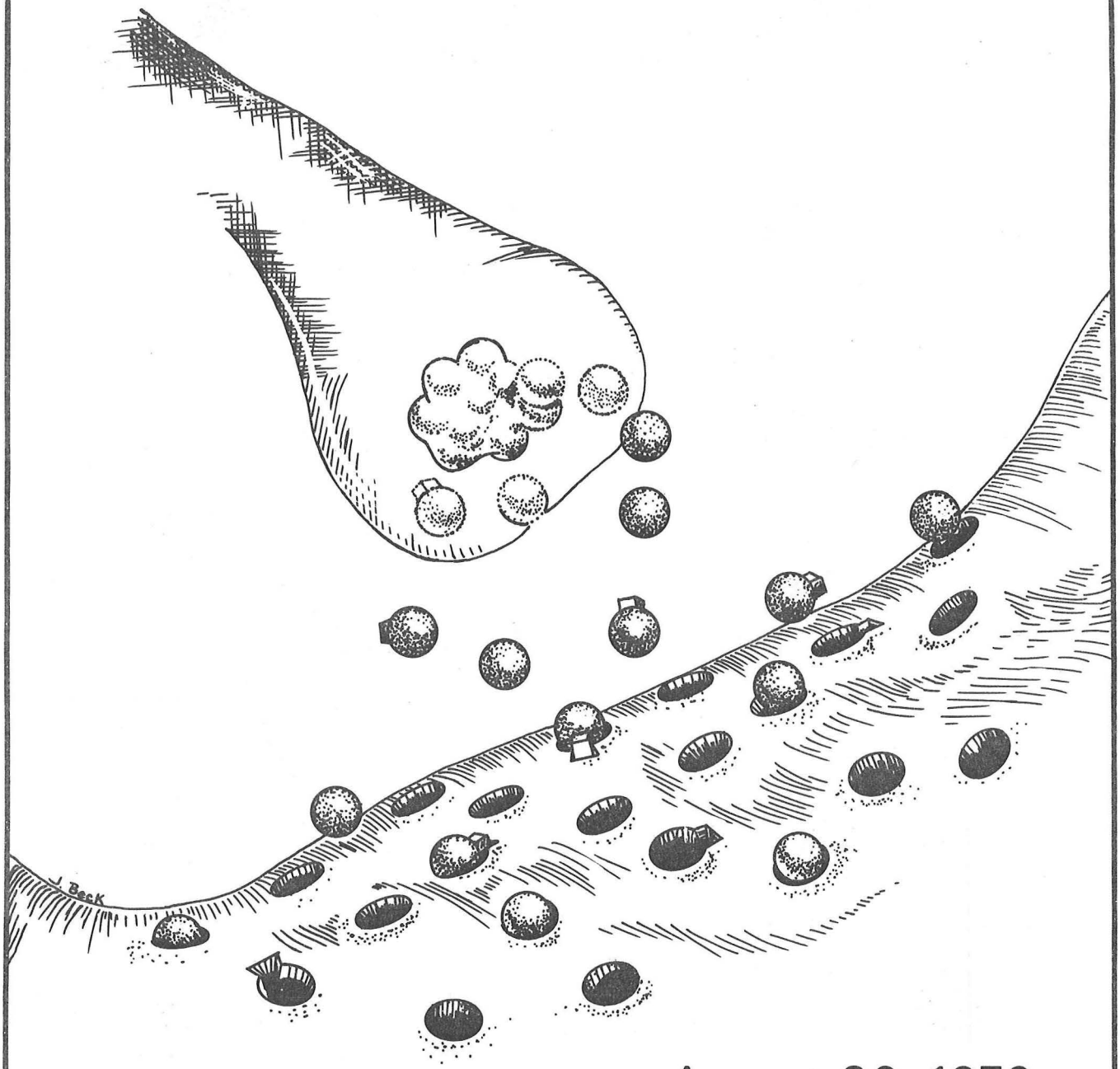
CATECHOLAMINE RECEPTORS

Relationship to Health and Disease



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RELATIONSHIP TO HEALTH AND DISEASE

I. INTRODUCTION

It is the purpose of this review to provide an update on catecholamine receptors, the effects they mediate and the role they play in the expression of physiological alterations in the sympathetic nervous system. In addition, the increasing evidence for their involvement in various clinical disorders and in the therapy of these conditions, will be discussed.

Following Ahlquists classical description of α- and β-receptors in 1948 (1), research into catecholamine receptors was slowly forthcoming. Subsequently, however, and particularly in the last decade there has been a virtual explosion of interest in these receptors and the events they mediate. In the past two years, for example, over 2000 articles have been published in which either α-, β- or dopamine receptors were the major consideration.

In attempting to review this rapidly expanding subject, I find myself in a position analogous to that of G. Alan Robison in 1968 (2) who described his review of research in cyclic AMP at that time as being difficult "because the subject refused to sit still. It was not simply that it behaved like a naughty child at the photographers, for that would be expected in any viable field of scientific research. Rather, it seemed more like an imaginary child who, in the course of having his picture taken, suddenly grew to adult proportions and then left the studio badly in need of a shave" (3).

Of necessity then, this review will be less than complete and I apologize if certain important areas of research have been omitted.

II. HISTORICAL PERSPECTIVE

The concept of a receptive mechanism was first introduced by Langley in 1905 (4) to explain the action of curare on skeletal muscle. Sir Henry Dale in 1906 (5) extended this concept to the mechanism of action of the sympathetic nervous system. In his classical paper on the sympatholytic action of the ergot alkaloids he recognized that what he called the sympathetic myoneuronal junction could also be called "the receptive mechanism for adrenaline"; and he used this mechanism to explain the fact that the ergot alkaloids prevented only the motor (excitatory) actions of epinephrine and had no effects on the inhibitory actions of epinephrine or on the excitatory actions of barium or Pituitrin.

Ergot alkaloids at that time were better known as a scourge that had afflicted many people from as early as 600 B.C. Epidemics of ergot poisoning due to ingestion of the ergot containing fungus *Claviceps purpurea*, which is formed on rye, had masqueraded under various names such as Holy Fire or St. Anthony's Fire. This designation was based on the characteristic gangrene that occurred in the extremities as well as the accompanying burning sensations due to severe vasospasm. However, it was a serendipitous finding which

led to Sir Henry Dale's discovery of ergots alpha-adrenergic blocking activity. Dale, while working at the Wellcome Laboratories in England, was involved with evaluating the pharmacology of ergots. However, one of his routine tasks at that time was to bioassay adrenal extracts (Wellcome adrenaline preparations). This was done by determining pressor effects in the cat. Since this was work of a routine nature, it was usually done at the end of the day after the regular experiments. After administering the adrenaline-containing solutions into cats that had received ergot during the normal day's experiments, Dale found that instead of the rise in blood pressure which adrenal extracts normally produced, he now observed a fall in blood pressure. Being an astute investigator, Sir Henry Dale reasoned that the ergot, in some way, might be modifying the effects of adrenaline and after additional experiments he concluded that pretreatment with ergot had affected the pressor response of adrenaline by blockade of its effect. Thus, this was the first demonstration of the ability of any drug to produce blockade of certain of adrenaline's effects and, in fact, it is the first demonstration of the alpha-adrenergic receptor.

A. J. Clarke in 1933 (6) extended Dale's concept into a general theory of drug action and postulated that the actions of catecholamines and other drugs are mediated by their interactions with specific cell surface structures termed "receptors", the response to these drugs being proportional to the number of receptors occupied by the drug.

Cannon and Rosenbleuth in 1937 (7) suggested that differential effects of various hormones in different tissues (excitatory in one tissue and inhibitory in another) could best be explained on the basis of there being one receptor which released two different effector substances which they called Sympathin E and Sympathin I. This concept remained unchallenged and was accepted as "physiological law" until Ahlquist's elegant studies were published in 1948 (1). Using six different amines (norepinephrine, methylnorepinephrine, dl- and l- epinephrine, methyl epinephrine and isoproterenol) he examined the effects of these agents on seven different tissues (heart, blood vessels, intestine, uterus, ureter, eye and nictitating membrane) in three different species of animals (cat, dog and rabbit) and concluded that there must be at least two distinct general types of adrenergic receptors. One type which he termed alpha associated with most of the excitatory functions and with at least one inhibitory function (intestinal smooth muscle relaxation). The other type beta associated with most of the inhibitory functions and with one important excitatory function (cardiac stimulation). Because of the opposing effects associated with each type of receptor, he correctly suggested that the customary signs, E (excitatory) and I (inhibitory) could not be universally applied and, therefore, that the concept of Sympathin E and I was incorrect. Rather he proposed that two different receptor types, α- and β-, were found in different tissues and that the order of potencies of the amines for these receptors was:

α: l-epi > NE >> isoproterenol
β: isoproterenol > l-epi > dl-epi >> NE

Definitive confirmation of Ahlquist's classification was, however, not forthcoming until the development of the β-adrenergic blocking agents, dichloroisoproterenol (8) and propranolol (9). Since that time numerous studies have substantiated Ahlquist's concept of two receptor types and have confirmed the order of potency of the various amines, as suggested by him.

A third type of catecholamine receptor, the dopamine receptor, has been identified and characterized. In 1957 Blaschko (10) tentatively suggested that dopamine might have a physiological role in its own right, in addition to its well-known function as a precursor of norepinephrine and epinephrine. In the same year dopamine was shown to be present in mammalian brain (11-13) and there has followed a prodigious amount of research on the physiology and pharmacology of this amine. The results of electrophysiological, biochemical, histological, behavioral and clinical studies have slotted together to build up an impressive array of evidence supporting the role of dopamine as a neurotransmitter. This evidence has been fully covered in several excellent reviews (11-16) and thus, will not be discussed in this presentation. More recently, peripheral dopamine receptors have been identified which mediate vasodilatation in the renal and mesenteric vascular beds (20-24). As a direct result of these studies, the therapeutic potential of dopamine in the management of shock has been realized, and this amine is now one of the most widely used drugs in the treatment of hypotensive disorders. In addition, dopamine receptors located on sympathetic ganglia (25,26) and post-ganglionic sympathetic nerve terminals (27,28) may play an important role in the local regulation of noradrenergic neurotransmission.

III. MECHANISMS OF HORMONE-RECEPTOR INTERACTION AND END-ORGAN RESPONSE

At least three different hormone-receptor interactions have been postulated and are now well-defined:

1. Steroid Receptors

Steroid drugs or hormones migrate through the cell wall of their target tissue and bind to a cytoplasmic receptor. The drug-receptor complex thus formed migrates to the nucleus where it interacts with DNA and results in the formation of a strand of mRNA (messenger RNA). mRNA, in turn, codes for the formation of a protein which mediates the action attributed to the hormone (e.g. aldosterone and sodium reabsorption in the kidney).

2. Cholesterol Receptors

These receptors are located on the surface of the cell (e.g. fibroblasts, hepatocytes and various tumor cells). After binding of the lipoprotein (LDL) with the receptor, the 'drug'-receptor complex is internalized, in toto, via pinocytotic vesicles. These vesicles fuse with lysosomes in the cytoplasm which hydrolyze the cholesterol ester component of the lipo-protein into its basic constituents, free cholesterol and fatty acid. The free cholesterol thus liberated is then utilized by the cell for metabolic processes such as formation of steroid hormones (29).

3. Catecholamine Receptors

Catecholamine receptors (as well as peptide and acetylcholine receptors) are located on the surface of the cell where they bind with catecholamines to form a "drug-receptor" complex. This complex remains on the surface of the cell and leads to activation of processes within and below the cell membrane. The post-receptor events are poorly understood, particularly where the receptor is of the "alpha" type.

In most cases, interaction of an agonist with beta or dopamine receptors results in activation of a coupler subunit which in turn activates a catalytic subunit (adenylate cyclase). The latter then results in catalytic conversion of ATP to cyclic AMP (cyclic 3'5' adenosine monophosphate).

