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Volume Editors
J. Marwaha and *W.J. Anderson* (Terre Haute, Ind.)

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Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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α-Adrenoceptors

Robert R. Ruffolo, Jr.

Department of Cardiovascular Pharmacology (MC-304), Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind., USA

Introduction

The area of research encompassing α-adrenoceptors and α-adrenergic drugs has undergone a rapid growth during the past several years. This stems in part from the discovery that α-adrenoceptors do not represent one homogeneous population. The existence of presynaptic α-adrenoceptors which function as 'autoreceptors' to inhibit neurotransmitter release when synaptic levels of norepinephrine are high represents a recent major development. Building upon this foundation, potent and highly selective α-adrenergic agonists and antagonists have been synthesized and utilized to investigate α-adrenergic mechanisms, and this has led to a more universally acceptable pharmacological subclassification of α-adrenoceptors. Many of these newer selective drugs have found clinical applications particularly in the area of cardiovascular disorders.

The intent of this review is to summarize the current status of α-adrenoceptors and α-adrenergic drugs. Since α-adrenoceptors exist throughout the body and subserve a variety of functions too numerous to address in one chapter, only those α-adrenoceptors involved in regulation of the cardiovascular system will be discussed since the functions of these receptors are particularly well understood, and treatment of a variety of cardiovascular disorders may be achieved with drugs which act upon these α-adrenoceptors. In addition, examples of most of the generalizations that may be made about α-adrenoceptors, as well as most of the exceptions to these generalizations, exist in the cardiovascular system which therefore serves as an excellent example of the current status of α-adrenoceptors.

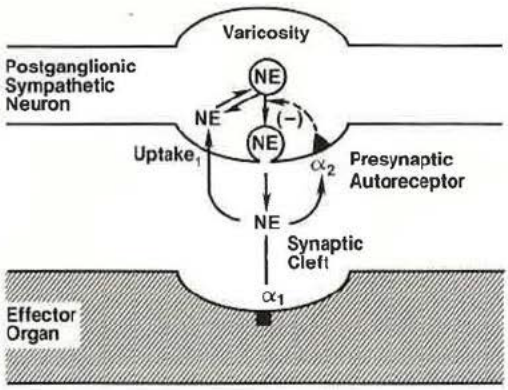

Fig. 1. Schematic representation of the adrenergic neuroeffector junction.

Subclassification of α-Adrenoceptors

Anatomical Subclassification of α-Adrenoceptors

The existence of postsynaptic α-adrenoceptors located on effector organs and mediating their response has been known for many years. However, the existence of presynaptic α-adrenoceptors which, when activated, reduce neurotransmitter release via a negative feedback mechanism, is a fairly recent observation [for reviews see 8, 64, 65, 130–132, 136, 167]. *Langer* [64] proposed that the postsynaptic α-adrenoceptor with mediates the response in an effector organ be termed α_1 and that presynaptic 'autoreceptor' be termed α_2. A very similar classification has been presented by *Berthelsen and Pettinger* [8] after a comprehensive review of the literature. This subdivision into postsynaptic α_1- and presynaptic α_2-adrenoceptors is presented schematically in figure 1. More often than not, this anatomical subclassification holds true. However, sufficient evidence exists to indicate that not all α_1-adrenoceptors are located postsynaptically [60, 138] and not all α_2-adrenoceptors are located presynaptically [24, 30, 57, 148–151, 155]. Particularly in the vasculature of several mammalian species, postsynaptic α_2-adrenoceptors mediating a contractile response (vasoconstrictor or vasopressor) have been demonstrated to coexist along with the 'classical' postsynaptic α_1-adrenoceptors in vivo [24, 30, 155]. The postsynaptic α_2-adrenoceptor has been the subject of a recent review by *Timmermans and van Zwieten* [150].

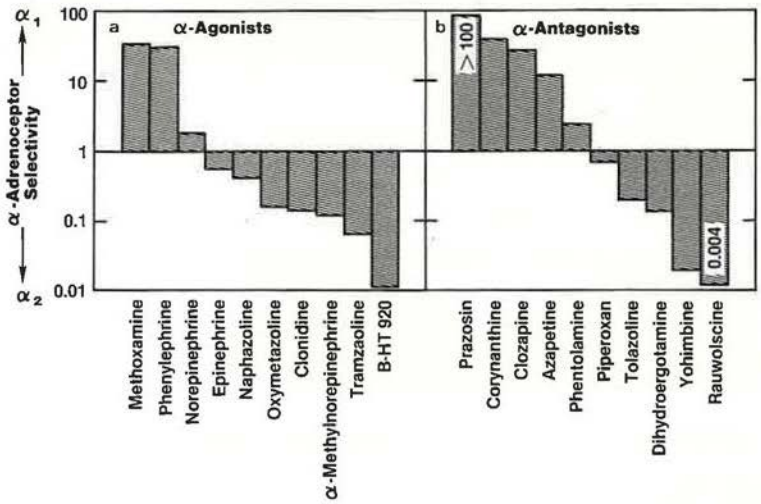

Fig. 2. Relative selectivities for α_1- and α_2-adrenoceptors of a series of α-adrenoceptor agonists (*a*) and antagonists (*b*) [modified from 8, 132, 151].

Pharmacological Subclassification of α-Adrenoceptors

Since many exceptions exist to the anatomical subclassification of postsynaptic α_1- and presynaptic α_2-adrenoceptors, criteria for a pharmacological subclassification have been developed which employ highly selective α-adrenergic agonists and antagonists as pharmacological tools. Among agonists, phenylephrine, methoxamine and cirazoline have been typically employed as selective α_1-adrenergic agonists [8, 65, 73] while clonidine, α-methylnorepinephrine, UK-14, 304, B-HT 920 and B-HT 933 are known as selective α_2-adrenoceptor agonists [151, 153, 154]. The natural neurotransmitter, norepinephrine, is a relatively *nonselective* agonist while the hormone, epinephrine, displays a slight selectivity for α_2-adrenoceptors [8].

