists) α-receptor mediated vasoconstriction in vitro the correlation approaches unity (Figure 11).

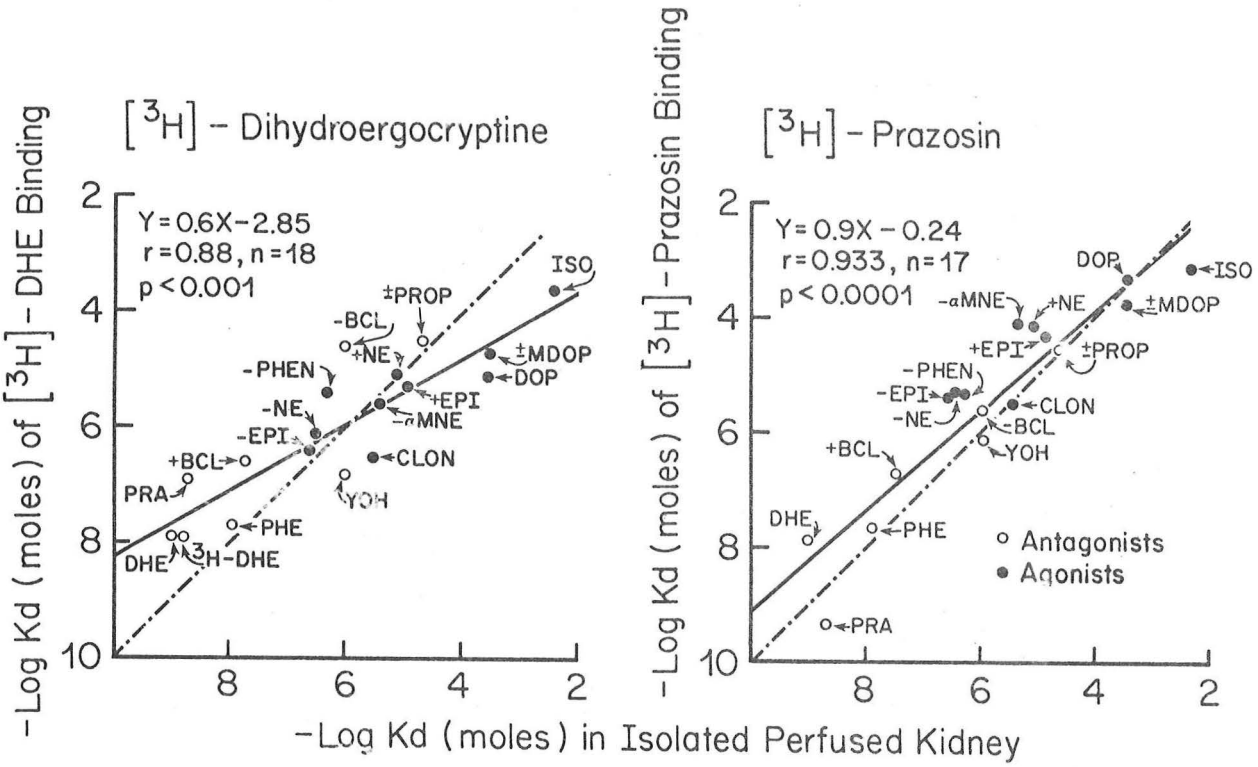

Figure 11. Correlation of vasoconstriction (X-axis) with binding to α_1 (on the right-Prazosin) or to $\alpha_1+\alpha_2$ (on the left-DHE) membrane receptors. The binding K_d is an expression of the capacity of each agent to displace ^{3}H-DHE (left) or ^{3}H-Prazosin from plasma membranes. The K_d on the X-axis is an expression of the agonist or antagonist activity of each drug.

α_2 adrenergic receptors have been demonstrated by Young and Kuhar, using autoradiographic techniques, to be located primarily in the cortex in proximal convoluted tubules (Figure 12). They incubated [^{3}H]-clonidine (α_2 agonist) or [^{3}H]-WB-4101 (α_1 antagonist) with guinea pig kidney slices. 10^{-4} M norepinephrine was used to establish blank values by excluding the radioligands from α_1 and α_2 receptors.