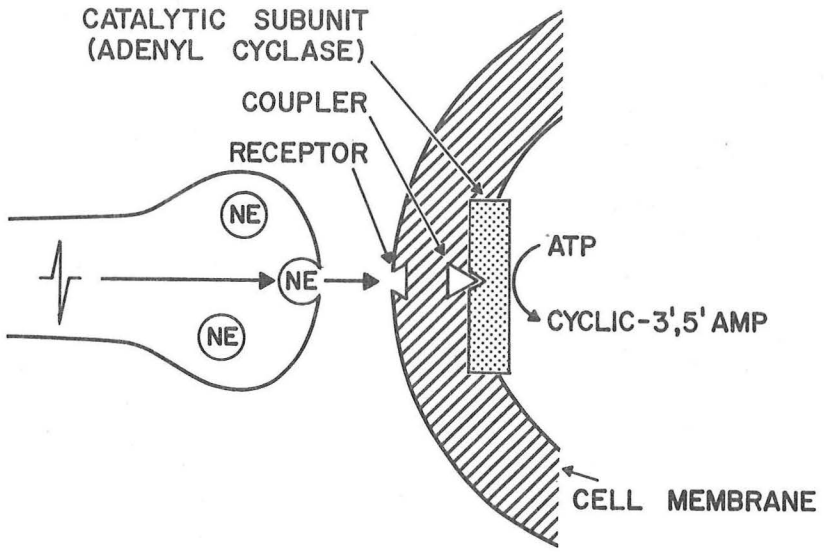

FIGURE 1. Events following β-receptor activation.

The events following the formation of cyclic AMP are complex and may involve the release of sequestered calcium possible via formation of a protein kinase. In addition, amplification systems are involved such that a single hormone or drug molecule results in the formation of a large number of product molecules e.g. 1 mole of epinephrine acting on hepatic adrenergic receptors may liberate 10^8 moles of glucose.

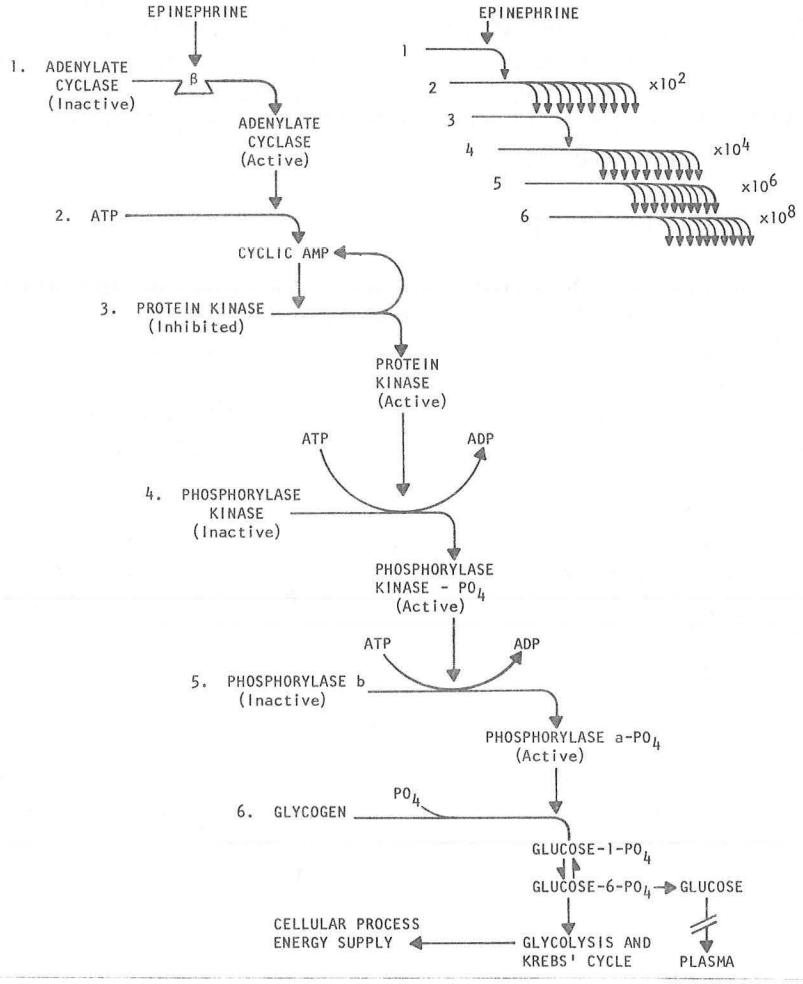

FIGURE 2. Intracellular events following β-receptor activation of an hepatocyte. Note amplification of the receptor activation process allows one mole of epinephrine to stimulate 10^8 moles of glucose.

The post-receptor events following interaction of alpha-adrenergic agonists with their receptors are poorly understood. Most likely, activation of smooth muscle alpha-receptors inhibits calcium binding to high affinity sites on the surface of the cell membrane and results in the liberation of intracellular calcium ions from surface vesicles, sarcoplasmic reticulum and mitochondria (30,31). In other tissues it has been postulated that activation of alpha-receptors opens calcium channels in the plasma membranes and permits the influx of ionized calcium (32,33). Both mechanisms, however, result in increased intracellular ionized calcium which in turn either 1) interacts with actin and myosin which results in

smooth muscle contraction in a process that utilizes ATP as an energy source (32); 2) activates phosphorylase thereby stimulating phosphorylase b kinase (33); or 3) stimulates guanylate cyclase with concomitant synthesis of cyclic GMP from GTP. The cyclic GMP thus formed may be involved in the stimulation of DNA synthesis (34).

In addition, in several different tissues derived from a variety of species, α-adrenergic receptor stimulation may counteract the effects of β-receptor stimulation by inhibiting the generation of cyclic AMP. These tissues include:

1) Human platelets (35)
2) MSH induced degranulation of melanocytes in the frog skin (36)
3) ADH action in the toad bladder (37)
4) Release of mediators from human lung mast cells (38)
5) Human adipocytes (39)

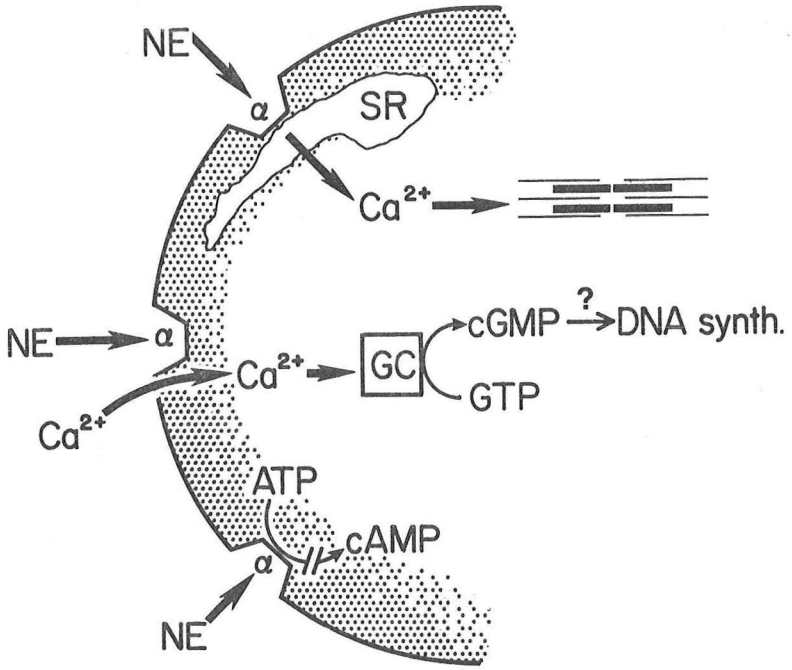

FIGURE 3. Post-receptor events following activation of α-adrenergic receptors.

IV. SUBCLASSIFICATIONS OF CATECHOLAMINE RECEPTORS

a) β_1/β_2 Receptors

In 1967 Lands and coworkers (40) provided evidence that the activity of sympathomimetic amines in eliciting β-receptor mediated responses differed in various tissues. Thus, the ability of various agonists to stimulate lypolytic activity in adipose tissue correlated well with their ability to induce cardiac stimulation. Lypolytic activity, however, did not correlate well with either bronchodilator or vasodepressor actions of these amines. In contrast. bronchodilator and vasodepressor activity corresponded closely. On the basis of these studies, they suggested a subclassification of β-receptors into β_1 as found in the myocardium and adipose tissue, and β_2 as found in vascular and bronchial smooth muscle.

The relative affinity ratios of the various amines used in their studies were as follows:

β_1/β_2: NE > isoproterenol > EPI

Accordingly, norepinephrine had the highest relative affinity for β_1 receptors and epinephrine the highest affinity for β_2 receptors. With the development of relatively specific β-receptor antagonists this subclassification has gained acceptance and is widely referred to in considerations of β-receptor mediated events.

Carlsson and Ablad (41,42), however, have challenged the β_1/β_2 hypothesis on the basis that studies with β_1-specific antagonists results in differential blockade patterns in different tissues, and have suggested that:

1) there are both β_1 and β_2 receptors in most tissues which mediate one and the same response

2) the relative frequencies or concentrations of β_1 and β_2 receptors vary in different organs. Thus, for example, in the heart and adipose tissue there are mainly β_1 receptors, while in bronchial and vascular smooth muscle there are mainly β_2 receptors. Moreover, the proportion of each type of receptor stimulated for a certain response depends on the relative affinities of the agonists for the β_1 or β_2 receptors, as well as the relative concentrations of each receptor type.

The basis for these objections to the Land's hypothesis is the finding that the β_1-selective antagonist metoprolol is a more potent inhibitor of inotropic responses to norepinephrine than of responses to epinephrine in isolated human atrial tissue. In addition, the nonselective blocker, propranolol shows no such differential blocking effects.

Similar patterns of differential blockade of α-receptor mediated responses to epinephrine and norepinephrine have also been reported by Melchiorre (43). This observation suggests that subclasses of postsynaptic α-receptors as well as β-receptors may exist.

However, while these considerations of Carlsson and Ablad and Melchiorre may be pharmacologically correct, their physiological significance remains unclear and, at present, they appear to add little to an already complex subject.

b) Release Modulating Receptors

A subclassification of adrenergic receptors which is physiologically relevant is based on recent evidence that in addition to postjunctional α-receptors, there exist α-adrenergic receptors located prejunctionally on postganglionic, noradrenergic nerve endings. Activation of these prejunctional α-receptors reduce stimulus-induced norepinephrine release, whereas blockade of these receptors increases the release of norepinephrine (44-47). These prejunctional α-receptors thus modulate sympathetic neurotransmission by inhibiting further norepinephrine release following activation of the sympathetic nervous system.

The clinical significance of prejunctional α-receptors, thus far, relates mainly to antihypertensive therapy. In view of the inhibitory action of these receptors, blockade by α-adrenergic antagonists would be expected to result in marked increments in norepinephrine release and thus heart rate and renin release. These factors would tend to counteract the hypotensive effects of α-blockers and may explain the apparent ineffectiveness of nonselective α-blockers such as phentolamine, in the therapy of essential hypertension (48). Failure to block prejunctional α-receptors may also explain the apparent efficacy and relative lack of tachycardia and renin release observed with prazosin (49) an α-receptor antagonist with selectivity for the postjunctional α-receptor. In support of this hypothesis, we have recently demonstrated in conscious rats that for a given reduction in arterial pressure, prazosin results in a significantly lesser increment in plasma norepinephrine concentration, heart rate and plasma renin activity (50-52).

Although both pre- and postjunctional α-adrenergic receptors are stimulated by α-receptor agonists and blocked by α-receptor antagonists, the affinities of various adrenergic agents for these receptors differs. In addition, in some tissues α-receptors which are anatomically postjunctional behavior functionally as prejunctional receptors, in so far as the potencies of various agonists and antagonists for these receptors is similar to that found in classical prejunctional α-receptors in peripheral vascular tissue. Similarly, α-receptors in tissues which are not sympathetically innervated (e.g. uterus and platelets) behave functionally as either pre-or

postjunctional α-receptors. As an anatomical classification is clearly not relevant in these tissues, a functional classification of α-receptors into α_1 and α_2 subtypes (Table 1) has been suggested (53) and is now well-accepted (54,56).

TABLE 1: FUNCTIONAL SUBCLASSIFICATION OF α-RECEPTORS

TISSUE	FUNCTION MEDIATED
α_1-RECEPTORS	
Vascular Smooth Muscle (Arteriole)	Constriction
Liver	?
Aorta	Constriction
Uterus	Contraction
α_2-RECEPTORS	
Sympathetic Nerve Terminal	Inhibition of NE Release
Platelet	Aggregation
Submandibular Gland	K+ Release
Parotid Gland	K+ Release
Medullary Vasomotor Center	Inhibition of Sympathetic N.S.
Kidney	Inhibition of Renin Release
CNS	Inhibition of Salivation
CNS	Inhibition of ACTH Release
CNS	Sedation
Frog Skin Melanocyte	Inhibition of MSH - Induced Dispersion of Melanocyte Granules

Adapted from Ref. 53 and 54

Inhibitory α-receptors have also been documented in the adrenal medulla and on cholinergic neurones and sympathetic ganglia which, like α-receptors on sympathetic nerve terminals, may also modulate neurotransmission of the autonomic nervous system (46,55).