Antagonists have also proven to be extremely useful tools to probe and subclassify α-adrenoceptors. Prazosin, which has been introduced clinically to treat hypertension, is a potent and highly selective α_1-adrenoceptor antagonist. The dissociation constant of prazosin at α_1-adrenoceptors is typically between 1 and 10 n*M*, and the selectivity for α_1-adrenoceptors (over α_2) is on the order of 100- to 1,000-fold [150]. Other potent and selective competitive α_1-adrenoceptor antagonists include WB-4101 and corynanthine [73]. Yohimbine and rauwolscine are commonly used as potent antagonists of α_2-

Table I. Radiolabeled α-adrenoceptor agonists and antagonists commonly used in radioligand binding studies to label the α-adrenoceptor subtypes

Radioligand	Reference
α_1-Selective	
[^{3}H]-Prazosin	50
[^{3}H]- WB-4101	40
[^{125}I]-BE 2254	33, 36
α_2-Selective	
[^{3}H]-Clonidine	40
[^{3}H]-*para*-Aminoclonidine	95
[^{3}H]-Guanfacine	146
[^{3}H]-Yohimbine	49
[^{3}H]-Epinephrine	157
[^{3}H]-Norepinephrine	157
Nonselective	
[^{3}H]-Dihydroergocryptine	171
[^{3}H]-Phentolamine	35

adrenoceptors, with selectivities ranging from approximately 30-fold to more than 100-fold [73]. Several of the more common α-adrenergic blocking agents, such as phentolamine and tolazoline, are relatively nonselective. The α_1/α_2-adrenoceptor selectivities of several adrenergic agonists and antagonists are presented in figure 2.

As expected, several α-adrenoceptor agonists and antagonists have been radiolabeled and proven to be useful ligands to characterize and subclassify α-adrenoceptors in binding studies [35, 131]. Several tritium and iodine labeled α-adrenergic agonists and antagonists with high specific activity and proven utility as radioligands are listed in table I. It is significant to note that ^{3}H-norepinephrine and ^{3}H-epinephrine, which are both relatively nonselective α-adrenoceptor agonists, tend to label predominantly α_2-adrenoceptors in radioligand binding studies.

Classes of α-Adrenergic Agonists

There are two major classes of α-adrenoceptor agonists: (1) the phenethylamines, which include compounds such as norepinephrine, phen-

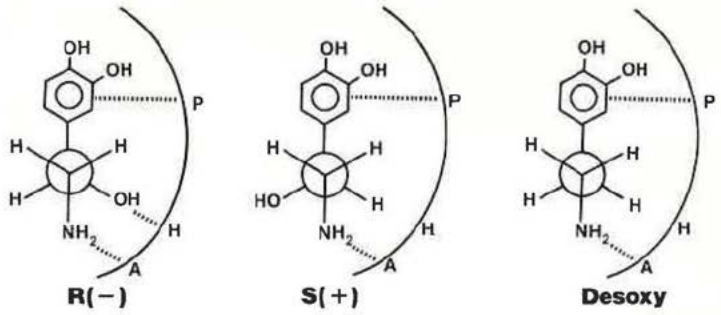

Fig. 3. Representation of the Easson-Stedman hypothesis for the stereoisomers of norepinephrine and the corresponding desoxy derivative, dopamine.

ylephrine and methoxamine, and (2) the imidazoli(di)nes, which include compounds such as clonidine, naphazoline and oxymetazoline. The similarities between these two classes of agonists far exceed the differences. However, the differences are what provide the greatest interest and perhaps contribute most to our understanding of the α-adrenoceptor.

The following discussion will detail several of the major differences in α-adrenergic activity known to exist between the phenethylamines and imidazolines. In general, the phenethylamines are either nonselective or show a selectivity for the α_1-adrenoceptor, although notable exceptions, such as α-methylnorepinephrine, exist. The imidazolines in general are either nonselective or show a selectivity for the α_2-adrenoceptor, and as expected, many exceptions to this generalization also exist. Among the phenethylamines, partial agonists are a rare occurence [9, 10, 34, 99]. However, among the imidazolines, partial agonists are more the rule rather than the exception [76, 92, 100, 101, 105, 107, 112, 116, 142].

A major difference between the phenethylamines and imidazolines is observed when assessing the applicability of the Easson-Stedman hypothesis to the α-adrenergic effects of these two classes of compounds. The hypothesis of *Easson and Stedman* [31] states that the R(−)-isomer of an optically active phenethylamine will be more active than the enantiomeric S(+)-isomer or corresponding desoxy derivative, with the two latter compounds being equally active to each other [85, 86]. This hypothesis, which is illustrated schematically in figure 3, predicts that only the R(−)-isomer of a phenethylamine will have the three important functional groups (i.e. aromatic ring, nitrogen atom and β-hydroxyl group) in the correct stereochemical configuration for interaction with α-adrenoceptors. The critical benzylic hydroxyl group will

not be available for interaction with the α-adrenoceptor for the S(+)-isomer and corresponding desoxy derivative because this functional group is incorrectly oriented or absent, respectively. This presumably would account for the lower activities of the S(+)-isomer and desoxy derivative relative to the R(−)-isomer and also for the fact that the S(+)-isomer and desoxy derivative are equal in activity to each other. The phenethylamines demonstrate a strict adherence to the Easson-Stedman hypothesis in all cases studied [85, 86]. However, in marked contrast, optically active imidazolines do not adhere to this hypothesis at α_1- or α_2-adrenoceptors [104]. Thus, while substitution of a hydroxyl group at the β-carbon atom of the phenethylamines *increases* α-adrenergic activity by approximately 100-fold [85, 86], similar hydroxyl substitution of an imidazoline produces a *decrease* in activity of up to 10-fold [99, 101, 103, 104, 112].