When α-receptors are activated in the proximal tubule, either by direct application of norepinephrine or stimulation of renal nerves,

reabsorption of sodium is enhanced (14-21). The physiologic and/or pharmacologic importance of these receptors is yet to be established. However, these preliminary findings of increased renal α_2 receptors could provide an explanation for 1) increased tubular reabsorption of sodium at given perfusion pressures in autoperfused Dahl and in spontaneously hypertensive rats and hypertensive man (22-24). 2) the requirement of small quantities of norepinephrine to demonstrate the differences between SH and normotensive perfused rat kidneys (25). 3) low renin hypertension. 4) Increased vascular sodium content of SH rats. 5) the remarkable tendency to salt and water retention in minoxidil treated patients.

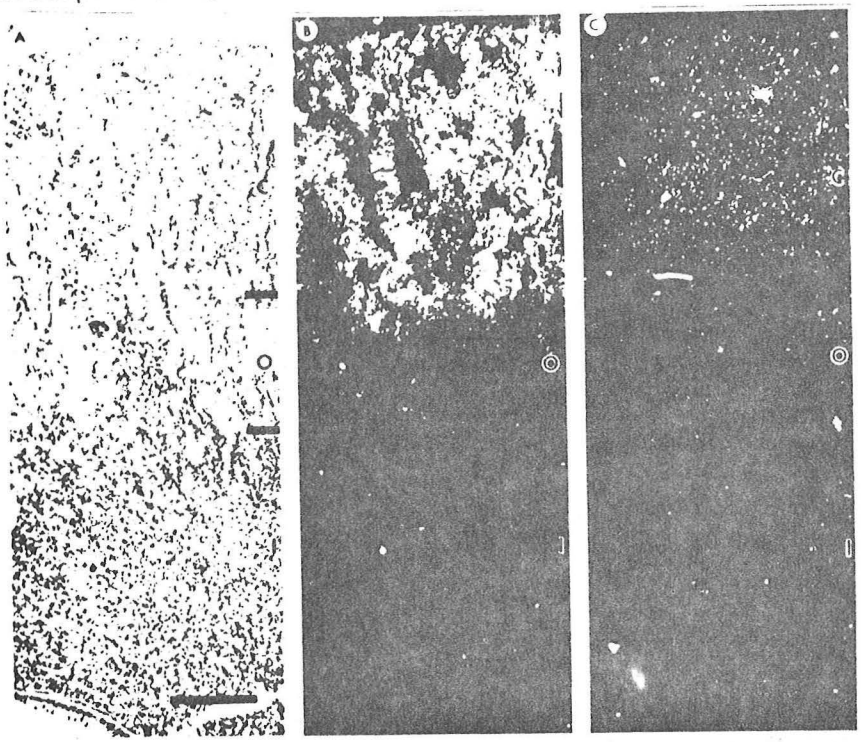

Fig. 1. α_2-Adrenergic receptors in the guinea pig kidney. The brightfield photomicrograph (panel A) shows the tissue whose receptors are shown labeled in the darkfield (panel B) with ^{3}H-clonidine. Notice the intense labeling in the renal cortex (C) which, under higher magnification, is on the proximal tubules. Negligible binding is observed in the outer (O) or inner (I) medullary zones or in the blank (panel C).

Figure 12. Autoradiographic demonstration of α_2 adrenergic receptors in renal cortex. Young and Kuhar (12).

The capacity for dietary restriction of sodium to control even severe human hypertension (26,27) could also be related to the capacity of dietary sodium to regulate renal α_2 receptors as in the Dahl strain of hypertensive rats (28).

Thus, α_1 receptors vasoconstrict and α_2 receptors probably (not yet established) enhance proximal tubular reabsorption of sodium. There is also an α-adrenergic receptor on juxtaglomerular cells which is inhibitory to renin release (29-34). While our early studies suggested (30,35) that this is an α_2 receptor,further studies are required to establish this receptor type (32) and also to determine its physiologic importance.