Finally, prejunctional β-, angiotensin, acetylcholine (nicotinic), adenosine and prostaglandin $F_{2\alpha}$ receptors which facilitate, and prejunctional dopamine, prostaglandin E_2, enkephalin and acetylcholine (muscarinic) receptors which inhibit norepinephrine release have also been identified in some but not all tissues examined (6-8).

V. IDENTIFICATION OF CATECHOLAMINE RECEPTORS BY RADIOLIGAND BINDING TECHNIQUES

Catecholamine receptors, like other hormone receptors, have two functions in mediating the action of their respective hormones. First, the receptor is responsible for selective recognition and binding of specific molecular structures, thereby functioning as a discriminator. Second, the receptor is responsible for initiating a sequence of steps that results in the physiological response to the catecholamine. Until recently, information about the recognition function of receptors could only be inferred from measurements of the biological responses to adrenergic agents. Because of this limitation, conventional pharmacological studies have not provided a clear understanding of how receptors discriminate among biological molecules and how they transmit information to the interior of the cell.

Recently a new approach to the study of catecholamine receptors has been the use of radioactive ligands (radioligands; the term "ligand" is used to mean an atom, group of atoms or a molecule that binds to a macromolecule) as probes to directly identify and study the receptor sites. By this technique the receptors can be quantitated, their specificity can be defined, the kinetics of their interactions with catecholamine ligands can be examined, their localization on the cell can be determined, and specific information about their role as transducers of information from the catecholamine to the cellular machinery can be deduced. In addition, alterations in the number or characteristics of receptors in various physiological and pathological states can be directly examined.

In 1974, three groups working independently, developed methods that appeared to permit the direct study of beta-adrenergic receptors. In each case the radioligand used was a potent beta-adrenergic antagonist. Levitzki et al. (56,57) used [^{3}H]propranolol, Lefkowitz et al. (58) used (-) [^{3}H]dihydroalprenolol, and Aurbach et al. (59) used [^{125}I]hydroxybenzylpindolol. Subsequently, Snyder and coworkers (60,61) and Seeman et al. (62,63) reported the successful identification of dopamine receptors using [^{3}H]dopamine and [^{3}H]haloperidol and the following year Williams and Lefkowitz (64,65) reported the identification of alpha-adrenergic receptors using [^{3}H]dihydro-ergocryptine, an ergot-alkaloid α-antagonists.

With the advent of these technologies to directly identify catecholamine receptors, significant new insights have been gained into the physiological control of receptor-mediated events and into the possible relationship of catecholamine receptors to the expression of various clinical disorders. A few of these insights will be discussed here, others will be covered subsequently in relationship to specific tissues or clinical entities.

a) Receptors and the Control of Tissue Sensitivity to Hormonal Stimulation

It has been known for some time that a wide variety of hormonal and other factors control tissue sensitivity to hormones and drugs. In particular tolerance and the opposite phenomenon, hypersensitivity are well-described entities. Obviously, the receptors, which are the first link in the chain of hormone response, are in a unique position to control tissue sensitivity to hormonal stimulation. However, prior to the advent of radioligand binding techniques it had not been possible to directly assess the contribution of receptor alterations to such regulatory phenomena.

Catecholamines appear to play an important role in regulating the function of their own receptors. Incubation of responsive cells with β-adrenergic agonists, results in a time-dependent loss of β-adrenergic binding sites with a concordant fall in catecholamine-sensitive adenylate cyclase activity (66,67). In contrast, β-adrenergic antagonists do not cause desensitization, but rather, protect against desensitization. Thus, physiologically, in tissues where there is tonic β-adrenergic stimulation, antagonists might be expected to produce a hypersensitive state. These observations provide an explanation for the development of tolerance or tachyphylaxis observed with prolonged administration of catecholamines. In addition, it has recently been reported that therapy with the β-adrenergic antagonist propranolol in normal volunteers, resulted in a time-dependent increase in β-adrenergic binding sites in human lymphocytes. The increase in binding sites persisted after withdrawal of the propranolol and was associated with a significant pulse rise on standing from 14 to 28 beats /minute (68). A similar increase in β-adrenergic binding sites has been demonstrated in rat cardiac muscle following the administration of propranolol (69). Thus, the above observation may explain the onset of ischemic symptoms, which is occasionally observed in patients with coronary artery disease, following the abrupt withdrawal of propranolol.

A similar desensitization of an α-adrenergic response in rat parotid cells has been demonstrated, which appears to be analogous to that described for β-adrenergic-adenylate cyclase coupled responses (70,71). In dissociated rat parotid acinar cells, α-adrenergic agonists stimulate the release of potassium. This physiological response has all the characteristics of an α-adrenergic response and is blocked by α-antagonists such as phentolamine. It was found that preincubation of the parotid acinar cells with epinephrine led to a fairly rapid decrease in the subsequent responsiveness of the cells to epinephrine (assessed by potassium release). It was further shown that the diminished responsiveness to epinephrine was associated

with a decrease in [^{3}H]dihydroergocryptine bindings to α-receptors in the intact parotid cells. Whereas the α-agonists, epinephrine caused desensitization of the α-adrenergic response and decreased [^{3}H]dihydroergocryptine binding, the α-antagonist phentolamine, when incubated with the cells simultaneously with epinephrine, blocked both the desensitization and the decrease in receptor binding.

As with β- and α-adrenergic receptors, changes in dopamine receptors may also be involved in the control of dopamine-mediated effects. For example, treatment of schizophrenics with dopamine antagonists results in an increase in brain dopamine receptor concentration (63,72,73).

In addition to regulating their own receptors, some hormones can regulate receptors for different ligands. This mechanism appears to be responsible for the hyperadrenergic manifestations of thyrotoxicosis. Cardiac muscle from hyperthyroid rats has an increased number of specific β-adrenergic binding sites, but a decreased number of α-adrenergic binding sites. The reverse situation exists in hypothyroid rats (74,75). In addition, cortisone (76) and butyrate (77) have also been shown to decrease and increase the number of β-adrenergic binding sites, respectively, in some tissues.

b) Catecholamine Receptors and Aging

All of the molecular events in hormone action subsequent to receptor binding may change with increasing age. Numerous examples of altered hormonal receptor responsiveness over the life span have been delinated (78,79). In some cases responsiveness is not significantly altered during senescence but may change during maturation. In a few situations responses may actually increase with age. However, in the vast majority of cases, ability to respond to a particular hormone decreases during senescence (80).

Many studies on hormone receptors during the aging process have been reported. In almost all of these studies the changes that do occur involve alterations in the number of receptors rather than changes in the ability of the receptors to bind the hormones. By far the largest group of these investigations show decreased concentrations of receptors during post-maturational life and senscence (80). With respect to catecholamine receptors for example, decreases in the number of β-receptors during senescence have been reported in human lymphocytes (81) and rat adipocytes (82), cerebellum (82) and corpus striatum (83). In addition, decreases in β-receptors during early adulthood occur in rat erythrocytes (84) and pineal (83), although β-receptors remain unaltered during adulthood in rat cerebral cortex (84).

As discussed in a recent grand rounds by Dr. Kaplan, plasma renin activity and the antihypertensive response to propranolol decrease with age. In view of the above observations, it is possible that these changes are mediated by decreases in renal β-receptors, which control renin release during senescence.

Age-related changes in α-adrenergic receptors have not been reported previously. However, we have found a parallel decrease in renal α-adrenergic receptors in both normal and spontaneously hypertensive rats (85). Interestingly, the ergot alkaloids which may act via α-adrenergic receptors, have recently been proposed for the treatment of senility, suggesting that some of the manifestations of senility may be due to age related changes in α-adrenergic receptors.

c) Catecholamine Receptors and Neoplasia

1) Normally, plasma membranes from adrenal cortical tissue contain an adenylate cyclase that responds only to the hormone ACTH. β-adrenergic agents do not stimulate the enzyme. Several years ago an adrenal cortical carcinoma was described which had the interesting property that its membrane-bound adenylate-cyclase responded to β-adrenergic agonists, as well as to ACTH (86). Recently, it has been found that whereas normal adrenal cortical tissue does not contain β-adrenergic receptor binding sites, membranes from the adrenal carcinoma do contain these binding sites (87). Thus, the malignant adrenal cortical tissue is able to synthesize and insert into its plasma membrane functional β-adrenergic receptors not normally present in adrenal cortical plasma membranes. The presence of these β-adrenergic binding sites in the adrenal plasma membranes confers catecholamine sensitivity on adrenal cortical adenylate cyclase.

2) A number of mutant lines of cultured lymphoma cells have also been described which have alterations in the β-adrenergic receptor adenylate cyclase system. One such mutant line contains β-adrenergic receptors, but not adenylate cyclase (88). The existence of such a line is compatible with the notion that the receptors and the catalytic activity of adenylate cyclase may be separately derived gene products. In addition, Spiegel et al. (89) and Charness et al. (90) have demonstrated that the maturation of rat reticulocytes is associated with a marked decrease in the activity of adenylate cyclase in the membranes, with little change in β-receptor binding sites. Thus, the differential loss of these two activities during maturation also supports the notion that the receptors and the enzyme are discrete entities.

TABLE 2

ADRENERGIC RECEPTORS

A. SYMPATHETICALLY INNERVATED TISSUES

EFFECTOR ORGAN	RESPONSE MEDIATED	
	ALPHA	BETA
ARTERIOLES:		
Coronary	Constriction	Dilatation
Skin and Mucosa	Constriction	
Skeletal Muscle	Constriction	Dilatation
Cerbral	Constriction	
Pulmonary	Constriction	Dilatation
Abdominal Visera	Constriction	Dilatation
Renal	Constriction	Dilatation
EYE:		
Radial Muscle	Contraction (Myriasis)	
Ciliary Muscle		Relaxation (Distant Vision)
GALLBLADDER AND DUCTS:		? Relaxation
HEART:		
S-A Node		Increase in heart rate (β_1)
Atria		Increase contractility and conduction velocity (β_1)
A-V Node		Increase automaticity and conduction velocity (β_1)
HIS-Purkinje		Increase automaticity and conduction velocity (β_1)
Ventricles		Increase contractility, conduction velocity and rate of idioventricular pacemaker
INTESTINE:		
Motility and Tone	Decrease	
Sphincter	Contraction	
KIDNEY:		
JG Cells	Renin Release +++	Inhibition of Renin Release
Tubules	? Sodium Reabsorption	

TABLE 2 (continued)

ADRENERGIC RECEPTORS

A. SYMPATHETICALLY INNERVATED TISSUES

EFFECTOR ORGAN	RESPONSE MEDIATED	
	ALPHA	BETA
LACRIMAL GLAND:	K^+ and water secretion	
LUNG:		
Bronchial Muscle	Constriction	Dilatation (β_2)
PANCREAS:		
B cells	Decrease insulin secretion	Increase Secretion
D cells	Decrease somatostatin secretion	Increase Secretion
A cells	Increase glucagon secretion	Increase Secretion
PARATHYROID:		Parathormone Release
PINEAL GLAND:		Melatonin Synthesis
SALIVARY GLANDS:		
Parotid	K^+ and water secretion	Amylase Secretion
Submandibular	K^+ and water secretion	Amylase Secretion
SEX ORGANS (MALE):	Ejaculation	
SKIN:		
Pilomotor Muscle	Contraction	
Sweat Glands	Secretion	
SPLEEN (Capsule)	Contraction	Relaxation
STOMACH:		
Motility and Tone		Decrease
Sphincter	Contraction	
THYROID	? T_4 Release	
URETER:		
Motility and Tone	Increase	

TABLE 2 (continued)

ADRENERGIC RECEPTORS

A. SYMPATHETICALLY INNERVATED TISSUES

EFFECTOR ORGAN	RESPONSE MEDIATED	
	ALPHA	BETA
URINARY BLADDER:		
Detrusor		Relaxation
Trigone and Sphincter Contraction		