In vasa deferentia completely desensitized to the imidazoline, oxymetazoline, phenethylamines such as norepinephrine, phenylephrine and methoxamine still produce maximal responses, whereas other imidazolines such as tetrahydrozoline, xylometazoline and naphazoline either produce no response or only a marginal response [106]. A similar lack of cross-desensitization between the phenethylamines and imidazolines has been observed in vivo by *Kobinger* et al. [63] for the hindlimb vasculature of the rat. Finally, for the phenethylamines, a single *meta* or *para* hydroxyl group on the phenyl ring is sufficient to confer full agonist activity at α-adrenoceptors [9, 10, 99]. However, only those imidazolines with a catechol (i.e. 3,4-dihydroxyphenyl) are full agonists [99, 101, 105]. In fact, it has recently been demonstrated that aromatic hydroxyl substitutions produce major alterations in *intrinsic activity* or *efficacy* of the imidazolines, but have no affect on this parameter for the phenethylamines [99].

The differences described above are significant and have led several investigators to propose that the imidazolines may interact with the α-adrenoceptor in a different manner than the phenethylamines [63, 77, 79, 96, 99, 101–106, 112]. These differences in activity may reflect differences in the manner in which the phenethylamines and imidazolines bind to and/or activate the α-adrenoceptor.

In addition to the two major classes of α-adrenergic agonists discussed above, a relatively novel class of azepine derivatives, such at B-HT 920, have recently been developed. Although these compounds are neither phenethylamines nor imidazolines, their pharmacological activity parallels that of the imidazolines, and most of the azepines studied to date are highly selective for α_2-adrenoceptors [59, 149, 154].

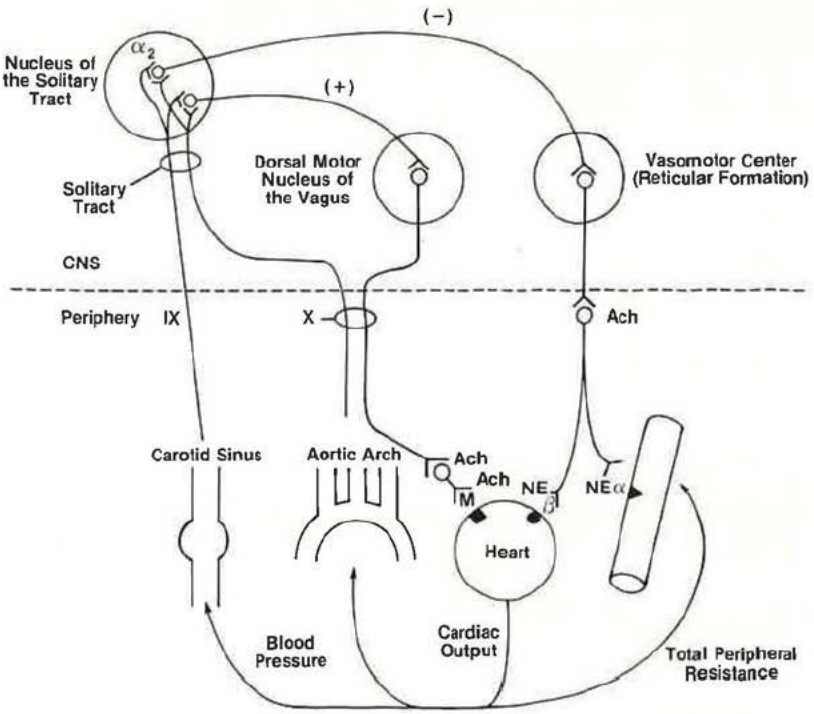

Fig. 4. Neuronal connections in the cardiovascular reflex loop involved in the regulation of blood pressure and heart rate. NE = Norepinephrine; Ach = acetylcholine; α = α-adrenoceptor; β = β-adrenoceptor; M = muscarinic cholinergic receptor.

α-Adrenoceptors in the Cardiovascular System

α-Adrenoceptors exist at virtually all parts of the cardiovascular system and subserve a variety of functions in the regulation of blood pressure. Indeed, specific α-adrenoceptor agonists and antagonists are used clinically to treat various disorders of the cardiovascular system such as hypertension and heart failure. The development of highly potent, specific and selective α-adrenergic drugs has contributed to the recent explosive growth of the field. The most exciting new developments in α-adrenoceptors have come from studies of the various roles that these receptors play in the regulation of blood pressure and heart rate. Since the functions of α-adrenoceptors in the cardiovascular system are so clearly understood, these receptors will be dis-

cussed in detail since they best illustrate the current status of α-adrenoceptors.