Before going further it would seem appropriate to briefly review the basis for classification of α-adrenergic receptors. Prior to 1977 α-receptors were classified anatomically, that is, presynaptic and postsynaptic. Post-synaptic receptors purportedly mediated vasoconstriction and presynaptic receptors were inhibitory to norepinephrine release. However, α-receptors with characteristics of "presynaptic" receptors are located postsynaptically (35,36). Thus, it was necessary to develop a functional basis for classification of α-receptors. Receptors which are most responsive to, or have higher affinities for methoxamine or phenylephrine (agonists), prazosin and WB4101 (antagonists) are α_1 receptors. Those which have relatively high affinities for clonidine, tramazoline, α-methyl norepinephrine (agonists) or yohimbine (blocker) are α_2 receptors. The naturally occurring catecholamines epinephrine and norepinephrine frequently lack specificity for an α_1

or α_2 type of receptor.

A major problem occurs in simply interpreting relative affinity sequence as described above because this approach fails to account for intrinsic activities of the various agents. Thus, comparison of efficacy ratios (i.e. EC_{20} α_1/EC_{20} α_2) eliminates this intrinsic activity variable and permits a fairly precise functional classification of receptor types (35). While this approach may be costly I see no other way to prevent hasty, arbitrary and unnecessary determinations of multiple subclassification of α adrenergic receptor types.

While many investigators have taken short-cuts by failing to take into account the intrinsic activity of the agents and others have failed to establish correlations of post receptor events there has been a great deal of progress in many areas. Let us now review several of these beginning with peripheral blood vessels.

The distribution and functional state of α-adrenergic receptors on veins and arterioles determine the hemodynamic effects of α-adrenergic blocking agents. α_1 adrenergic receptors are located on arterioles and on veins whereas α_2 receptors are primarily on veins (37-46). Prazosin an α_1 receptor blocker, for example, during chronic administration has a singular effect of decreasing arteriolar resistance with very little or no effect on veins (47). Thus, prazosin causes miminal orthostatic effect on blood pressure except with the first one or two doses when the effect can be dramatic or tragic. The latter observation suggests that

either 1) α_1 receptors ordinarily play a predominant role in maintaining venous tone until after their blockade at which time α_2 receptors assume this functional role or 2) for some peculiar reason the first dose of prazosin can block α_2 receptors in those patients susceptible to the first dose phenomenon. The first alternative is analogous to the appearance of α_2 receptors in salivary glands after administration of the sympathetic suppressant reserpine (48). A similar increase in available or functioning α_2 receptors could occur in veins after prazosin administration.

Prazosin is dramatically effective in treating heart failure during the first one or two doses. However, the hemodynamic effect from venodilation dissipates within 24 hours I suspect that this "tolerance" is due to assumption of adrenergic functioning by changes in post synaptic α_2 receptor functioning.

Phenoxybenzamine, an irreversible α-adrenergic blocking agent,also has selectivity for α_1 receptors. With the first dose of phenoxybenzamine both venous and arteriolar dilation occur and orthostasis can be severe. However, with chronic administration this drug is predominantly an arteriolar dilator (47).

Epinephrine induces platelet aggregation by an α_2 type of adrenergic receptor (47,48,49). As in several other tissues in which post-synaptic events of α_2-receptor activation have been characterized. This effect is mediated through inhibition of adenyl cyclase resulting in suppression

of cyclic AMP levels. Interestingly, clonidine and other exogenous α-receptor agonists are "partial agonists" of this receptor (53,54). That is, their maximal capacity for producing an effect are much less than that of endogenous catecholamines and they induce blockade of activation, even for epinephrine and norepinephrine. A similar partial agonist (and antagonist) activity of clonidine occurs in parotid gland cells as a possible explanation of the "dry mouth" side effect (55). Whether this interesting and complex pharmacological relationship with synthetic α_2 agonists obtains with other α_2 receptors is a question of considerable basic and clinical importance.

α_2 adrenergic receptor activation usually causes inhibitory effects (35). This inhibitory nature may be because of an anatomic-functional link between α_2 receptor mediated effects and adenyl cyclase. While there is a spectrum of agonists (see below) for adenyl cyclase activation, many organs or tissues have α_2 receptors which, when activated inhibit adenyl cyclase and thus modulate in a down regulatory way the cyclic AMP mediated functional effects.

