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Perspective

α_2 Adrenoceptors: Classification, Localization, Mechanisms, and Targets for Drugs

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Introduction

The concept of pre- and postjunctionally located α adrenoceptors, as well as the more recent subdivision into α_1 and α_2 subtypes, has initiated during the last decade a renaissance of interest in this class of receptors and in the drugs interfering with them. This interest has been further stimulated by the detection of previously unknown locations and functions of α adrenoceptors, the availability of new techniques, such as radioligand binding, and the increased knowledge of the processes linking α adrenoceptor activation to the pharmacological effect. In this paper, emphasis is directed toward α adrenoceptors that are presently classified as α_2. The discovery of this type prompted the application of a nomenclature for α adrenoceptors. The functional relevance of α_2 adrenoceptors is still growing. They are probably of high physiological significance and already serve as targets for various therapeutically useful drugs.

Classification

The classification of adrenergic receptors into α and β was suggested by Ahlquist[1] in 1948 to account for the effects of some sympathomimetic amines and was firmly grounded by Powell and Slater[2] and Moran and Perkins[3] in 1958 through the blockade of β adrenoceptors by dichloroisoproterenol. The subdivision of β adrenoceptors into β_1 and β_2 types, originally demonstrated by Furchgott[4] and Lands et al.,[5] is an accepted concept that is of therapeutic relevance. The need for an analogous subdivision of the α adrenoceptor population was first realized after the discovery and characterization of α adrenoceptors located at the varicosity membrane of noradrenergic nerve endings. Until then the classical α adrenoceptors were the so-called postsynaptic or postjunctional receptors, the stimulation of which induces a pharmacological effect. Many experimental findings suggest that presynaptic α adrenoceptors are involved in the regulation of transmitter (e.g., norepinephrine) release through a negative-feedback mechanism mediated by the neurotransmitter itself (Figure 1). The concept of presynaptic control of neurotransmitter release via α adrenoceptors (and other receptor systems) has been extensively treated in a number of reviews.[6-11]

It was found that in rabbit heart[12] and cat spleen[13] the presynaptic α adrenoceptors could be differentiated from the postsynaptic ones with respect to the relative activities of agonists and antagonists. In the rabbit pulmonary artery, α adrenoceptor agonists[14] and antagonists[15] clearly showed a differential drug selectivity of pre- and postsynaptic α adrenoceptors. The pharmacological, functional, and anatomical dissimilarity among pre- and postsynaptic α adrenoceptors led originally[16] to the identification of the α_1 adrenoceptor as the postsynaptic receptor, which mediates excitatory responses (e.g., vasoconstriction), and the α_2 adrenoceptor as the presynaptic receptor, which mediates inhibitory effects. While at first the terms α_1 and α_2 receptors were proposed as synonyms for post- and presynaptic α adrenoceptors, respectively, the existence of α_2 adrenoceptors outside noradrenergic terminal axons, on some organelles lacking synapses and even at postsynaptic sites possessing the general characteristics of those found presynaptically, made it necessary to use these prefixes solely for receptors with different relative activities and affinities of agonists and antagonists, respectively, irrespective of the location or function of the receptor.[17-19]

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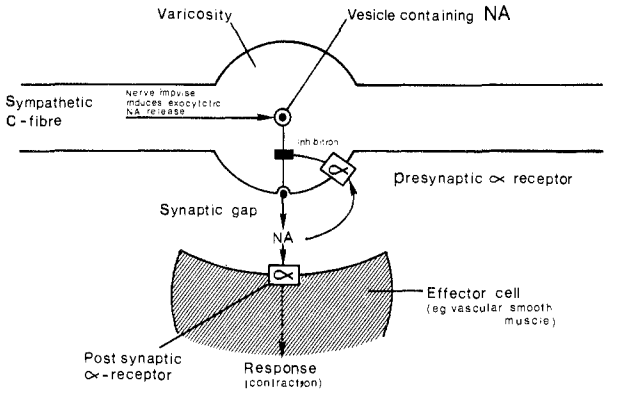