Central α_2-Adrenoceptor

Clonidine is an α-adrenoceptor agonist with antihypertensive activity resulting from within in the central nervous system [15, 58, 61, 117, 118, 120, 161]. The drug is hypothesized to interupt the normal cardiovascular reflex loop whose function is to regulate blood pressure and heart rate and maintain them within relatively narrow ranges. A highly schematic representation of the cardiovascular reflex loop is presented in figure 4. Pressure receptors in the carotid sinus and aortic arch sense changes in peripheral blood pressure and initiate the cardiovascular reflex. Afferents from the carotid sinus and aortic arch enter the central nervous system through cranial nerves IX (glossopharyngeal) and X (vagus), respectively, and form, in part, the solitary tract in the medulla. The first synapse in the cardiovascular reflex loop occurs in the nucleus of the solitary tract [18], and in this nucleus is believed to be one of the primary sites of action of clonidine [22, 42, 69, 70, 93, 94, 119]. Receptors of the α_2-subtype are postulated to exist postsynaptically on dendrites of neurons in the nucleus of the solitary tract. Synapses are made within the nucleus of the solitary tract with *inhibitory* neurons that course to the vasomotor center in the reticular formation, and with *excitatory* neurons which send connections to the dorsal motor nucleus of the vagus. When blood pressure is elevated, or when α_2-adrenoceptors in the nucleus of the solitary tract are stimulated, several events will occur. Firstly, the inhibitory neurons to the vasomotor center are activated and sympathetic outflow, which originates from the vasomotor center and innervates the peripheral vasculature, heart, and kidney, is reduced. As a result, peripheral vascular tone, heart rate, and renin release are decreased producing, in turn, a decrease in total peripheral resistance and cardiac output. Secondly, activation of the excitatory neurons from the nucleus of the solitary tract which terminate in the dorsal motor nucleus of the vagus, causes an enhanced cholinergic outflow to the heart, producing a further decrease in heart rate and cardiac output [62]. The result of the combined decrease in sympathetic outflow and increase in parasympathetic outflow resulting from central α_2-adrenoceptor stimulation is a decrease in blood pressure with a concurrent bradycardia [45, 46].

While the antihypertensive activity of clonidine results from its pharmacological selectivity for central α_2-adrenoceptors in the nucleus of the solitary tract, it is also known that the physicochemical properties of clonidine-like imidazol(id)ines are also critical to the antihypertensive efficacy of such

compounds [for review see 154]. Highly lipophilic imidazolidines, such as clonidine, which readily penetrate the blood-brain barrier and gain access to their site(s) of action in the brain stem, are potent antihypertensive agents. Conversely, many imidazolidines with similar selectivities as clonidine for α_2-adrenoceptors, but with low lipophilicity, do not readily penetrate the blood-brain barrier and are either weak antihypertensive agents, or completely devoid of all antihypertensive activity. Such compounds are still effective in lowering blood pressure when injected beyond the blood-brain barrier into specific brain regions such as the nucleus of the solitary tract [21, 22] or into the cerebral ventricles [141] or cisterna magna [81, 88, 110, 113]. Since these compounds with low lipophilicity are still active when the blood-brain barrier is bypassed, it has been concluded that one major factor affecting the antihypertensive activity of clonidine-like imidazolidines following systemic administration is their ability to penetrate the blood-brain barrier and this, in turn, is highly dependent upon overall lipophilicity.

Many properties of a molecule will determine overall lipophilicity which, as indicated above, is critical for antihypertensive efficacy of clonidine-like imidazolidines. For these particular compounds, the most important determinant of lipophilicity is the extent of ionization occurring at physiological pH, and this property is governed by the ionization constant or pK_a [147, 152, 153]. Imidazolidines in the ionized species possess low lipophilicity and will penetrate the blood-brain barrier slowly, whereas the un-ionized form is highly lipophilic and will penetrate the barrier rapidly. Thus, the ratio of the un-ionized:ionized species is a major determinant of the antihypertensive efficacy and potency of many clonidine-like imidazolidines. There exists an excellent correlation between the antihypertensive potencies of a series of clonidine-like imidazolidines and their pK_a [115] such that those compounds with low pK_a, and which are therefore significantly un-ionized at physiological pH, will penetrate the blood-brain barrier rapidly and be potent antihypertensive agents, whereas those imidazolidines with high pK_a and which are extensively ionized at physiological pH will penetrate the blood-brain barrier to a lesser extent (or at a slower rate) and be weaker antihypertensive agents.

Clonidine is not metabolized to a great extent in man [71] and the limited metabolism that does occur does not take place in the brain. As a result, termination of the central antihypertensive effects of clonidine and clonidine-like imidazolidines is likely to be by diffusion out of the central nervous system. It has recently been demonstrated that the pK_a of clonidine-like imidazolidines, and therefore their ratios of un-ionized:ionized species, also

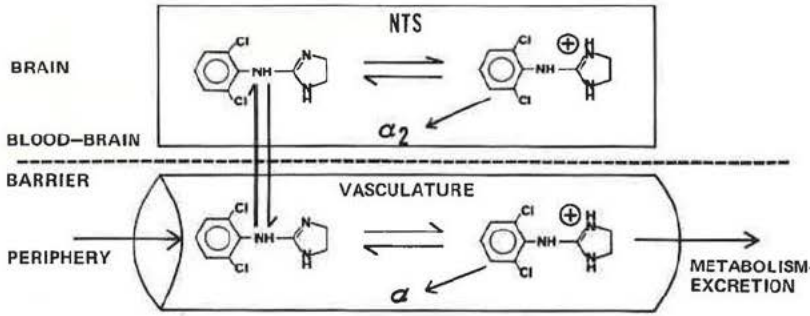

Fig. 5. Schematic representation of the various pharmacological activities of the antihypertensive agent, clonidine. NTS = Nucleus tractus solitarii.

governs the diffusion of these compounds out of the brain [115]. As expected, high proportions of the un-ionized species with high lipophilicity are associated with a more rapid exit from the central nervous system by diffusion through the blood-brain barrier in the reverse direction [115].