Examples of probable α_2 adrenergic receptors inhibitory to adenyl cyclase activation are listed below. Further studies are indicated in some of the tissues which take intrinsic activities (see above) into account and the use of more specific agonists and antagonists before the α_2 nature of the receptors is assured.

Agonist for activating adenyl cyclase	Organ	Effect
Vasopressin	toad bladder (analogue of mammalian collecting duct)	Increased H_2O permeability (55)
Melanocyte stimulating Hormone	canaliculi of frog skin	dispersion of granules→darkening (56,57)
Prostaglandin E_1	platelets	agglutination (50,51)
Epinephrine	fat cells	lipolysis (58-60)
Immunologic mechanisms	mast cells	histamine release (61)
Epinephrine	pancreatic islets	insulin release (62,63)

One of the dilemmas proposed by a discussion in which a pharmacologic receptor can be demonstrated is "how and when are these receptors important". For example we know that under most circumstances blockade of the numerous β-adrenergic receptors with propranolol causes few effects. Does that mean that most β-adrenergic receptors are simply artifacts? Did they function during growth and development but play little role in normal life? Similarly, with α-adrenergic receptors we can ordinarily block α_1 adrenergic receptors using prazosin with practically no side effects except for the first dose when hypotension and syncope can be tragic.

The availability of α_2 blockers will be of particular interest for determining the pathophysiological roles of these receptors in many neuroendocrine disease processes. It is even conceiveable that in some diseases the α_2 selective blockers might affect only abnormal α_2

receptors such as those in the kidney of genetically determined hypertension.

Alternatively, of course the exciting hypotheses of today may be laid waste tomorrow. A good example is the recent enthusiasm we had for the post versus the presynaptic receptor effects of prazosin as a possible explanation for the lack of orthostatic hypotension, tachycardia and failure of ejaculation. During the last two years substantive evidence has accumulated that the unique effect of prazosin is because of its functional α_1 selectivity on arterioles and not because of any post-versus pre-synaptic selectivity (64-67).

In summary, we are in the midst of rapid advancements both pharmacologically and conceptually concerning α-adrenergic receptors and their pathophysiologic roles. α-receptors in each organ or cell can be classified by binding studies into α_1 or α_2 which classification usually correlates with pharmacologic responses.

α_1 receptors are located postsynaptically on both arteries and on veins. When they are blocked for a few hours by prazosin α_2 post-synaptic receptors appear to assume the function of α_1 receptor on veins.

α_2 receptors are present postsynaptically on many neuroendocrine systems and, in those tissues studied, have been found to exert a suppressive effect by inhibiting adenyl cyclase.

There is an increase in renal α_2 adrenergic receptors of rats which are genetically predisposed to develop hypertension. In the Dahl strain of rat these α_2 receptors are further increased by high dietary sodium. Since these proximal tubular α_2 receptors may mediate increased sodium retention this genetically determined abnormality is a promising hypothesis as an underlying hypertensive mechanism.

References

1. Mitchell, HC, Graham, RM, Pettinger, WA: Renal function during long-term treatment of hypertension with minoxidil. Comparison of benign and malignant hypertension. Ann of Int Med 93:676-681, 1981.
2. Mitch, WE, Walser, M, Buffington, GA, Lemann, J.Jr.: A simple method of estimating progression of chronic renal failure. Lancet 2:1326-1328, 1976.
3. Lew, E.: The new build and blood pressure study. Transactions of the association of life insurance. Underwriters of America 155-168, 1979.
4. Lew, E.: High blood pressure, other risk factors and longevity: The insurance viewpoint. Am J Med 55:281-294, 1973.
5. Mitchell, HC, Pettinger, WA: Dose response of clonidine on plasma catecholamines in the hypernoradrenergic state associated with vasodilator β-blocker therapy. In press. J of Cardiovas Pharmacol.
6. Haeusler, G.: Clonidine-induced inhibition of sympathetic nerve activity: No indication for a central presynaptic or an indirect sympathomimetic mode of action. Naunyn Schmiedebergs Arch Pharmacol 16:120-122, 1971.
7. Mitchell, HC, Pettinger, WA: Renal function in long-term minoxidil-treated patients. J of Cardiovas Pharmacol 2(Suppl.2):S163-S172, 1980.
8. Graham, RM, Brabson, JH, Stephenson, WH, Pettinger, WA: Increased renal alpha-adrenergic receptors in genetically hypertensive rats. Clin Res 26:363A, 1978.