B. NONINNERVATED TISSUES

ADIPOSE TISSUE:	Inhibit Lipolysis	Lipolysis +++ (β_1)
ADRENAL GLAND:	Inhibit Catecholamine Release	
BONE MARROW		Eosinophil Release
CNS:		
Sympathetic Activity	Decrease +++ (α_2)	
ACTH Release	Inhibit (α_2)	
Sedation	Induced (α_2)	
Salivation	Inhibit (α_2)	
Stereotyped Behavior		Increase
Memory		Increase (Learned responses)
Growth Hormone	Increase Release	Decrease
ADH	? Increase Release	? Decrease Release
CHOLINERGIC NEURON:	Inhibit Transmission	
GANGLIA (SYMPATHETIC):	Inhibit Transmission	Facilitate Transmission
LIVER		
Hepatocytes	Glycogenolysis/gluconeogenesis (α_2)	Glycogenolysis/gluconeogenesis
Hepatocytes	Potassium Loss	
Kupffer Cells	Lipolysis/gluconeogenesis	
MAST CELL	Enhance Antigen-Induced Release of Histamine, SRS-A	Inhibit Release

TABLE 2 (continued)

ADRENERGIC RECEPTORS

B. NONINNERVATED TISSUES

EFFECTOR ORGAN	RESPONSE MEDIATED	
	ALPHA	BETA
PLATELET:	Aggregation	Inhibition Aggregation
POLYMORPHONUCLEARS:		Lysosome Release
SKELETAL MUSCLE:		K^+ uptake ($?\beta_2$), lactate production, tremor ($?\beta_2$)
SYMPATHETIC NERVE TERMINAL:	Decrease NE Release (α_2)	Increase NE Release
UTERUS:		
Motility and Tone	Increase (Pregnant)	Decrease (nonpregnant)

C. RESPONSE UNCERTAIN

TISSUE	RECEPTOR	COMMENT
Adrenal Cortical Tumor	β	
Cerbellum	β_2	
Cerebrum:		
Whole	α,β	
Caudate Nucleus	α	
Hypothalamus	β	
Fibroblasts	β	Cultured Cells (3T3)
Glioma	β	Cultured Cells (C6TG1A)
Lymphocytes	β	Decreased Numbers in C.L.L.
Lymphoma	β	Mouse Wild-Type S49
Mononuclears	β	Decrease Number w/age
Red Blood Cells	β	
Transformed Fetal Lung	β	Cultured Cells (VA2)

VI. ADRENERGIC RECEPTORS: TISSUE DISTRIBUTIONS AND RESPONSES MEDIATED

In Table 2 are shown the adrenergic receptors identified in various tissue and the responses they mediate. These have been subdivided into: 1) tissues which are sympathetically innervated; 2) tissues which are not sympathetically innervated; and 3) tissues where adrenergic receptors have been identified on the basis of radioligand binding studies, but in which the responses to adrenergic stimulation or blockade are uncertain.

Subclassifications of α and β receptors are included, where these have been defined. The tissues in which dopamine receptors have been identified and the responses they mediate will be discussed separately. Obviously, it is beyond the scope of this review to give an update on the recent advances in adrenergic receptors in all of these tissues. Thus, only recent advances which provide either interesting insights into the physiological control of the receptor mediated reponse in a particular tissue or which have particular clinical relevance, will be discussed here.

VII. ADRENERGIC RECEPTORS: PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

A. ASTHMA

a) Polymorphonuclear Leukocytes and Tolerance to β-Adrenergic Agonists

Decrease bronchodilator responses to catecholamines is a frequent therapeutic problem in asthmatics treated chronically with β-adrenergic agonists (91-93). In addition, β-agonist therapy diminishes the generation of leucocyte cyclic AMP in both normal and asthmatic subjects (94,95).

As mentioned previously, catecholamine-induced target-cell hyporesponsiveness has been shown to be associated with a decrease in the number of adrenergic receptors. To investigate the possibility that a similar phenomenon is responsible for the decreased bronchodilator response and generation of leucocyte cyclic AMP in asthmatics, Galant et al. (96) recently reported the characterization of polymorphonuclear β-receptors in both normal and asthmatic subjects, using the radioligand [^{3}H]dihydroalprenolol.

The results of this study are shown in Table 3. After six days of treatment with terbutaline, the number of binding sites decreased by 85% and this decrease was similar in the two groups. When terbulatine was stopped, the number of binding sites increased towards pretreatment levels. It was further shown in this study that 1) the decrease in number of binding sites appeared to develop over several days and, although reversible, required more than 24 hours withdrawal before returning to the control levels and 2) that the number of binding sites was markedly reduced in chronically treated asthmatics.

TABLE 3: DECREASE IN DIHYDROALPRENOLOL (DHA) BINDING BY THE β-ADRENERGIC AGONIST, TERBUTALINE

SUBJECT NO.	TYPE	INITIAL DHA* BINDING (fmol/mg)	EFFECT OF TERBUTALINE ON DHA BINDING (fmol/mg)	
			+†	-‖
1	Asthmatic	28.0	3.4	22.4
2	Asthmatic	22.7	0	20.0
3	Asthmatic	22.7	5.7	14.3
4	Control	16.0	6.6	16.0
5	Control	25.4	6.4	21.6
6	Control	25.1	0	25.0
7	Control	19.2	0	19.0
MEAN ± S.E.		22.3 ±1.6	3.2 ±1.3	19.8 ±1.2

*All untreated †terbutaline for 6 days before testing (2.5 mg.p.o. qid)
‖Terbutaline discontinued for 7 days before testing. Adapted from ref. 96

These data thus provide an explanation for the decreased catecholamine-induced generation of leucocyte cyclic AMP and suggest that a similar mechanism, viz: a decrease in bronchial smooth β-adrenergic receptors, may mediate the decrease bronchodilator response to catecholamines observed in asthmatics.

b) Alpha-Adrenergic Hyper-Responsiveness in Asthma

Allergic asthma may be initiated by contact between inhaled antigens and IgE-sensitive pulmonary mast cells, resulting in the noncytotoxic release of biologically active mediators of anaphylaxis (e.g. histamine and SRS-A) (97,98). It is the interaction of these mediators with various lungs cells that causes the airway obstruction. *In vitro* examination of the immunological release of mediators from human lung tissue has demonstrated that neurohormones are capable of modulating the secretory reaction: β-adrenergic agonists suppress mediator release (99), whereas α-adrenergic (100) and cholinergic agonists (100,101) enhance mediator release. In addition, several lines of evidence suggest that abnormal α-adrenergic function may contribute to asthma: α-adrenergic stimulation of both animal (102) and human (103,104) bronchial muscle *in vitro* produces constriction, administration of catecholamines after β-adrenergic blockade may induce bronchoconstriction in both normal and asthmatic subjects (104-106) and α-adrenergic blocking agents may prevent the bronchospasm induced by histamine (107) or exercise (108).

With the above considerations in mind, it is of interest that Henderson and coworkers (109) recently reported increased α-adrenergic responsiveness in asthmatic subjects, as compared to normal controls. This hyperresponsiveness to α-adrenergic stimulation was measured by the capacity of phenylephrine to constrict the cutaneous vascular bed and to dilate the pupillary sphincter muscle. Highly significant differences in the doses required to reduce cutaneous blood flow by 50% and to dilate the pupil by 0.5 mm were observed between the asthmatic and normal subjects. The effects on cutaneous blood flow before and after various adrenergic blocking agents is shown in figure 4 below.

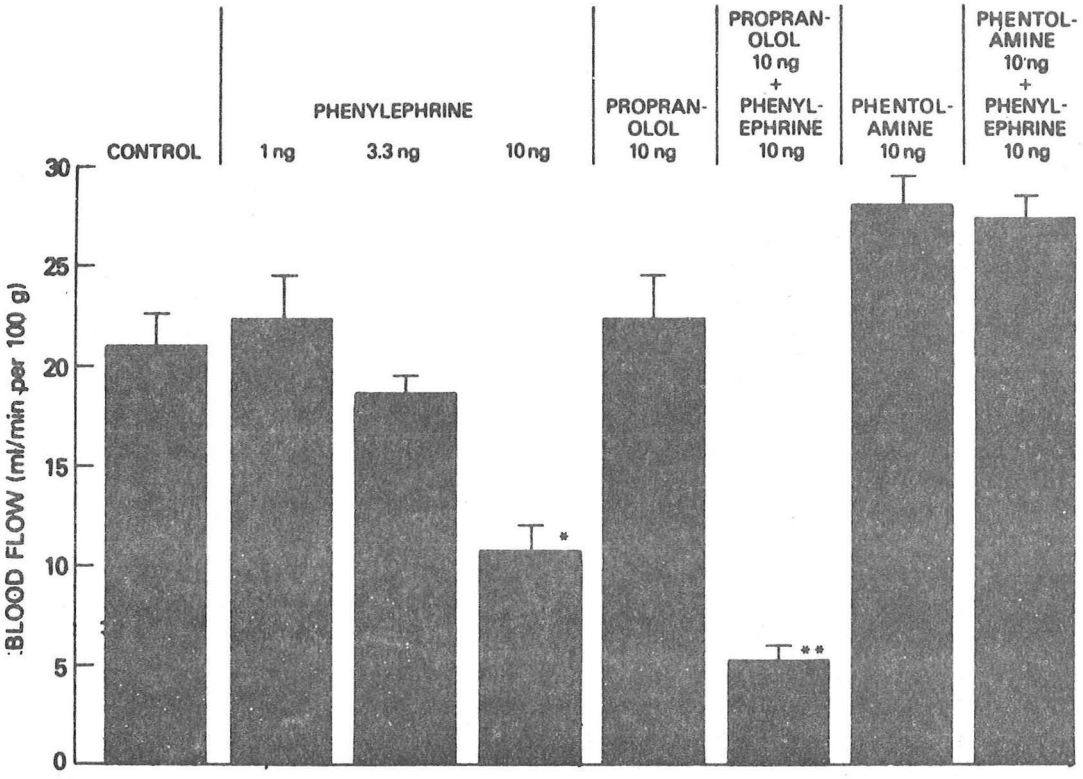

FIGURE 4. Effect of phenylephrine, propranolol and phentolamine, singly and in combination, on cutaneous blood flow *†p < 0.01

The results of this study suggest that further investigations into the therapeutic value of α-adrenergic antagonists are warranted. In normal subjects receiving propranolol, addition of an α-adrenergic antagonist does not alter peak expiratory flow rates either basally

or after exercise (110). It is possible, however, that these agents may be effective in asthmatic subjects. Additionally, the findings of Henderson et al. (109) suggest that α-adrenergic agonists should be used with caution in patients with asthma.

B. GLAUCOMA

Most cases of glaucoma can be assigned to one of two general categories: angle closure glaucoma or open angle glaucoma. The latter is far more common (approximately 100 times more common than angle closure) and the clinical presentation and treatment of the two types are markedly different.

Angle closure glaucoma occurs in individuals with an anatomically abnormal "crowded" anterior chamber; they are anatomically predisposed to sudden rises in intraocular pressure when the relationship between the iris and the crystalline lens creates a relative pupillary block. This block prevents the aqueous humor (which is secreted behind the iris) from entering the anterior chamber through the pupil. The aqueous humor is, therefore, unable to escape the eye through the normal drainage channels in the iridocorneal angle. Since the fluid is unable to escape intraocular pressure rises rapidly resulting in pain, ciliary injection and blindness (due to damage of the optic nerve), if left untreated. Therapy consists of miotic drops, carbonic anhydrase inhibitors (to decrease the outflow of aqueous humor) and osmotic agents (oral or intravenous). Once the attach has subsided, definitive therapy consists of creating a hole in the peripheral iris (peripheral iridectomy), which permits the aqueous humor to enter the anterior chamber.

In contrast open angle glaucoma is an insidious disease seldom causing symptoms until irreparable damage has occurred. Open angle glaucoma is due to impaired drainage of aqueous humor. Surgery is relatively ineffective (creation of a hole in the sclera for egress of the aqueous humor) and carries the risk of cataract formation and infection (111). Therapy for open angle galucoma is thus, essentially medical.

In addition to parasympathomimetic agents, β-adrenergic agonists have been used in this condition to decrease the outflow of aqueous humor. However, miotics result in spasm of accommodation which produces blurring of distant vision, which is intolerable in young patients and individuals with previously impaired visual activity due to cataracts. The β-agonist agents (particularly adrenaline) sting when instilled in the eye and many patients develop a local allergy to them. Carbonic anhydrase inhibitors are effective in lowering intraocular pressure. However, side-effects include drug sensitivity, malaise, fatigue and the risk of renal stone formation.

β-adrenergic blocking agents comprise of a new class of medications that lower intraocular pressure and which appear to be relatively free of side-effects. Propranolol (112-115) practolol (116), pindolol (117), oxprenolol (118), atenolol (119) and timolol (120-123) have all been shown to lower intraocular pressure. The mechanisms by which these agents lower intraocular pressure are unclear. Evidence to date suggests that at least the first phase of intraocular pressure reduction is due to reduced secretion of aqueous humor. It is puzzling that both β-adrenergic agonists and antagonists can lower intraocular pressure. The fact that the effects of β-adrenergic agonists and antagonists are not additive suggests that their mechanism of action is similar. However, β-adrenergic antagonists in addition to their efficacy in situations where β-agonists are also useful, may also be effective in patients who are unresponsive to β-agonists.