A schematic representation of the antihypertensive effects of clonidine, and the relationship of this effect to the extent of ionization at physiological pH, is depicted in figure 5. Following systemic administration, clonidine will exist in the blood in an equilibrium between the ionized and un-ionized forms, with the relative proportions of each species being determined by the pK_a. The ionized form will interact with postsynaptic vascular α-adrenoceptors [110, 154] and mediate a pressor response, which is particularly apparent following intravenous administration. The un-ionized form (mainly) will penetrate the blood-brain barrier to gain access to the site(s) of action in the brain. Again, a new equilibrium between the ionized and un-ionized form will be established within the central nervous system, the extent of which also being determined by the pK_a. The ionized form [115, 154] is believed to be the species responsible for activation of central α_2-adrenoceptors which mediate the decrease in sympathetic outflow and the increase in parasympathetic outflow which ultimately produces the antihypertensive and bradycardic response. While the ionized species appears to interact with the central α_2-adrenoceptor, it is the un-ionized species which will penetrate the blood-brain barrier in the reverse direction and exit the central nervous system to terminate the antihypertensive response. In the periphery, the drug is subsequently removed from the blood by metabolism and/or excretion.

The antihypertensive activity of α-methyldopa has a similar mechanism of action as clonidine [162], although physicochemical properties of the molecule play a lesser role. α-Methyldopa is actively transported into the brain by an aromatic amino acid transport mechanism. In the brain, α-methyldopa is sequentially decarboxylated and β-hydroxylated to form α-methylnorepinephrine which is a potent and selective α_2-adrenoceptor agonist and which interacts with α_2-adrenoceptors in the nucleus of the solitary tract to produce a decrease in blood pressure and heart rate [21, 22]. The effect of α-methylnorepinephrine is not terminated by diffusion out of the central nervous system as is the case for clonidine, but rather by enzymatic degradation by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO).

Peripheral α-Adrenoceptors

Vasculature. The predominant innervation to the vasculature is adrenergic where postganglionic sympathetic nerve terminals liberate norepinephrine in response to electrical stimulation. The liberated norepinephrine will activate postjunctional α-adrenoceptors which, in turn, mediate vasoconstriction and a concomitant increase in total peripheral resistance and bood pressure. In addition, the liberated neurotransmitter will activate prejunctional α_2-adrenoceptors which inhibit further norepinephrine release via the negative feedback system. The presynaptic autoinhibitory α_2-adrenoceptor at the vascular neuroeffector junction has been studied extensively [131, 132] and is similar to the α_2-adrenoceptor found presynaptically in other tissues.

The nature of the postjunctional α-adrenoceptor which mediates vasoconstriction has been the target of many recent investigations. In most nonvascular tissues, the postjunctional α-adrenoceptor is of the α_1-subtype. While postsynaptic α_1-adrenoceptors in the vasculature were identified early on, recent studies in vitro indicate that postsynaptic α-adrenoceptors in blood vessels may not represent one homogeneous population [23, 26, 53, 91, 97, 108, 109, 111, 139, 140, 143, 158]. However, the most important contributions concerning the nature of the postsynaptic vascular α-adrenoceptor(s) have come from recent studies in vivo. *Drew and Whiting* [30] identified two types of α-adrenoceptors mediating pressor responses in the cat and rat. One type was prazosin-sensitive and classified as α_1, while the second prazosin-resistant type was not classified at that time. Subsequent investigations occuring simultaneously and independently by several groups [24, 25, 29, 155] indicated that α_1- and α_2-adrenoceptors are both present in the vasculature of the rat and both subtypes are located postjunctionally and mediate

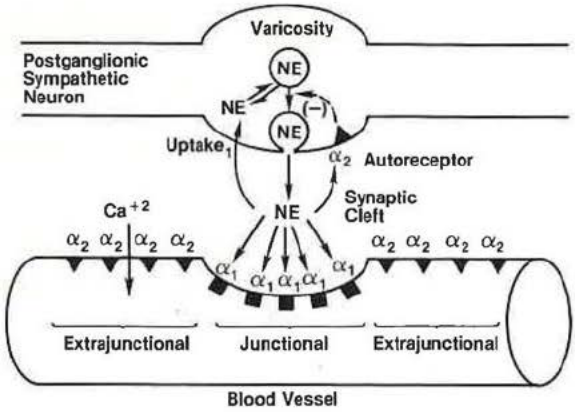

Fig. 6. Proposed adrenergic vascular neuroeffector junction depicting postsynaptic 'junctional' α_1-adrenoceptors, postsynaptic 'extrajunctional' α_2-adrenoceptors and presynaptic α_2-adrenoceptors.

vasoconstriction. Similar results have been obtained in the dog [16] and rabbit [72, 74].

It is now generally accepted that vasoconstrictor responses in many species may be mediated by a mixed population of postsynaptic vascular α_1- and α_2-adrenoceptors. However, the physiological function and/or distribution of these receptors is just now beginning to be understood. By using a variety of α_1-selective, α_2-selective and nonselective α-adrenoceptor antagonists, *Yamaguchi and Kopin* [174] observed that the pressor responses to exogenously administered catecholamines were selectively antagonized by α_2-blockers. Conversely, the pressor response evoked by sympathetic nerve stimulation was selectively antagonized by α_1-adrenoceptor antagonists. These authors postulated that postsynaptic α-adrenoceptors located close to the neuroeffector junction (i.e. junctional receptors) were of the α_1-subtype while those located at a distance away from the neuroeffector junction (i.e. extrajunctional receptors) were of the α_2-subtype. This hypothesis is illustrated schematically in figure 6. *Langer and Shepperson* [66] and *Langer* et al. [67, 68] have shown, using neuronal uptake inhibitors, that postjunctional vascular α_1-adrenoceptors are located in the vicinity of the neuronal uptake pump (uptake$_1$) and that postjunctional α_2-adrenoceptors are positioned away from this site (fig. 6). These results, and those recently obtained by *Wilffert* et al. [170], strongly suggest the existence of junctional α_1- and extrajunctional α_2-adrenoceptors located postsynaptically in the vasculature.