9. Pettinger, WA, Sanchez, A., Gandler, T., Saiz, J., Saavedra, J.: Dietary sodium regulates abnormal renal α-adrenergic receptors in the Dahl hypertensive rat. Clin Res in press.

10. Mitchell, HC, Pettinger, WA: Dose response effect of clonidine on plasma norepinephrine in the hypernoradrenergic state of vasodilator-treated patients. Clin Res 28:817A, 1980.

11. Schmitz, JM, Sagalowsky, A., Pettinger, WA, Graham, RM: α-adrenergic receptors in the rat kidney correlation of [^{3}H] dihydroergocryptine binding with α-adrenergic stimulation and inhibition of renal vasoconstriction. Submitted for publication.

12. Young, WS,III, Kuhar, MJ: α_2-adrenergic receptors are associated with renal proximal tubules. Europ J of Pharmacol 67:493-495, 1980.

13. Chan, YL: The role of norepinephrine in the regulation of fluid abosrption in the rat Proximal tubule. J Pharmacol Exp Ther 215:65-70, 1980.

14. Gill, JR, Casper, AGT: Effect of renal alpha-adrenergic stimulation on proximal tubular sodium reabsorption. Am J Physiol 223: 1201-1205, 1972.

15. Gottschalk, CW: Renal nerves and sodium excretion. Annu Rev Physiol 41:229-240, 1979.

16. DiBona, GF: Neurogenic regulation of renal tubular dosium reabsorption. Am J Physiol 233:F73-F81, 1977.

17. DiBona, GF: Neural control of renal tubular sodium reabsorption in the dog. Fed Proc 37:1214-1217, 1978.

18. Slick, GL, Aguilera, AJ, Zambrashi, EJ, DiBona,GF, Kaloyanides, GJ: Renal neuradrenergic transmission. Am J Physiol 229:60-65, 1975.

19. Bello-Reuss, E., Colindres, RE, Pastoriza-Munoz, E., Mueller, RA, Gottschalk, CW: Effects of acute unilateral renal denervation in the rat. J Clin Invest 56:208-217, 1975.

20. Bello-Reuss, E., Pastoriza-Munoz, E., Colindres, RE: Acute unilateral renal denervation in rats with extracellular volume expansion. Am J Physiol 232:F26-F32, 1977.

21. Colindres, RE, Gottschalk, CW: Neurocontrol of renal tubular sodium reabsorption in the rat: Single nephron analysis. Fed Proc 37:1218-1221, 1978.

22. Tobian, L., Johnson, MA, Lange, J., Magraw, S.: Effect of varying perfusion pressures on the output of sodium and renin and the vascular resistance in kidneys of rats with "post-salt" hypertension and Kyoto spontaneous hypertension. Circ Res 36&37(Suppl.I): 162-170, 1975.

23. Norman, RA, Jr., Enobakhare, JA, DeClue, JW, Douglas, BH, Guyton, AC: Arterial pressure-urinary output relationship in hypertensive rats. Am J Physiol 234:R98-R103, 1978.

24. Guyton, AC, Coleman, TG, Cowley, AW, Jr., Manning, RD, Jr., Norman, RA, Jr., Ferguson, JD: A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. Circ Res 35:159-176, 1974.

25. Steele, TH, Underwood, JL: Blunted natriuresis in isolated perfused spontaneously hypertensive rat (SHR) kidney. Clin Res 26:511A, 1978.

26. Kempner, W: Compensation of renal metabolic dysfunction: Treatment of kidney disease and hypertensive vascular disease with rice diet. N C Med J 6:61-117, 1945.

27. Pickering, GW: The nature of essential hypertension (Textbook). New York, Grune & Stratton, 1961.

28. Pettinger, WA , Sanchez, A., Gandler, T., Saiz, j., Saavedra, J.: Dietary sodium regulates abnormal renal α-adrenergic receptors in the Dahl hypertensive rat. In press. Kidney Int (Abstract).