Timolol has recently been released in the U. S. for the therapy of open angle glaucoma and appears to be the most effective β-receptor antagonists in this condition. Unlike pilocarpine, timolol does not induce spasm of accommodation, nor does it affect the pupil. Tolerance to its effects has not been observed, although a "short term" escape from its initial intraocular pressure lowering effects may be observed. Its efficacy may be related to its potency in blocking β-adrenergic receptors which is 5 to 10 times that of propranolol. In addition, timolol is devoid of local anesthetic properties which limits the usefulness of propranolol in glaucoma.

A summary of the use of β-blocking agents in open angle glaucoma is shown below:

1. Effect on intraocular pressure is maximal after first or the first few administrations; however, with some β-blockers, the effect tends to lessen as treatment continues.

2. Mechanism of action appears to be reduction of aqueous humor secretion.

3. Side-effects with topical administration are usually minimal; β-blockers do not affect the pupil and do not induce spasm of accommodation. However, slowing of resting pulse rate may be observed.

4. Timolol eyedrops:

   a) Have proved at least as effective as pilocarpine
   b) Have a long duration of effect (need to be given only once or twice a day).
   c) To date, do not appear to be associated with marked tachyphylaxis (although a short term "escape" from the initial intraocular pressure lowering effect may be observed in some cases.

d) Are often additive to miotics and C.A. inhibitors.

C. HEART

a) α-Adrenergic Receptors

Wenzel and Su in 1966 (124) were the first to propose the existence of α-adrenergic receptors in rat myocardial strips. Since that time an array of confusing and contradictory reports on the role of myocardial α-adrenergic receptors have been published. For example:

1) Some workers report that stimulation of myocardial α-adrenergic receptors results in negative inotropic and chronotropic effects (125-128) while others suggest increased inotropic, but no chronotropic effects (129-132).

2) Both a decrease (128) and no change in cyclic AMP (129) levels have been reported following myocardial α-adrenergic receptor stimulation.

3) Both an increase (133) and no change in cyclic GMP levels (129) have been reported following myocardial α-adrenergic receptor stimulation.

4) Evidence from some studies suggest an interconversion of of myocardial β to α receptors". Evidence from other studies refute such an interconversion (129).

5) There is evidence that under some circumstances α-agonists can attenuate cyclic AMP generation by a mechanism which is blocked by α-receptor antagonists; in other circumstances this attenuation cannot be blocked by α-antagonists (128).

Much of the confusion is due to a) the variety of preparations examined e.g. isolated atrial and ventricle strips, intact animals, isolated perfused hearts and isolated myocytes; b) the variety of different animal species examined e.g. guinea pig, rat, rabbit, cat etc.; c) the variety and often unphysiological conditions employed e.g. high and low calcium concentrations in the perfusion media, and finally d) the variety of α-agonist doses used - some physiological, others clearly industrial.

In addition, despite the pharmacological evidence for the existence of myocardial α-adrenergic receptors in a variety of species including man (9), radioligand binding studies have been hampered by the failure to identify myocardial α-adrenergic receptors in several species including the dog and the guinea pig. A suitable animal model to study human myocardial α-receptors may thus not exist.

Despite these considerations, myocardial α-adrenergic receptors in man, may play an important role in circulatory homeostasis and an understanding of the functions mediated by these receptors could lead to significant therapeutic advances in such conditions as shock, congestive heart failure, myocardial infarction etc.

My own interpretation of myocardial α-adrenergic receptor, which is purely speculative, but is based on the available evidence is as follows:

1) Myocardial α-adrenergic receptors are atypical in their interactions with a variety of agonist and antagonists.

2) As suggested by Wenzel and Su (124) both α-stimulatory and α-inhibitory receptors are present in normal myocardium.

3) Under normal physiological conditions, neither type of α-receptor play a major role in the regulation of myocardial inotropic or chronotropic effects.

4) Under conditions of decreased myocardial drive e.g. hypothyroidism and certain shock state, α-stimulatory receptors may play an important role in maintaining myocardial contractility.

5) Under circumstances of increased myocardial drive, α-inhibitory receptors may predominate and prevent excessive cardiac stimulation.

6) α-inhibitory receptors may act by either decreasing cyclic AMP levels or by mitigating the increased cyclic AMP generated by β-stimulating agents.

7) α-stimulatory receptors mediate positive inotropic but not chronotropic effects by increasing transsarcolemmal calcium influx. Availability of calcium as a substrate for this effect, may be the basis for the therapeutic efficacy of calcium administration in cardiogenic shock.

b) Myocardial Ischemia

Myocardial ischemia is frequently complicated by the development of a number of arrhythmias including ventricular fibrillation, the mechanism of which remains unclear. In several animal species, clamping or transection of the aorta increases cyclic AMP levels in myocardium (135-137). This increase is prevented by β-receptor blockade (135-137).

It has been suggested that increases in cyclic AMP levels in ischemic tissue occur in association with the development of ventricular fibrillation (138,139). In dogs with distal coronary artery ligations which do not develop ventricular fibrillation, cyclic AMP levels in ischemic tissue are reported not to rise (138).

As the increase in cyclic AMP levels in ischemic myocardial tissue might be due to an alteration in β-adrenergic receptors, Amal Mukherjee, James Willerson and coworkers at this institution recently investigated the effects of myocardial ischemia on β-adrenergic receptors, using radioligand binding techniques (140).

Myocardial ischemia was effected in dogs by proximal occlusion of the left anterior descending coronary artery for periods of 15 minutes to 8 hours. In these studies, the number of β-adrenergic receptors increased markedly within one hour and persisted for at least 8 hours. In contrast, the affinity of the β-receptors for the radioligand, and cholinergic receptors, remained unchanged in the ischemic myocardium. In addition, the increase in β-receptor number was associated with a decrease in myocardial norepinephrine content.

Thus, these data suggest that an increase in β-adrenergic receptors may be causally related to the increased cyclic AMP levels that develop in ischemic myocardium and may be an etiologic factor in the development of ventricular arrhythmias.

D. KIDNEY

Renal Osteodytrophy

Renal osteodystrophy remains a serious complication of chronic renal failure. Increased parathyroid hormone (P.T.H.) secretion, decreased 1,25-dihydroxy-vitamin D_3 production and their effects on bone and changes in calcium and phosphorus metabolism contribute to the development of renal osteodystrophy (141). Raised P.T.H. secretion may persist despite therapy and lead to the continued progression of bone disease (142).

P.T.H. secretion has been shown both *in vivo* and *in vitro* to be modulated by parathyroid β-adrenergic receptors (143,144). In addition the report of the successful treatment of primary hyperparathyroidism with propranolol (145) has led to a preliminary investigation of the role of β-adrenergic blockade in renal osteodystrophy (146).

This study was performed in 9 patients with chronic renal failure treated with propranolol for hypertension, and in 25 untreated patients with chronic renal failure. Age, sex distribution, length of renal failure and duration of dialysis were similar in both groups. However, P.T.H. and alkaline phosphatase levels were 4.5 and 2-fold higher in the untreated group, than in the propranolol-treated group, despite similar calcium, albumin, phosphate and magnesium levels. In addition, radiological evidence of renal osteodystrophy was more frequent in the untreated patients.

These data suggest that β-blockade may mitigate against the increased P.T.H. secretion of chronic renal failure and thus, may prevent or retard the onset of renal osteodystrophy.

These interesting findings suggest that prospective studies are needed to determine whether propranolol or other β-adrenergic antagonists are useful as adjuncts in the management of renal osteodystrophy.

Hypertension

α-adrenergic receptors mediate sympathetically-controlled renal vascular resistance. In human essential hypertension and in the spontaneously hypertensive rat, an animal paradigm of the disease, renal vascular resistance is increased and may be involved in the pathogenesis of these forms of hypertension. To examine the role of α-adrenergic receptors in this increased renal vascular resistance, we recently quantitated α-adrenergic receptors in the kidneys of spontaneously hypertensive rats (SHR) and in age and sex-match normotensive controls (NCR) (85).

In all groups of hypertensive rats the number of renal α-receptor number were significantly higher than in the match NCR. In addition, mean arterial pressure, heart rate and plasma norepinephrine levels were also higher in the spontaneously hypertensive animals.

These findings suggest that in addition to enhanced sympathetic nerve activity, increase renal α-adrenergic receptors may contribute to the increased renal vascular resistance observed in SHR. As discussed previously in all cases examined increased catecholamine levels suppress the number of adrenergic receptors. Thus, the finding of increased renal α-adrenergic receptors, despite higher levels of plasma norepinephrine, suggests that a possible molecular mechanism for the increased renal vascular resistance in SHR, is a failure of the normal suppression of α-adrenergic receptors by the endogenous levels of norepinephrine.

E. LIVER CELL ADRENERGIC RECEPTORS

For many years it was believed that the adrenergic receptor concerned in the effect of catecholamines on carbohydrate metabolism in the liver, was of the β-type (147,148). More recently, it has become clear that the usual techniques for receptor classification (i.e. the complementary use of selective agonists and antagonists) were difficult to apply in the intact organism. This was partly because of the complexity of the hormonal control of hepatic metabolism. Thus, adrenergic agonist and antagonists can cause changes in plasma insulin, glucagon, lactate and free fatty acids, each of which will indirectly affect the functioning of the liver. In addition, liver cells are unmatched in their ability to inactivate hormones and drugs. It is not surprising then, that there has been a good deal of uncertainty about the receptors on hepatocytes.

It is now clear, as a result of studies in perfused livers, liver slices and isolated hepatocytes, that α - as well as β-adrenergic receptors can increase gluconeogenesis and glycogenolysis in the liver (149-154). Stimulation of hepatic β-receptors is associated with an increase in cyclic AMP and phosphorylase activity (155). In contrast, only phosphorylase activity is increased upon stimulation of α-receptors (156). This increase in phosphorylase activity may result from an increase in cytoplasmic calcium or from reduction in the activity of hepatic phosphorylase phosphatase (which inactivates glycogen phosphorylase) (157).

With regard to the sub-classification of the α- and β-receptor of the liver, it has been suggested that the β-receptors are normally of the β_2 type (158). In contrast, receptors of the β_1 type have been found in a malignantly transformed cell line, Zajdela hepatoma (158). The α-receptors would seem to be of the α_2 (53) or postsynaptic type (described in studies of neurotransmission in smooth muscle), since phenylephrine, methoxamine and amidephrine are effective agonists (149). Selective antagonists have not yet been tested, however, and such experiments are likely to be complicated by the capactiy of the liver cells to inactivate drugs.

In addition to effects on carbohydrate metabolism in the liver, catecholamine receptors mediated vasoconstriction (α) and dilatation (β) in hepatic blood vessels (159). Kupffer cells are also known to respond to adrenaline with an increase in lipolysis and gluconeogenesis (160).

α-Receptors on hepatic parenchymal cells have also been described which mediate transient net loss of potassium (161) and thus may be a major factor in adrenaline hyperkalemia

(153). Whether these receptors are the same ones which mediate effects on carbohydrate metabolism, remains unclear. However, under some circumstances the loss of potassium can be dissociated from the increase in glucose release (161).

F. PLATELETS

a) Introduction

Human platelets are a readily accessible source of human "tissue" which have provided unique insights into adrenergic as well as prostaglandin pharmacology, some of which may be directly relevant to several clinical disorders.

α-adrenergic receptors on human platelets mediate aggregation, whereas stimulation of β-adrenergic receptors on human platelets, inhibits platelet aggregation (162). Both types of adrenergic receptors are couple to platelet adenylate cyclase. Stimulation by α-adrenergic agents inhibits, and stimulation by β-adrenergic agents increases platelet adenylate cyclase activity (162). Moreover, platelet α-adrenergic receptors have been identified by radioligand binding studies using [^{3}H]dihydroergocryptine and the binding characteristics to this receptors correlate closely with changes in adenylate cyclase activity (163). In addition, prolonged exposure to α-adrenergic agonists, as with the rat parotid acinar cells discussed previously, results in a time-dependent decrease in platelet aggregation plus a concomitant decrease in α-adrenergic receptor concentration (164).