Figure 1. Pre- and postjunctional α adrenoceptors of a noradrenergic synapse. Norepinephrine (NA) released from the varicosity stimulates postsynaptic α adrenoceptors situated at the target organ. Presynaptic α adrenoceptors located at the varicosity membrane control a negative feedback of the release of transmitter NA. Activation by endogenous (autoinhibition) as well as by exogenous agonists induces an inhibition of the amount of transmitter NA released per nerve impulse; a blockade induces a facilitation of the amount of transmitter NA released per nerve impulse.

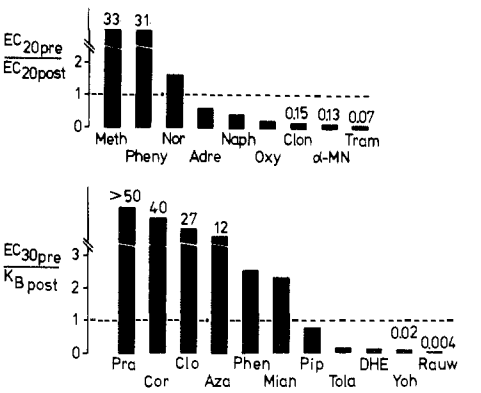

Figure 2. Ratio of pre- and postsynaptic α adrenoceptor stimulating (upper part) and blocking (lower part) activities of a number of α-adrenoceptor agonists and antagonists in the rabbit isolated pulmonary artery. EC_{20} (pre) = concentration inhibiting [^{3}H]noradrenaline overflow by 20% (presynaptic effect). EC_{20} (post) = concentration inducing 20% of the maximal contraction (postsynaptic effect). From left to right: (±)-methoxamine, (-)-phenylephrine, (-)-norepinephrine, (-)-epinephrine, naphazoline, oxymetazoline, clonidine, (-)-*erythro*-α-methylnorepinephrine, tramazoline. EC_{30} (pre) = concentration facilitating [^{3}H]norepinephrine release by 30% (presynaptic effect). K_B (post) = antagonism against (-)-phenylephrine- and (-)-norepinephrine-induced contraction (postsynaptic effect). From left to right: prazosin, corynanthine, clozapine, azapetine, phentolamine, mianserin, piperoxan, tolazoline, dihydroergotamine, yohimbine, rauwolscine. Data taken from ref 22.

Details of the α_1/α_2 subclassification have been reviewed.[10,11,17,18,20,21]

It goes without saying that the development and firm establishment of the concept of two distinct types of α adrenoceptors have heavily depended on the availability of selective drugs that would allow identification of both subtypes. During the course of establishing this concept, there has been an intensive feedback between experimental results and further experimentation. Once drugs with increasing selectivity for either site were found, they were used again to reevaluate other findings mostly made with less selective drugs. At present, agonists, as well as antagonists, are available with a high degree of specificity for either type of α adrenoceptor. It seems best to introduce at this stage of the paper an enumeration of drugs that have ultimately provided the tools for the characterization of α-adrenoceptor populations. This collection of formulas will certainly be liable to extension and refinement in the future, since this rapidly expanding field of research seems to be very versatile in producing new and interesting compounds. The structures have been depicted in Chart I. Although it seems beyond the scope of the present paper, selective agonists and antagonists of α_1 adrenoceptors have also been included to allow an adequate comparison.