29. Pettinger, WA, Augusto, L., Leon, AS: Alteration of renin release by stress and adrenergic receptor and related drugs in unanesthetized rats. In: Comparative Pathophysiology of Circulatory Disturbances (Bloor, CM, ed), Plenum Publishing Company, New York, 1972, pp. 105-117.

30. Pettinger, WA, Keeton, TK, Campbell, WB, Harper, DC: Evidence for a renal α-adrenergic receptor inhibiting renin release. Circ Res 38:338-346, 1976.

31. Vandongen, R., Peart, WS: Inhibition of renin secretion by alpha-adrenergic stimulation in the isolated rat kidney. Clin Sci Mol Med 47:471-479, 1974.

32. Morris, BJ, Reid, IA, Ganong, WF: Inhibition by α-adrenoceptor agonists of renin release in vitro. Europ J Pharmacol 59:37-45, 1979.

33. Vandongen, R., Strang, KD, Poesse, MH, Birkenhager, WH: Suppression of renin secretion in the rat kidney by a nonvascular α-adrenergic mechanism. Circ Res 45:435-439, 1979.

34. Capponi, AM, Vallotton, MB: Renin release by rat kidney slices incubated in vitro. Circ Res 39:200-203, 1976.

35. Berthelsen, S., Pettinger, WA: A functional basis for classification of α-adrenergic receptors. Life Sci 21;595-606, 1977.

36. Pettinger, WA: Unusual alpha adrenergic receptor potency of methyldopa metabolities on melanocyte function. J Pharmacol Exp Ther 201:622-626, 1977.

37. Reid, JL, Hamilton, C: Catecholamines and blood pressure regulation: The role of α-adrenoceptors. J of Cardiovas Pharmacol 2(Suppl.2): S325-S335, 1980.

38. Tanaka, T., Starke, K: Antagonist/agonist-preferring α-adrenoceptors of α_1/α_2-adrenoceptors? Europ J Pharmacol 63:191-194, 1980.

39. Yamaguchi, I., Kopin, IJ: Differential inhibition of alpha-1 and alpha-2 adrenoceptor-mediated pressor responses in pithed rats. J Pharmacol Exp Ther 214:275-281, 1980.

40. Kobinger, W., Ludwig, P.: Investigation into different types of post-and presynaptic α-adrenoceptors at cardiovascular sites in rats. Europ J Pharmacol 65:393-402, 1980.

41. Rusch, NJ, DeMey, JG, Vanhoutte, PM: Effect of BL-5111-A, prazosin and phentolamine on responses of canine cutaneous veins to adrenergic activation. Arch Int Pharmacodyn 244:341-343, 1980.

42. DeMey, JG, Vanhoutte, PM: Differences in pharmacological properties of postjunctional alpha-adrenergic receptors among arteries and veins. Arch Int Pharmacodyn 244:328-329, 1980.

43. Drew, GM, Whiting SB: Evidence for two distinct types of postsynaptic α-adrenoceptor in vascular smooth muscle in vivo. Br J Pharmac 67:207-215, 1979.

44. Timmermans, PBMWM, Van Zwieten, PA: Postsynaptic α_1-and α_2-adrenoceptors in the circulatory system of the pithed rat: Selective stimulation of the α_2-type by B-HT 933. Europ J Pharmacol 63:199-202, 1980.

45. Drew, GM: Postsynaptic α_2-adrenoceptors mediate pressor responses to 2-N, N-dimethylamino-5, 6-dihydroxy-1,2,3,4-tetrahydronaphthalene (M-7). Europ J Pharmacol 65:85-87, 1980.

46. Hirst, GDS, Neild, TO: Evidence for two populations of excitatory receptors for noradrenaline on arteriolar smooth muscle. Nature 283:767-768, 1980.

47. Mulvihill-Wilson, J., Pettinger, WA, Mitchell, HC: The effect of sodium on the α-adrenergic receptor number in hypertensive man. Submitted for publication.