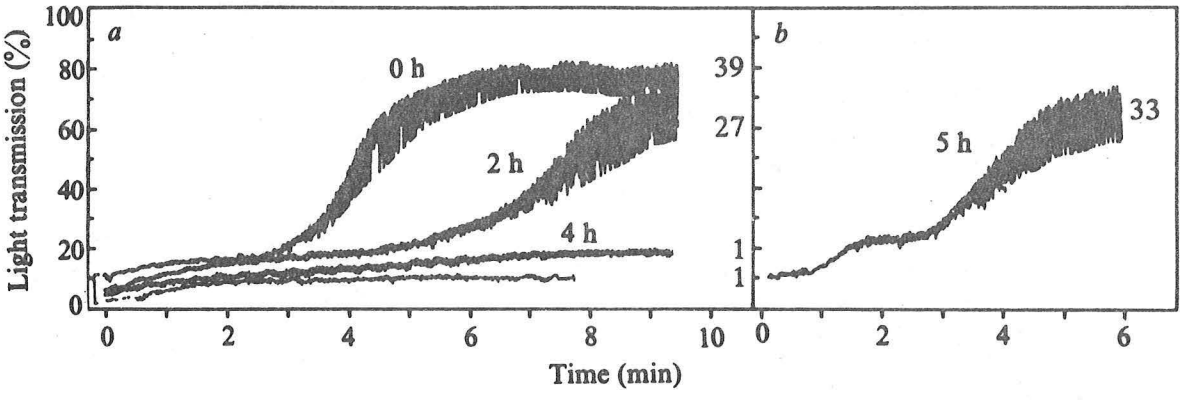

FIGURE 5. Effect of incubation with adrenaline on platelet aggregation. Within 2 hours aggregation time is increased and by 4 hours no aggregation occurs (a). In platelets incubated without adrenaline for up to 5 hours, aggregation occurs normally (b).

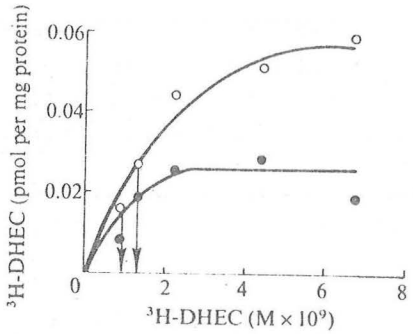

FIGURE 6. ^{3}H-dihydroergocryptine (^{3}H-DHEC) binding to platelet α-adrenergic receptors with (●) and without (o) prior incubation with adrenaline for 4.5 hours.

b) Estrogens and Platelet Function

It is well known that estrogen therapy is associated with an increased incidence of thromobotic events. This phenomenon has generally been attributed to an estrogen-induced "hypercoagulable state" resulting from the excessive liberation of coagulation factors from the liver. Teleologically, this estrogen-induced state may serve as a protective factor in preventing excessive hemorrhage at parturition. Estrogens also increase platelet aggregation in humans and this effect may contribute to the increased incidence of thrombotic complications. However, the mechanisms for estrogen's effects on platelet aggregation has not been defined.

In rabbits, estrogen inhibits platelet aggregation, while α-adrenergic agonists, as in humans, induced platelet aggregation. As hormones may regulate receptors for different ligands (e.g. thyroxine increases cardiac β-receptors), Goldfien et al. (165) recently investigated the effect of estrogen on rabbit platelet α-adrenergic receptors, using radioligand binding studies. In platelets from oopherectomized rabbits, estrogen decreased α-adrenergic receptor concentration by 40%, without altering the binding affinity of the radioligand. This finding

suggests that a decrease in the number of platelet α-receptors may be the mechanism by which estrogen decreases platelet aggregation in the rabbit. By analogy, an increase in α-adrenergic receptors may be responsible for the estrogen-induced increase in human platelet aggregation.

c) Essential Thromocythemia

Essential thrombocythemia is a myeloproliferative disorder associated with an increased platelet count and complicated by thrombosis or hemorrhage (166). The hemorrhagic diathesis may be related to abnormal platelet function and diminished responsiveness of platelets in this disorder to a number of aggregating agents has been demonstrated in vitro (167,168).

Recently, Kaywin et al. (169) have reported that α-adrenergic receptors and the aggregating response to epinephrine were decrease in two patients with essential thrombocythemia, as compared to platelets from normal controls. In contrast, platelets from two other patients with essential thrombocythemia responded normally to and contained a normal number of α-adrenergic receptors. This finding suggests that a deficiency of α-adrenergic receptors may account for the diminished functional responsiveness of platelets to epinephrine in some patients with essential thrombocythemia.

Whether this receptor defect results from the platelets derivation from a malignant progenitor or from events that occur as the platelet circulates, remains unknown. It is possible, however, that delineation of this defect may serve as a useful indicator of progression of the disease.

DOPAMINE RECEPTORS: PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

A. PROLACTIN, DOPAMINE RECEPTORS AND DOPAMINERGIC AGONISTS

i) PROLACTIN AND DOPAMINE RECEPTORS

The identification and measurement of prolactin in human serum has led to rapid advances in the understanding of normal human prolactin physiology as well as in the recognition of disorders of its secretion. Prolactin secretion is influenced by a number of factors, as shown in Table 4.

The chemical nature of prolactin inhibitory factor (PIF) has not yet been elucidated, nor is it clear whether a prolactin releasing factor exists. An inhibitory factor is release by the hypothalamus in response to afferent dopaminergic stimuli or to the administration of dopamine agonists. These drugs applied directly to the pituitary in vitro can also cause

TABLE 4. FACTORS AFFECTING HUMAN PROLACTIN SECRETION*

PHYSIOLOGICAL	
Sleep	++
Nursing	+++
Breast Stimulation (non-postpartum)	+
Stress	++
Hypoglycemia	+
Glucose	± or -
Strenuous exercise	+
Sexual intercourse (women)	+
Pregnancy	+++
Estrogens	+
Hypothyroidism	+
PHARMACOLOGICAL	
1. Dopaminergic Agonists	
L-dopa	--
Apomorphine	--
Ergot derivatives (Bromocryptine, lergotrile)	--
2. Dopaminergic Antagonists	
Phenothiazines, butyrophenones	++
Metoclopramide	+++
3. Others	
Thyrotropin releasing factor	++
Opiates	++

* + increased, decreased secretion.

cause suppression of prolactin release, but until recently it was assumed that this mechanism was probably not of significance in physiologic situations (170). Increasing evidence that dopamine might normally act on the pituitary and failure to isolate and characterized a separate PIF in animals, have led Mac Leod and others (171-174) to suggest that dopamine may be the natural or physiological PIF. This view is supported by recent work *in vivo* showing that small doses of L-dopa, administered systemically, effectively suppress prolactin in monkeys whose pituitary glands have been completely separated from

the hypothalamus by section of the pituitary stalk and by interposition of a silastic barrier (174). Evidence has also been presented that the ergot derivatives, bromocryptine and lergotrile, have a direct pituitary as well as a hypothalamic locus of action (175,176). This concept is important in accounting for the therapeutic efficacy of these drugs in many patients with prolacting-secreting pituitary tumors whose pituitary-hypothalamic connections may have been compromised or destroyed by prior surgical intervention.

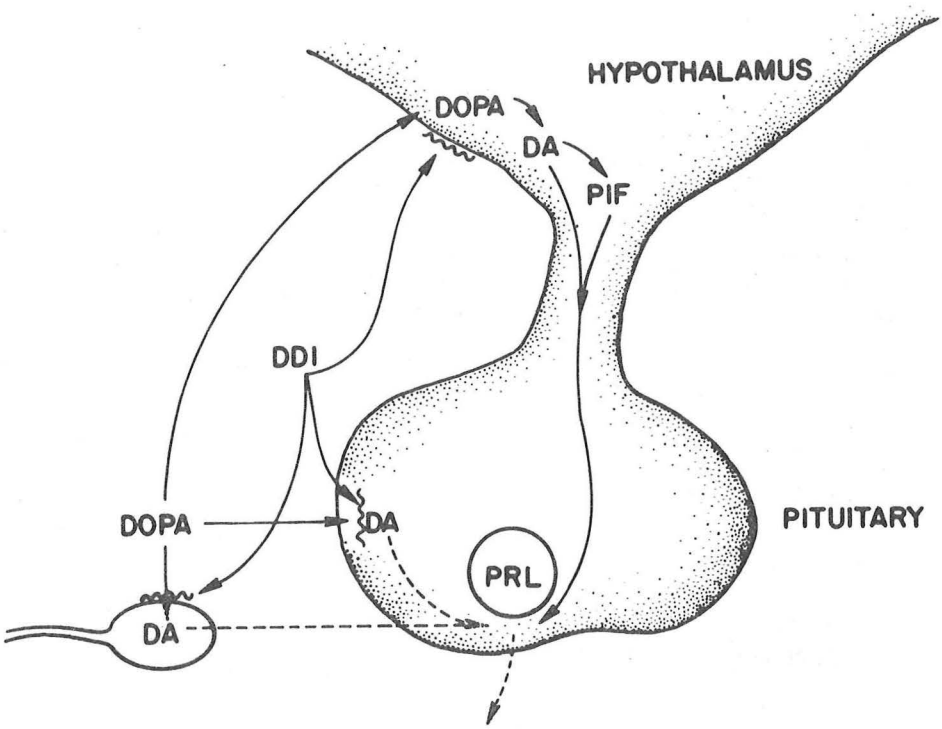

FIGURE 7. Proposed mechanism for the effect of pretreatment with carbidopa, a dopa decarboxylase inhibitor (DDI), on the prolactin (PRL) suppressive action of L-dopa. Because the blood brain barrier is relatively impermeable to the DDI, the peripheral conversion of dopa to dopamine in the pituitary and peripheral nerve terminals is selectively blocked whereas the central conversion of dopa to dopamine is unimpaired and the PRL-suppressive effects of dopamine, due either to its release into the portal system or by stimulating the release of PRL-inhibiting factor, remain intact.

As a result of these insights into the physiology and pathophysiology of prolactin secretion, it is not surprising that an increasing number of conditions associated with hyperprolactinemia are being identified and found to be amenable to therapy with dopaminergic agonists. (Table 5)

TABLE 5. CAUSE OF HYPERPROLACTINEMIA

A. Amenable to Therapy with Dopaminergic Agonists

Hyperprolactinemic impotence
Hyperprolactinemic amenorrhea ± galactorrhea

1. Post o/c pill
2. Pituitary tumor

Hyperprolactinemic short luteal phase
Post-partum galactorrhea
Pituitary tumor
Destructive lesions of the hypothalamus
Acromegaly

B. Others

DRUGS a) Dopamine depleting drugs (e.g. α-methydopa, reserpine)
b) Dopamine receptor blocking drugs (e.g. phenothiazines, butyrophenones)

Primary Hypothyroidism (↑TRF)

11) DOPAMINERGIC AGONISTS

In view of the increasing applicability of these agents a thorough understanding of their pharmacological and toxic effects is essential. Bromocryptine is the prototype of the dopaminergic agonists and will be discussed in some detail.

Bromocryptine (2-bromo-α-ergocryptine) is an ergot alkaloid which belongs to the cyclic peptide group of lysergic acid derivatives. It is a weak base quite insoluble in water. It is commercially available as the methanesulphonate. The addition of the bromine atom alters the pharmacological action of the compound and gives it its major therapeutic use, that of inhibition of prolactin secretion via agonism of central dopaminergic receptors (177).

Toxicity

Animals and human studies indicate a high therapeutic to toxic ratio (178). Teratogenicity has not been found and no adverse effects on fertility, embryonal development and subsequent viability of the fetus have been reported (179,180).

Pharmacologic Properties

Bromocryptine is rapidly and completely absorbed. Peak levels occur 2-3 hours after oral administration. It is extensively metabolized in the liver and primarily excreted via the biliary system.

Pharmacological Activity

Bromocryptine is very specific to the pituitary prolactinotrophe. Its effects on other hormones and other systems, especially the central nervous system, are much less specific and less clearly defined.