The physiological role of the vascular postsynaptic junctional α_1-adrenoceptors appears to be in maintaining normal vascular tone. Presumably, these receptors which are located in the vicinity of the neurovascular junction would interact with endogenous norepinephrine liberated from sympathetic nerves. In contrast, the physiological role of the extrajunctional α_2-adrenoceptors is not fully understood. It has been argued that the extrajunctional α_2-adrenoceptors would not normally interact with liberated norepinephrine since they are located at a distance from the adrenergic nerve terminal [66]. *Langer and Shepperson* [66] indicate that the highly efficient neuronal uptake pump (fig. 6) keeps synaptic levels of norepinephrine sufficiently low and thereby prevents diffusion of the neurotransmitter to the extrajunctional sites. It has been proposed that the extrajunctional α_2-adrenoceptors may respond to circulating epinephrine acting as a blood-borne hormone [66]. While circulating catecholamines may be below the levels required to exert a physiological effect, it has been suggested that in times of stress, these levels may be elevated to threshold levels where postsynaptic vascular α_2-adrenoceptors are activated [19, 66]. It has also been postulated that the circulating levels of catecholamines acting as hormones may not need to be as high as expected to elicit effects from extrajunctional vascular α_2-adrenoceptors since these receptors, which are located at a distance from the sympathetic nerve endings, may behave more like 'denervated' receptors and exhibit an exaggerated sensitivity to catecholamines [66]. Consistent with this hypothesis is the observation that rat aorta, which is not innervated [84], exhibits an exaggerated response to several α_2-adrenoceptor-selective agents, whereas aortas from other species which *are* innervated do not exhibit such an exaggerated sensitivity [97, 108, 109, 111].

It has recently been established that junctional α_1-adrenoceptors do not rely upon extracellular calcium to produce a vasoconstrictor response, whereas the extrajunctional α_2-adrenoceptors are highly dependent upon extracellular calcium to produce vasoconstriction (fig. 6) [151, 159, 160]. As a result, α_1-adrenoceptor-mediated vasoconstriction is not altered by the new class of compounds, the calcium entry blockers (or calcium slow channel-blocking agents), whereas vasoconstriction mediated by extrajunctional α_2-adrenoceptors is highly sensitive to blockade by the calcium entry blockers [159, 160]. It has been postulated that the efficacy of the calcium entry blockers in hypertension, angina, and certain vasospastic disorders, such as Raynaud's syndrome, may result from the ability of these agents to inhibit the vasoconstrictor response mediated by extrajunctional α_2-adrenoceptors.

Heart. The cardiac adrenergic neuroeffector junction is in many respects similar to neuroeffector junctions in other tissues as far as α-adrenoceptors are concerned. Presynaptic α_2-adrenoceptors on postganglionic sympathetic nerve terminals have been identified in isolated hearts from many species. As in other organs, the presynaptic α_2-adrenoceptors, when activated, mediate an inhibitory effect on neurotransmitter release [27, 44]. In vivo studies in pithed rats also indicate the existence of presynaptic α_2-adrenoceptors which modulate stimulation-evoked norepinephrine release [28, 66]. As such, α-adrenoceptor antagonists may produce positive inotropic and chronotropic responses [5; 6] by enhancing neurotransmitter liberation [134, 135] which results from loss of the autoinhibition mediated by presynaptic α_2-adrenoceptors. In electrically driven hearts, in vivo and in vitro, selective α_2-adrenoceptor agonists, such as clonidine, decrease heart rate in conjunction with inhibition of transmitter release [128, 129].

The predominant adrenergic receptor located postsynaptically in the heart is the β_1-adrenoceptor which mediates a large positive inotropic and chronotropic response [3, 11]. However, the existence of postsynaptic α-adrenoceptors was suggested many years ago [37–39, 168]. Recent studies indicate that postsynaptic α-adrenoceptors do exist in the hearts of many mammalian species, including man, and mediate a positive inotropic response with little or no change in heart rate [3, 7, 78, 82, 83, 125, 126, 163–166; for reviews, see 4, 11, 121]. The mechanism by which cardiac α-adrenoceptors increase force of contraction has not been established, but it appears not to be associated with the accumulation of cAMP or stimulation of adenylate cyclase [2, 12, 13, 89] and in this respect, α-adrenoceptors differ from β_1-receptors in the myocardium. Other differences between the α- and β-adrenergic effects in the heart include the rate of onset and duration of action which are particularly long for α-adrenoceptor-mediated inotropic effects [14, 124]. Differences in various electrophysiological actions mediated by α- and β-adrenoceptors have also been observed [38; for review see 11]. Furthermore, while β_1-adrenoceptor-mediated inotropic responses occur at all frequencies of stimulation, the effect mediated by α-adrenoceptors is apparent only at low rates [4, 11].

The subtype of the cardiac α-adrenoceptor has been the topic of some controversy. Using classical techniques to characterize the postsynaptic cardiac α-adrenoceptor, *Schumann and Endoh* [123] and *Schumann* et al. [125] observed differences between postsynaptic α-adrenoceptors in the heart and postsynaptic α-adrenoceptors in other organs. Most of the physiological and radioligand binding data indicate that the postsynaptic α-adrenoceptor of the

heart is of the α_1-subtype [17, 32, 47, 48, 55, 90, 122, 123, 156, 172]. However, since differences may exist between the cardiac α-adrenoceptor and the postsynaptic α-adrenoceptor in other organs [121, 125], in addition to the fact that norepinephrine does not stimulate this receptor [165], the possibility that the cardiac α-adrenoceptor may represent an atypical subset of the α_1-type must be considered [137].