Peripheral Presynaptic α_2 Adrenoceptors

Noradrenergic Nerve Endings. Presynaptic α_2 adrenoceptors located at the noradrenergic nerve terminals mediating the autoinhibition of norepinephrine release are considered the prototypes of α_2 adrenoceptors. Their drug specificity has been determined in detail with the presynaptic α_2 adrenoceptors of the rabbit pulmonary artery.[14,15] The stimulation-induced release of [^{3}H]norepinephrine from the rabbit isolated pulmonary artery is inhibited by activation of presynaptic α_2 adrenoceptors. The contraction of the artery is brought about via postsynaptic α_1 adrenoceptors, which constitute a homogeneous population in this organ.[23] Accordingly, pre- (α_2) and postsynaptic (α_1) activities of α-adrenoceptor agonists and antagonists have been determined (Figure 2).[14,15,22] The presynaptic/postsynaptic activity ratios vary 500-fold for agonists and more than 10 000-fold for antagonists showing appreciable selectivity of some drugs. Clonidine (**11**), α-methylnorepinephrine (**16**), and tramazoline (**10**) selectively stimulate the α_2 adrenoceptor, whereas phenylephrine (**1**) and methoxamine (**2**) preferentially activate the α_1 adrenoceptor. Yohimbine (**22**) and especially its diastereoisomer rauwolscine (**23**) are selective antagonists of the α_2 adrenoceptor. Prazosin (**17**) and another yohimbine diastereoisomer, corynanthine (**18**), display the highest selectivity for the α_1 adrenoceptor.

Presynaptic α adrenoceptors have been found at almost all noradrenergic axons where they have been assumed to exist. Presynaptic/postsynaptic activity ratios for agonists have also been determined in other tissues under in vivo or in vitro conditions, e.g., the rabbit heart,[12] ear artery,[24] and autoperfused hindlimb,[25] the rat heart,[26,27] anococcygeus muscle,[28,29] and vas deferens,[30,31] the cat autoperfused hindlimb[27] and circulatory system,[32] the dog heart,[33] and

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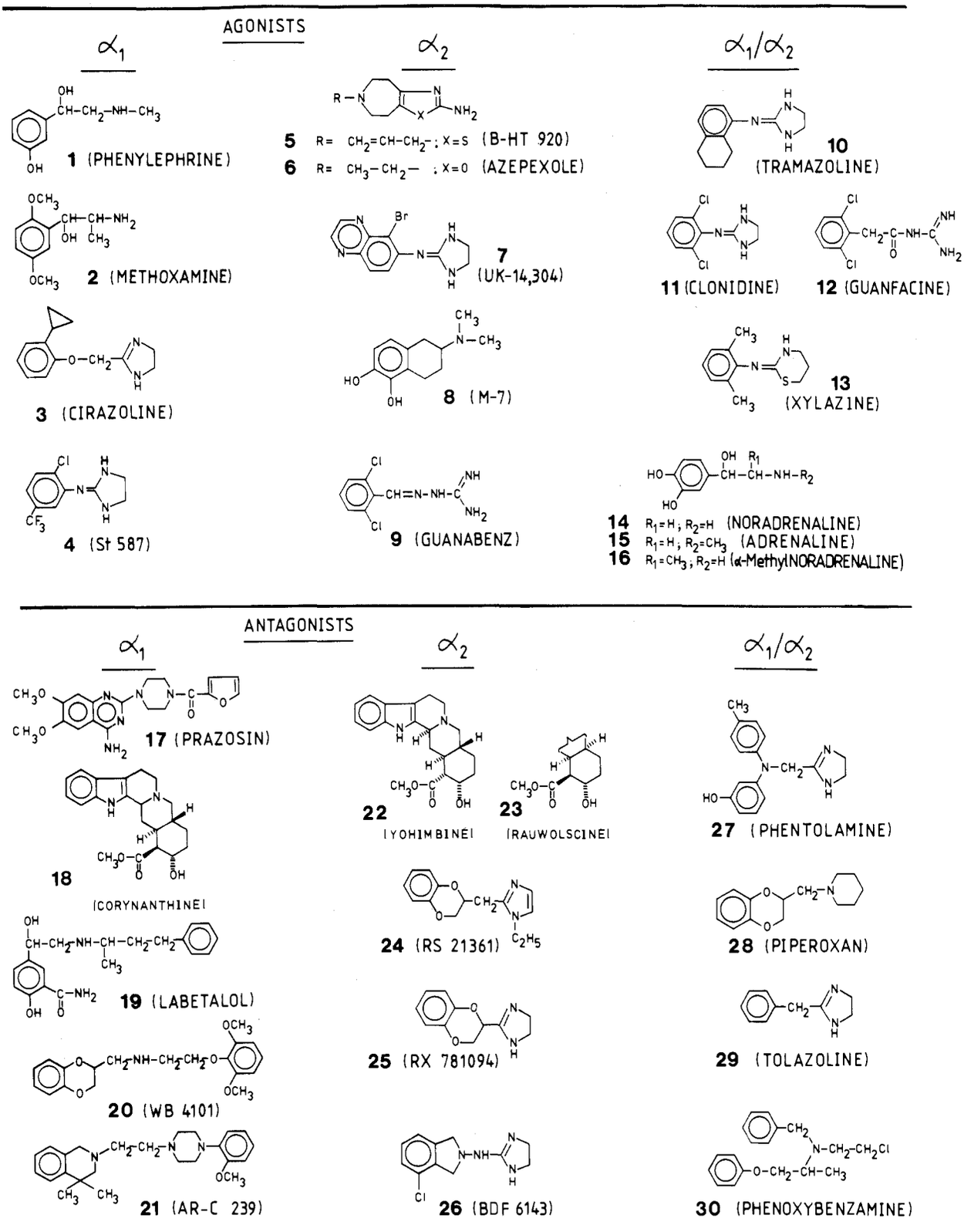
Chart I. Collection of Formulas of Agonists and Antagonists of α_1 and α_2 Adrenoceptors