Effects on Pituitary Dependent Hormone

1. Prolactin site of action pituitary ± hypothalamus.
2. FSH and LH - In man, no discernible effects on FSH when assessed with random measurements of basal serum values (181-183), although LH may be inhibited (183). In hyperprolactinemic impotent males and hyperprolactinemic amenorrheic females, bromocryptine restores normal pulsatile serum LH secretion (184,185) and ovulation (186), respectively. These actions are probably due to its prolactin inhibitory effects rather than to any direct effect (186).
3. Thyrotrophin (TSH)
   a) No effect on basal or stimulated levels in normals
   b) Decreases basal TSH levels in hypothyroidism (187). As the response also seen with L-dopa (188), it may be mediated by activation of dopaminergic receptors.
4. ACTH and MSH
   a) No effect in normal on ACTH (189).
   b) Acute administration of bromocryptine to patients with Cushing's disease (189) or Nelson's Syndrome (190) reduce ACTH levels.
   c) In animals bromocryptine inhibits MSH secretion (191).
5. Adrenal androgens (Dihydroepiandrosterone and dihydroepiandrosterone sulphate).
   a) In hyperprolactinemic states associated with increased adrenal androgens,bromocryptine lowers the androgen levels (192), probably via its prolactin inhibitory effects.
6. Growth Hormone
   (c.f. section on acromegaly)

Nonpituitary Effects

1. Central Nervous System

   In man bromocryptine has a powerful central nervous system stimulating effect and marked antidepressant activity. Cases

have been reported of visual hallucinations, a schizophrenic-like state, and mania (193). These side-effects may limit bromocryptine's usefulness in the therapy of Parkinsonism and acromegaly, where large doses are required.

In addition to the use of bromocryptine in Parkinsonism, its use in other degenerative (Huntington's chorea) (186) and metabolic (portasystemic encephalopathy) (194) central nervous system disorders is under review.

2. Cardiovascular System
(c.f. section on dopamine receptors and hypertension)
3. Peripheral Vascular System
Digital vasospasm (Raynaud's Phenomenon) and erythromelagia (tender red edematous feet) have been reported with bromocryptine, although its potential for vasoconstriction is much less than with other ergot alkaloids.
4. Gastrointestinal Tract
a) Bromocryptine frequently produces nausea and vomiting (195) due to an action on dopamine sensitive medullary chemoreceptor areas. Interestingly, the dopaminergic antagonist, metoclopramide may abolish these adverse effects in patients with Parkinson's disease, without reducing the antiparkinsonian effects of bromocryptine (196).
b) Bromocryptine inhibits intestinal smooth muscle (197) and clinically constipation is a common complaint (10-20%) in patients treated for acromegaly and Parkinson's disease where large doses are required.
5. Effects on Water and Electrolyte Excretion
As bromocryptine lowers prolactin levels, its effects on water and electrolyte excretion may result from a direct action on the kidney or may be due to its prolactin inhibitory effects. Studies on the effect of prolactin on water and electrolyte excretion must be interpreted with caution, as heterologous ovine prolactin used in these studies contains vasopressin (198). Thus, the finding that prolactin reduces free water, sodium and potassium excretion (199) is probably erroneous and due entirely to the effects of vasopressin contamination (198). Prolactin, per se, probably has little effect on water and electrolyte excretion when administered acutely to normal subjects (198), and any effects of bromocryptine are independent of its prolactin suppressing action.

Del Pozo and Ohnhaus, 1976 (200) showed that short-term administration of bromocryptine was without effect on renal water, sodium and potassium excretion in normals. However, the finding by Edwards et al. 1975 that bromocrytpine inhibits the increase in aldosterone following furosemide (201), suggests that dopamine receptors may play a role in aldosterone homeostasis. This relationship was examined in an elegant study by

Cary et al. 1979 (202). In this study, the effect of stimulation or blockade of dopamine receptors with bromocryptine and mot clopramide, respectively, on the renin-angiotensin-aldosterone system, plasma prolactin and angiotensin stimulated aldosterone release, was examined in normal subjects. The results of this study suggest that aldosterone production is under maximum tonic dopaminergic inhibition, which can be overriden with stimulation by angiotensin. Whether this inhibition of aldosterone production is mediated by central or peripheral dopamine receptors, remains unclear. The finding by Liddle and coworkers that dopamine inhibits angiotensin stimulated, but not basal aldosterone biosynthesis, in isolated bovine adrenal cells (203), suggests that adrenal cortical dopamine receptors may be involved. However, this latter study must remain in question, as other dopaminergic agonists were not tested, and the response was not shown to be suppressible by specific dopaminergic antagonists.

6. Clinical Use

The indications for bromocryptine therapy are shown in Table 6.

TABLE 6. USES OF BROMOCRYPTINE IN CLINICAL PRACTICE

A. Established Uses

Hyperprolactinemic impotence
Hyperprolactinemic amenorrhea
Hyperprolactinemic short luteal phase
Hyperprolactinemic galactorrhea
Postpartum galactorrhea
Acromegaly
Parkinson's disease

B. Under Investigation

Breast cancer
Fibrocystic disease of the breast
Mastodynia
Premenstrual tension
Bladder instability
Hypertension
Portasystemic encephalopathy
Cushing's disease
Nelson's syndrome

7. Adverse Effects

The most commonly reported side effects of bromocryptine during clinical use are nausea, vomiting (central dopaminergic response), postural hypotension (c.f. section on hypertension and dopamine receptors), nasal congestion, constipation (direct effect on gut to decrease motility) and mood changes (? direct central dopaminergic effect). With high doses or in occasional

susceptible patients, hallucinations (central dopaminergic effect), fatigue, erythromelalgia, digital vasospasm (ergot α-receptor mediated vasoconstrictor effect), bladder disturbances (retention - ? ergot α-receptor effect) and alcohol intolerance have been reported. Dyskinesias can occur in Parkinsonian patients but are less prominent than with L-dopa. Diplopia, ergotism, angina and arrhythmias are uncommon side-effects.

The incidence of most side-effects appears to be dose related, and at doses exceeding 10 mg. daily any of the above side-effects may occur. Most side-effects can be overcome by taking the drug with meals and starting at low doses such as 1.25 mg. with subsequent increases over a period of 1 to 2 weeks to full dosage.

B. PARKINSONISM

In parkinsonism there is a gross reduction in striatal dopamine content in approximate proportion to the degree of cell loss found at post mortem in the pars compacta of the substantia nigra, and in approximate proportion to the degree of akinesia in life (204). The action of dopaminergic agonists in reversing the symptoms of parkinsonism is probably due to the agonist effects of the drugs on the remaining postsynaptic dopamine receptors in the nigrostriatum and also possibly in the limbic system. In contrast to the situation in parkinsonism, in hyperprolactinemia and acromegaly,motor centers of the central nervous system are not damaged and there is probably no reduction in regional dopamine content in the brain. The actions of dopaminergic agents in these endocrine disorders is likely to result from stimulation of extracerbral pituitary dopamine receptors (205).

In addition to dopaminergic agonists, L-dopa, the precursor of dopamine, is also effective in parkinsonism and acts by increasing the production of dopamine in the brain. Dopamine, per se, does not cross the blood brain barrier and is thus ineffective in Parkinson's disease. The activity of L-dopa is enhanced by the administration of the dopa-decarboxylase inhibitor, carbidopa. Carbidopa does not cross the blood brain barrier and thus only inhibits the peripheral conversion of L-dopa to dopamine (206). This action prevents the peripheral metabolism of L-dopa which reduces the dosage requirements of L-dopa, and thus the adverse circulatory effects of dopamine. Central dopamine releasing drugs (e.g. piribedil) have also been tested but are only modestly potent in man (205).

Bromocryptine (2-bromo-α-ergocryptine), thus far, appears to be the most useful of the dopaminergic agonists, although apomorphine, norpropyl-noraporphine, lergotrile and lisuride (other dopaminergic agonists) have also been shown to have antiparkinsonian activity (207-214). Bromocryptine acts via nonadenylate cyclase linked dopamine receptors (2). It has a long duration of action and is particularly useful in reducing the severity and frequency

of "on-off" reactions observed with L-dopa. These reactions result from rapid fluctuations in plasma and brain dopa levels accompanying frequent multiple oral L-dopa dosages (205). This type of response probably results from progression of the disease resulting in continued loss of dopaminergic neurons from the substantia nigra (205).

From the studies of the use of bromocryptine in parkinsonism (207-214) it has emerged that:

1) High doses of bromocryptine (50-100 mg. daily) elicit a therapeutic response comparable to that of L-dopa in many patients.
2) In a minority of patients, increasing the dose of dopaminergic drugs (bromocryptine or less commonly L-dopa) to very high levels can lead to an exacerbation of parkinsonism.
3) The main value of bromocryptine is reduction in the severity and frequency of "on-off" reactions and in the treatment of patients with severe dyskinesias induced by L-dopa
4) The dose of bromocryptine should be increased gradually concomitantly reducing the intake of L-dopa in patients already receiving this drug.
5) Optimal results are frequently achieved with a combination of submaximal doses of bromocryptine and L-dopa.
6) While bromocryptine induces less dyskinesia than L-dopa, psychiatric reactions (hallucinations, psychoses, etc.) are more common and take longer to resolve after stopping therapy.
7) Other dose-dependent, reversible adverse effects of bromocryptine include emesis, hypotension, cardiac arrhythmias, digital vasospasm, conjunctival irritation, diplopia, nasal suffiness, constipation and erythromelalgia.

C. ACROMEGALY

The link between dopamine receptors and acromegaly is based on the observation that patients with acromegaly frequently respond with a paradoxicial lowering of serum growth hormone to administration of dopaminergic agonists including L-dopa (215,216), 2-α-Br-ergocryptine (bromocryptine) (217,218) and lergotrile mesylate (219). This action in acromegalics contrasts with that seen in normal subjects who characteristically exhibit a rise in serum growth hormone after dopaminergic stimulation.

The mechanism by which dopaminergic agonists lower growth hormone levels is unclear, but is probably mediated by dopamine receptors as all dopaminergic agonists have similar paradoxical effects on growth hormone secretion (218-223). Recently, it has been suggested that in acromegaly the somatotrophs have acquired inhibitory dopamine receptors,whereas in normal subjects dopaminergic agonists act at the hypothalamic level to inhibit growth hormone

secretion (224).

There is, in addition, evidence that growth hormone secretion is mediated via central α-adrenergic receptors, as acute administration of the centrally acting α-adrenergic agonist, clonidine, increases growth hormone levels in animals (225-227) and man (228,229). Interestingly, this effect of clonidine is not observed with chronic oral administration of the drug to male pubertal hypertensive subjects, in doses which suppress sympathetic nerve activity and renin release (230). In addition, acute administration of clonidine increases prolactin levels in animals (231) and man (232).

Whether the acute effect of clonidine on growth hormone and prolactin is mediated by central pre or postsynaptic receptors, remains unclear. However, as presynaptic α- and dopamine receptors are inhibitory to stimulus induced norepinephrine release (46), clonidine and the dopaminergic agonists, at least in normals, may both be acting by a presynaptic mechanism. In this context, it may be interesting to try treating acromegalics with the presynaptic α-adrenergic agonist, clonidine.

In the therapy of acromegalics, the major advantage of dopaminergic agonists (233) is their lack of effect on pituitary function, other than growth hormone and prolacting secretion and avoidance of the complications of surgical or radiation therapy. Their disadvantages are that the majority of patients only show a partial response, and the degree of compliance required with long-term therapy. They are, however, useful adjuncts to surgical and radiation therapy and in a few large studies of bromocryptine treatment used alone, the results obtained over a limited period compared favorably with those obtained by radiotherapy (229,234,235).

D. SCHIZOPHRENIA

The close similarity of amphetamine psychosis to acute paranoid schizophrenia has been recognized since Connell (236) and Carlsson and Lindqvist (237) described the actions of various neuroleptic drugs on dopamine turnover and suggested that the therapeutic effects of these agents might be related to their ability to block dopamine receptors. Subsequently, Randrup and his colleagues (238,239) initiated a program of research which established the role of dopamine in the behavioral actions of the amphetamines. In addition, van Rossum (240) suggested that dopamine receptor blockade was related to the antipsychotic potency of neuroleptics and Randrup and Munkrad (239) demonstrated a selective reversal by these agents of the behavioral changes induced in animals by amphetamines.

From these observations developed what may be referred to as the "dopamine hypothesis" of schizophrenia (241,242) - that some

(or perhaps all) of the symptoms of schizophrenia arise from excessive activity of dopaminergic mechanisms, and that the effects of this excess (and thus the symptoms of schizophrenia) can be reduced by the dopamine receptor blockade induced by neuroleptic drugs. However, there are substantial objections to the dopamine overactivity hypothesis of schizophrenia as:

1) CSF studies of homovanillic acid (a dopamine metabolite) following probenecid administration (243,244) have yielded no evidence of increased dopamine turnover even though, with this technique, it is possible to demonstrate increased turnover in amphetamine psychosis (245).
2) Homovanillic acid and dihydroxyphenylacetic acid levels (metabolites of dopamine which reflect changes in dopamine content and dopamine turnover) are similar in the brains (caudate, putamen and nucleus accumbens) of schizophrenics and normal controls (246).
3) Studies of prolactin secretion in unmedicated acute (247)and chronic (248) schizophrenic patients have revealed no evidence of the decrease in prolactin secretion, which might be expected if there were increased dopamine release from the tuberoinfundibular system.
4) Schizophrenic illnesses can occur in patients with longstanding Parkinson's disease (249), and there appears to be no particular modification of the symptoms of one disease by the other. The significance of this coincidence is enhanced by the observation, previously discussed (c.f. section on Parkinson's disease), that dopamine is as depleted in the mesolimbic regions as in the corpus striatum in Parkinson's disease (250).