48. Bylund, DB, Martinez, JR: α_2-adrenergic receptors appear in rat salivary glands after reserpine treatment. Nature 285:229-230, 1980.

49. Hoffman, BB, Mullikin-Kilpatrick, D., Lefkowitz, RJ: Heterogeneity of radioligand binding to α-adrenergic receptors. J Biol Chem 255:4645-4652, 1980.

50. Wood, CL, Arnett, CD, Clarke, WR, Tsai, BS, Lefkowitz, RJ: Commentary: Subclassification of alpha-adrenergic receptors by direct binding studies. Biochem Pharmacol 28:1277-1282, 1979.

51. Kafka, MS, Tallman, JF, Smith, CC, Costa JL: Alpha-adrenergic receptors on human platelets. Life Sci 21:1429-1438, 1977.

52. Alexander, RW, Cooper, B., Handin, RI: Characterization of the human platelet α-adrenergic receptor. J Clin Invest 61:1136-1144,1978.

53. Lasch, P., Jakobs, KH: Agonistic and antagonistic effects of various α-adrenergic agonists in human platelets. Naunyn-Schmiedeberg's Arch Pharmacol 306:119-125, 1979.

54. Jakobs, KH: Synthetic α-adrenergic agonists are potent α-adrenergic blockers in human platelets. Nature 274:819-820, 1978.

55. Handler, JS, Bensinger, R., Orloff, J.: Effect of adrenergic agents on toad bladder response to ADH, 3',5'-AMP, and theophylline. Amer J Physiol 215:1024-1031, 1968.

56. Abe, K., Robinson, GA, Liddle, GW, Butcher, RW, Nicholson, WE, Baird, CE: Role of cyclic AMP in mediating the effects of MSH, norepinephrine & melatonin on frog skin. Endocrinology 85:674-682, 1969.

57. Pettinger, WA: Unusual alpha adrenergic receptor potency of methyldopa metabolites on melanocyte function. J Pharmacol Exp Ther 201:622-626, 1977.

58. Lafontan, M., Berlan, M.: Evidence for the α_2 nature of the α-adrenergic receptor inhibiting lipolysis in human fat cells. Eur J Pharmacol 66:87-93, 1980.

59. Kather, H., Simon, B.: Adrenoceptor of the alpha$_2$-subtype mediating inhibition of the human fat cell adenylate cyclase. Eur J Clin Invest 1981, In press.

60. Kather, H., Pries, J., Schrader, V., Simon, B.: Inhibition of human fact cell adenylate cyclase mediated via alpha-adrenoceptors. Eur J Clin Invest 10:345-348, 1980.

61. Austen, KF: Reaction mechanisms in the release of mediators of immediate hypersensitivity from human lung tissue. Federation Proc 33:2256-2262, 1974.

62. Nakadate, T., Nakaki, T., Muraki, T., Kato, R.: Regulation of plasma insulin level by α_2-adrenergic receptors. Eur J Pharmacol 65:421-424, 1980.

63. Nakadate, T., Nakaki, T., Muraki, T., Kato, R.: Adrenergic regulation of blood glucose levels: Possible involvement of postsynaptic alpha-2 type adrenergic receptors regulating insulin release. J Pharmacol Exp Ther 215:226-230, 1980.

64. Mulvihill-Wilson, J., Graham, RM, Pettinger, WA, Muckleroy, C., Anderson, S., Gaffney, FA, Blomqvist, CG: Comparative effects of prazosin and phenoxybenzamine on arterial blood pressure, heart rate, and plasma catecholamines in essential hypertension. J of Cardiovas Pharmacol 1(Suppl):S1-S7, 1979.

65. Dubocovich, ML, Langer, SZ, Massingham, R.: Lack of correlation between presynaptic inhibition of noradrenaline release and end organ responses during nerve stimulation. Br J Pharmac 69:81-90, 1980.

66. Kalsner, S., Chan, CC: Adrenergic antagonists and the presynaptic receptor hypothesis in vascular tissue. J Pharmacol Exp Ther 211:257-264, 1979.

67. Robie, NW: Evaluation of presynaptic α-receptor function in the canine renal vascular bed. Am J Physiol 239:H422-H426, 1980.