Several recent reports indicate that postsynaptic α_1-adrenoceptors in the heart may undergo marked and rapid changes in number in response to various disease states. Myocardial ischemia in the cat has been reported to result in an acute and reversible increase in postsynaptic myocardial α_1-adrenoceptors [17]. These findings are consistent with the observation that enhanced α-adrenergic responses have been obtained in ischemic myocardium [127]. Chronic heart failure in the guinea pig produced by aortic constriction likewise resulted in an increase in myocardial α_1- (and β_1-) adrenoceptors [54]. It has been proposed that the increase in the number of myocardial α_1-adrenoceptors results from an apparent compensatory up-regulation secondary to the decrease in endogenous catecholamine levels that accompanied the induction of heart failure. Finally, *Woodcock and Johnston* [173] have observed a decrease in the number of myocardial α-adrenoceptors in rats made hypertensive by surgical removal of one kidney and contralateral constriction of the renal artery.

Kidney. The existence of α-adrenoceptors in the kidney has been suspected for many years since α-adrenergic drugs produce a variety of renal effects. The functions and locations of the renal α-adrenoceptors are now only beginning to be understood [for review, see 144]. Radioligand binding studies indicate that α_1- and α_2-adrenoceptors coexist in the kidneys of a variety of mammalian species; however, the number, proportion and distribution of each α-adrenoceptor subtype may vary from species to species [51, 75, 144].

The anatomical location of the renal α-adrenoceptors and the functions they subserve are not completely understood. It is believed that α-adrenoceptors of the α_1-subtype exist in the renal vasculature and mediate a vasoconstrictor response [43] and thereby modulate, in part, renal blood flow. In the rat, α_2-adrenoceptors of the juxtaglomerular apparatus have been proposed to inhibit renin release [87, 144]. α-Adrenoceptors also enhance sodium and water reabsorption in the proximal convoluted tubules. While the α-adrenoceptor subtype responsible for this effect has not been definitely established, recent findings tend to implicate the α_2-subtype [144]. In addition, gluconeo-

OH	OH	CH_3	Alkyl	Substitution
				Receptor type
+	++	−	+, −	α_1
++	+++	++	+, −	α_2
				
+++	−		−	α_1
++++	−		−	α_2

Fig. 7. Differences in the structure-activity relationships for the α_1- and α_2-adrenoceptor agonist effects of phenethylamines and imidazolines.

genesis in the proximal convoluted tubule has been shown to be under α_1-adrenergic control [41, 56].

The non-uniform and differential distribution of α_1- and α_2-adrenoceptor in the kidney, and the various functions these α-adrenoceptor subtypes subserve, such as regulation of renal blood flow, renin secretion, sodium and water reabsorption and gluconeogenesis, indicate the complex nature of α-adrenergic effects in this organ. No doubt our knowledge about renal α-adrenergic mechanisms will grow in the next several years with the intent that these sites may become important targets for drug action in disease states.

Structure-Activity Relationships of α-Adrenergic Agonists

The structural demands made by α_1- and α_2-adrenoceptors have recently been reviewed in detail [96]. While a comprehensive review cannot be reproduced herein, several of the more important substitutions of phenethylamines and imidazolines will be discussed with emphasis on the differences between imidazolines and phenethylmines as well as differences between α_1- and α_2-adrenoceptors. The most important structural modifications of imid-

azolines and phenethylamines, and their relative significance at α_1- and α_2-adrenoceptors, are summarized in figure 7. Aromatic ring hydroxylation of the phenethylamines and imidazolines is critical for the α_2-adrenergic effects of both classes of agonists, but especially so for the imidazolines [99]. At α_1-adrenoceptors, aromatic ring hydroxylation of the phenethylamines affects largely affinity (i.e. binding to the receptor), whereas for the imidazolines, *both* affinity and efficacy (i.e. ability to activate the receptor subsequent to binding), but especially efficacy, are affected by aromatic hydroxylation [99]. For both classes of compounds, aromatic ring hydroxylation produces the following rank order of potencies at α_1-adrenoceptors: 3,4-dihydroxy > 3-hydroxy > 4-hydroxy > nonphenolic (i.e. nonhydroxyl substituted). At both α_1- and α_2-adrenoceptors, aromatic hydroxyl substitution appears to be more critical for the imidazolines than for the phenetylamines.

The most important substitution at the benzylic carbon atom is also the hydroxyl group. Most interesting is the fact that benzylic hydroxyl substitution produces opposite effects on the activities of the phenethylamines and imidazolines [99, 101, 112]. While benzylic hydroxyl substitution of a phenethylamine produces an increase in activity of approximately two orders of magnitude [86], the analogous substitution of the imidazolines results in a decrease in activity of up to 10-fold [99, 101, 112]. Recent studies indicate that the reason for the opposite effects that benzylic hydroxyl substitution has on the phenethylamines and imidazolines is that the phenethylamines adhere strictly to the Easson-Stedman hypothesis while the imidazolines do not [98, 104], and this represents a major difference between the imidazolines and phenethylamines. While benzylic hydroxyl substitution of the phenethylamines no doubt produces an enhancement in agonist activity at both α-adrenoceptor subtypes, the effect is greater at α_2-adrenoceptors [99].

Substitution at the α-carbon atom can produce dramatic effects in the agonist activity of phenethylamines (the imidazolines cannot be substituted at this position). The most important substitution at the α-position of phenethylamines is the methyl group. This substitution produces a dramatic increase in activity at α_2-adrenoceptors while producing no change, or even a decrease in activity at α_1-adrenoceptors [98, 114, 133]. As a result, α-methyl-substituted phenethylamines are highly selective for α_2-adrenoceptors relative to their α-desmethyl analogs. This position of substitution, therefore, represents a critical point of divergence in the structural requirements of α_1- and α_2-adrenoceptors for phenethylamines. Similar observations have been made for phenethylamines possessing the α-ethyl substitution [9].