These observations suggest that increased dopamine release is not necessary for typically schizophrenic symptoms to be expressed and until recently it has been difficult to reconcile the therapeutic efficacy of dopamine-receptor blocking agents in this condition. With the report by Owen and co-workers (246) that dopamine receptor density is increased in the brains of schizophrenics (Figure 8) one might speculate that, as with renal α-receptors in spontaneously hypertensive rats (vide supra), the mechanism for the symptoms in schizophrenia, is overactivity of dopaminergic mechanisms resulting from a failure of the endogenous neurotransmitter to suppress dopamine receptor density in the mesolimbic regions. Such a mechanism would explain the lack of evidence for increased dopamine release as well as the therapeutic efficacy of dopamine-receptor antagonists. Obviously, this hypothesis remains to be substantiated.

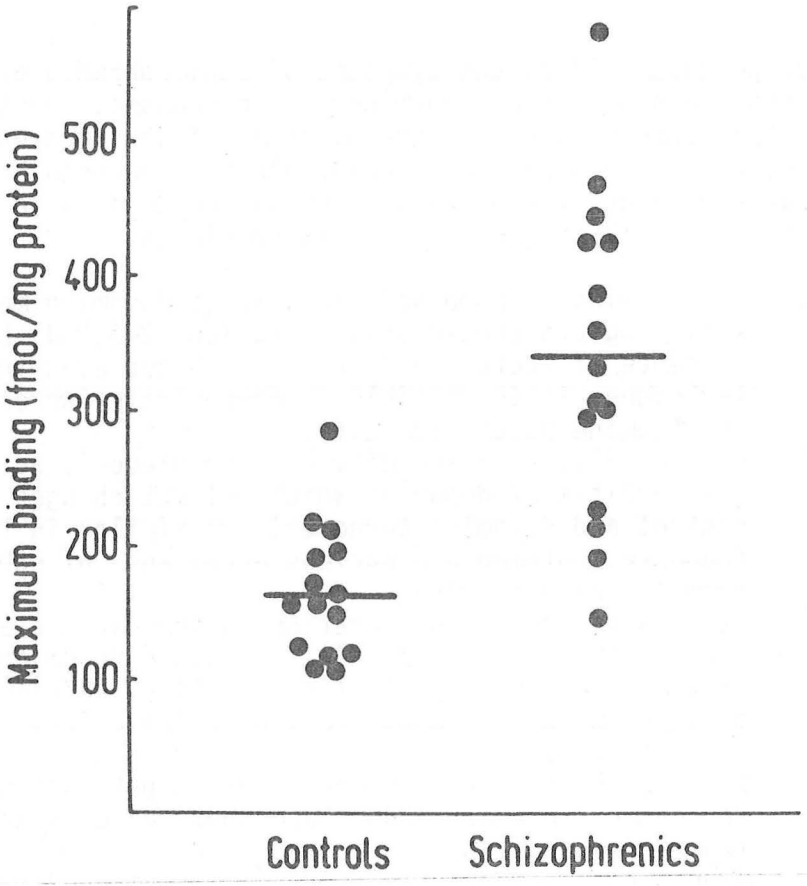

FIGURE 8. Dopamine-receptor density (as assessed by maximum specific spiroperidol binding in caudate nucleus in schizophrenics and controls ($p < 0.001$, controls vs. schizophrenics).

E. HYPERTENSION

Administration of the dopamine precursor L-dopa results in an increase in central nervous system (CNS) catecholamine content and a reduction in efferent sympathetic nerve activity, concomitant with a fall in arterial blood pressure (251-256). In addition, therapy with L-dopa or the dopaminergic agonist, bromocryptine lowers systolic and diastolic blood pressure and may limit the therapeutic potential of these agents in patients with Parkinson's disease (257-260). These observations suggest that dopamine receptors contribute to arterial blood pressure homeostasis.

Theoretically, stimulation of dopamine receptors may lower arterial pressure by several mechanisms:

1) A reduction in renal and mesenteric vascular resistance (261)
2) Inhibition of sympathetic neurotransmission presynaptically either at the level of the sympathetic ganglia (262) or at the post-ganglionic sympathetic nerve terminals (263).
3) Via a central action - either by increasing CNS catecholamine content which inhibits sympathetic outflow (251-256) or by a direct inhibitory effect on the vasomotor center in the medulla (264).

Systemic administration of low doses (1-10 μg/kg/min) of dopamine (which does not cross the blood brain barrier) to normal man, decreases renal and mesenteric vascular resistance via an action on dopamine receptors in these vascular beds (261). However, arterial pressure does not fall as skeletal-muscle vascular resistance and cardiac output increase (261). When high doses (> 10 μg/kg/min) are administered, blood pressure increases due predominantly to α-receptor mediated vasoconstriction (261). Thus, it is unlikely that dopamine receptors mediate a reduction in arterial pressure by a peripheral mechanism, at least in normotensive subjects. Evidence for a central hypotensive action is the finding that intracerbraventricular administration of bromocryptine lowers arterial pressure in animals (264).

Recently, evidence has accumulated that central dopamine receptors in addition to a role in normal blood pressure control, may contribute to the maintenance of hypertension in the rat and man. Thus, Judy et al., 1978 (265) demonstrated that administration of L-dopa plus the peripheral dopa-decarboxylase inhibitor, carbidopa (which, as discussed previously, increases CNS dopamine), decreased sympathetic nerve activity and arterial blood pressure in spontaneously hypertensive rats. In contrast, L-dopa alone, increased arterial pressure markedly. In addition, Stumpe et al., 1977 (266) demonstrated that plasma prolactin concentration was up to four times higher in male patients with essential hypertension than in normotensive controls. Oral administration of bromocryptine suppressed plasma prolactin and lowered arterial pressure (Figure 9). It was concluded that 1) in hypertensive patients the raised prolactin levels reflected a defect in central dopamine control which is normalized by bromocryptine; and 2) that the antihypertensive effect of bromocryptine suggests that reduced CNS dopaminergic activity may be a factor in the maintenance of essential hypertension. In this study the increase in plasma prolactin and the antihypertensive response to bromocryptine were more marked in patients with high to normal plasma renin activity than in those with low plasma renin activity. As discussed previously, sympathetic nerve activity decreases in response to central dopaminergic stimulation. In addition, as high plasma renin activity has been postulated to reflect increased sympathetic outflow (267,268), the above findings further suggest that a defect in central dopamine control may contribute to the increased sympathetic activity observed in some patients with essential hypertension.

Whether these findings will hold true in a larger group of patients, the extent to which a defect in central dopamine activity contributes to the maintenance of arterial hypertension and the full therapeutic potential of bromocryptine as an antihypertensive agent, remains to be determined. However, these provocative and interesting studies obviously warrant further investigation.

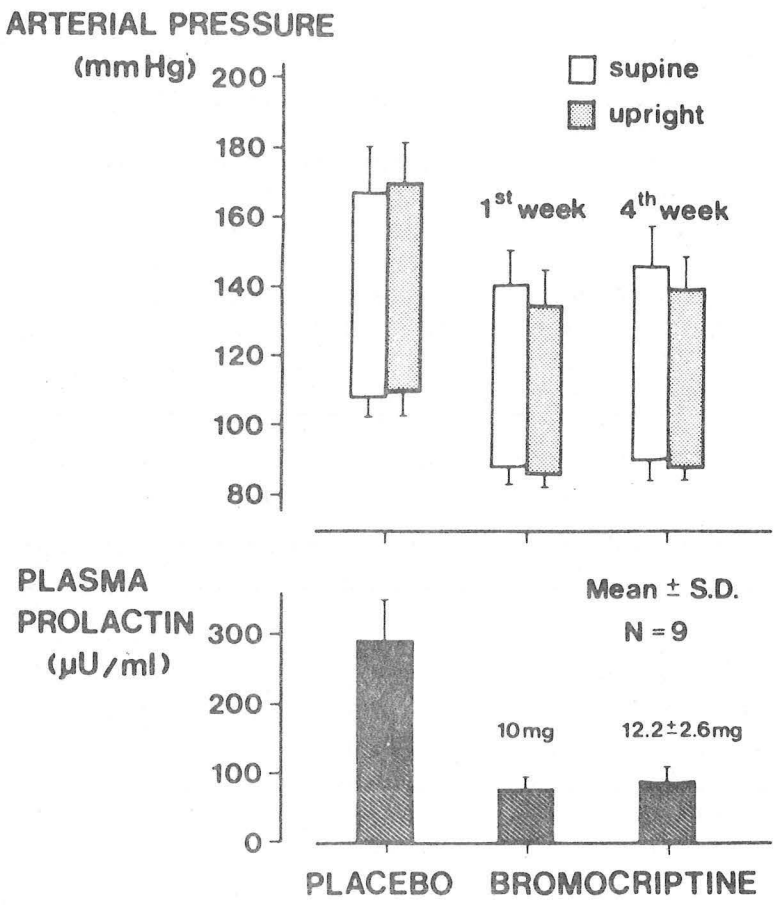

FIGURE 9. Arterial pressure and plasma-prolactin responses to bromocryptine in nine hypertensives with hyperprolactinemia.

SUMMARY

As can be seen from the preceding discussion on dopamine receptors, it is becoming increasingly clear that abnormalities in central dopaminergic systems may be involved in the expression of a number of distinct clinical entities. While the role of these systems in each of these entities remains to be substantiated and clarified, on the basis of the available evidence the following generalizations can be made:

TABLE 7: CLINICAL IMPLICATIONS OF CENTRAL DOPAMINE RECEPTORS

1) Prolactin secretion is regulated by inhibitory dopaminergic mechanisms acting on the pituitary and/or the hypothalamus. An abnormality in this system or blockade of dopamine receptors in these regions results in hyperprolactinemia plus a variety of associated conditions (e.g. amenorrhea, galactorrhea, etc.) which are amenable to therapy with dopaminergic agonists.

2) Loss of dopaminergic neurons and a resultant decrease in striatal and substantia nigra dopamine content leads to the extra pyramidal manifestations of Parkinson's disease.

3) Dopamine receptors in medullary chemoreceptor areas control some (if not all) forms of centrally-mediated emesis. The interaction of various dopaminergic antagonists with these receptors differs from that with dopamine receptors in the corpus striatum, as metoclopramide can inhibit the emetic effects of bromocryptine, without altering its antiparkinsonian actions.

4) Development of dopamine receptors on somatotrophs of acromegalics may account for the therapeutic efficacy of dopaminergic agonists in this condition.

5) Increased dopamine receptors in the mesolimbic regions of the brain (caudate, putamen, nucleus accumbens), possibly due to a failure of endogenous levels of dopamine to suppress these receptors normally may account for the symptoms of schizophrenia and the therapeutic effects of neuroleptics.

6) The ability of dopamine receptors in the mesolimbic regions to interact with dopaminergic agents differs from that of dopamine receptors in the corpus striatum. Thus, the incidence of extrapyramidal side-effects observed with various neuroleptics is in agreement with their ability to block dopamine-receptors in the corpus-striatum. (c.f. Ref. 241) This observation may have important clinical implications. It suggests that specific agents may be forthcoming which are effective in, for example, schizophrenia with producing side-effects due to blockade of dopamine receptors in other regions of the brain.

7) Dopaminergic mechanisms in the medullary vasomotor center may control sympathetic outflow and thus be involved in normal blood pressure homeostasis. In addition, decreased dopaminergic activity in this region may result in the increased sympathetic nerve activity observed in some patients with essential hypertension.

CONCLUSION

In this brief review, I have attempted to highlight some of the more interesting and clinically relevant advances in catecholamine receptor pharmacology. Perhaps one of the more important insights that has been forthcoming with the development of newer technologies, is the dynamic relationship which exists between the catecholamine neurotransmitters and their receptors. When the molecular machinery is functioning physiologically, harmoneous interplay between transmitter and receiver results in sustained rallies. In contrast, minor aberrations in either player results in the pathological expression of numerous and varied faults.

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