Many phenethylamine and imidazoline derivatives have been synthesized with *N*-substituents or imidazoline ring substituents, respectively. In general, *N*-methyl substitution of phenethylamines produces a slight increase in activity at α_1- and α_2-adrenoceptors [1, 169]. Larger *N*-substituents produce a decrease in activity at both α_1- and α_2-adrenoceptors [1, 169; for review see 96]. For the imidazolines, virtually any manipulation or substitution of the imidazoline ring reduces activity at α_1- and α_2-adrenoceptors [96]. However, one interesting difference between α_1- and α_2-adrenoceptors has been reported for *N*-substituted imidazolines. While alkyl substitution at this position dramatically reduces or abolishes activity at α_2-adrenoceptors [20, 52, 145], such substitutions do not produce a *complete loss* of activity at α_1-adrenoceptors, with a few *N*-substitutions even slightly enhancing α_1-activity [80].

It is apparent from this brief account of some of the more important substitutions of imidazolines and phenethylamines that marked differences in the structure-activity relationships exist between these two classes of agonists. In addition, significant differences exist in the structural requirements made by α_1- and α_2-adrenoceptors, within each class of compound.

Conclusions

α-Adrenoceptors may be subdivided based on their anatomical distribution within the synapse. Presynaptic α-adrenoceptors are generally of the α_2-subtype and modulate neurotransmitter liberation via a negative feedback mechanism. Postsynaptic α-adrenoceptors are usually of the α_1-subtype and mediate the response of the effector organ. While the anatomical subclassification of presynaptic α_2- and postsynaptic α_1-adrenoceptors is generally applicable, many exceptions to this classification exist since postsynaptic α_2-adrenoceptors have been demonstrated, and presynaptic α_1-adrenoceptors have been proposed. A more useful classification of α-adrenoceptor subtypes is based on a pharmacological characterization in which selective agonists and antagonists are used. Among agonists, phenylephrine, methoxamine and cirazoline are markedly selective for α_1-adrenoceptors, whereas clonidine, α-methylnorepinephrine and UK-14,304 are selective for α_2-adrenoceptors. Among antagonists, prazosin and corynanthine are highly α_1-selective whereas yohimbine and rauwolscine are selective for α_2-adrenoceptors.

At present, two major classes of α-adrenergic agonists are known and have been highly characterized. These classes are the phenethylamines,

which are structurally related to norepinephrine, and the imidazolines, which are structurally related to clonidine. A series of azepine derivatives has recently been developed and the activity of this class is pharmacologically similar to the imidazolines. There are many similarities between the phenethylamines and imidazolines, however, major differences between these two classes of agonists have been observed and have led to the conclusion that the phenethylamines and imidazolines interact differently with α-adrenoceptors.

α-Adrenoceptors are critical in regulating the cardiovascular system at the levels of the central nervous system and peripheral effector organs (i.e. heart, vasculature and kidney). Postsynaptic α_2-adrenoceptors in the nucleus of the solitary tract regulate the sympathetic outflow which originates from the vasomotor center of the medulla and innervates the heart, vasculature and kidneys. Also regulated by central α_2-adrenoceptors is the parasympathetic outflow which originates in the dorsal motor nucleus of the vagus and innervates the heart. When central α_2-adrenoceptors are activated, sympathetic outflow is inhibited and parasympathetic outflow is increased with the net result being decreases in vascular tone, total peripheral resistance, and blood pressure, with a concomitant decrease in heart rate. Postsynaptic α-adrenoceptors in the vasculature represent a mixed population of α_1/α_2-adrenoceptors, with both subtypes mediating vasoconstrictor responses. Pharmacological studies indicate that the postsynaptic vascular α_1-adrenoceptors are located in the vicinity of the adrenergic neuroeffector junction, whereas the postsynaptic vascular α_2-adrenoceptors are located extrajunctionally. While the physiological role of the different populations of postsynaptic α-adrenoceptors has not been established, it has been proposed that the junctional α_1-adrenoceptors may respond mainly to the neurotransmitter, norepinephrine, liberated by sympathetic nerves, whereas the extrajunctional α_2-adrenoceptors may respond to circulating epinephrine liberated from the adrenal glands and acting as a hormone, as well as exogenously administered α-adrenergic drugs. Recent studies indicate that junctional α_1-adrenoceptors utilize intracellular calcium to elicit a vasoconstrictor response, whereas the source of calcium required for vasoconstriction mediated by extrajunctional α_2-adrenoceptors is extracellular.

In the heart, presynaptic α_2- and postsynaptic α_1-adrenoceptors have been identified. The presynaptic α_2-adrenoceptors inhibit neurotransmitter liberation when activated, while the postsynaptic α_1-adrenoceptors mediate an increase in the contractile state of the heart with little or no change in heart

rate, in constrast to myocardial β_1-adrenoceptors which increase both the rate and force of contraction. The number and response of myocardial α_1-adrenoceptors is known to undergo rapid and reversible changes in response to experimentally-induced disease states such as heart failure, myocardial ischemia and hypertension.

Both α_1- and α_2-adrenoceptors have been identified in the kidney and their functions are just beginning to be understood. Studies indicate that renal α_1-adrenoceptors may regulate renal blood flow and gluconeogenesis, whereas renal α_2-adrenoceptors may inhibit renin secretion from the juxtaglomerular apparatus and enhance sodium and water reabsorption in the proximal convoluted tubules.

Fairly complete structure-activity relationships have been performed for the α_1- and α_2-adrenergic effects of the imidazolines and phenethylamines. Within each class of agonist, differences in the structural requirements of α_1- and α_2-adrenoceptors have been identified and characterized. In addition, major differences in the structure-activity relationships of phenethylamines and imidazolines have also been observed and suggest further that these two classes of α-adrenergic agonists may differ in their interactions with α-adrenoceptors.

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R.R. Ruffolo, Jr., Ph.D., Department of Cardiovascular Pharmacology (MC-304),
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285 (USA)

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