the mouse vas deferens.[34] The in vitro methods and preparations utilized in the evaluation of agonists and antagonists of presynaptic α_2 adrenoceptors have recently been reviewed.[35]

In all tissues examined so far, the presynaptic α_2 adrenoceptors appear to be similar to those of the rabbit pulmonary artery. Thus, phenylephrine and methoxamine are selective stimulants of postsynaptic α_1 adrenoceptors. Clonidine and tramazoline are rather selective for α_2 adrenoceptors. The presynaptic/postsynaptic selectivity ratios of antagonists originally determined in the cat spleen[13] and rabbit pulmonary artery (Figure 2) have been confirmed and extended to other experimental prepara-

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tions and arrangements (see ref 22).

Cholinergic Nerve Endings. Inhibition of acetylcholine release can be effected via stimulation of α adrenoceptors located at central, preganglionic autonomic, and postganglionic parasympathetic neurons.[7,9,22,36,37] Relative potencies of agonists at α adrenoceptors of the cholinergic neurons of the guinea pig ileum have been established.[36,38-41] The receptors obviously fulfill the criteria for α_2 adrenoceptors. A linear correlation between the relative potencies of agonists to inhibit cholinergic transmission (guinea pig ileum) and the activities to impair the release of noradrenaline (rabbit pulmonary artery) has a correlation coefficient of 0.96.[42] Receptors with characteristics of α_2 adrenoceptors have also been demonstrated to be present at cholinergic nerve endings in the guinea pig gallbladder,[43] chicken stomach,[44] cat submaxillary gland,[45] and rabbit jejunum.[46] Studies with antagonists have confirmed the similarity between presynaptic α_2 adrenoceptors at cholinergic and noradrenergic neurons.

Serotonergic Nerve Endings. The serotonergic nerve fibers are endowed with both serotonin receptors and α_2 adrenoceptors. It has been shown that phentolamine (**27**) increased the stimulation-evoked [^{3}H]serotonin overflow from rat brain cortex slices by a competitive antagonism at the presynaptic α_2 adrenoceptors.[47] Similarly, noradrenaline inhibited depolarization-induced [^{3}H]serotonin release from slices of rat hippocampus.[48]

Noradrenergic Cell Bodies. Noradrenergic cell bodies in isolated superior cervical sympathetic ganglia of the rat are probably hyperpolarized through activation of α_2 adrenoceptors.[49] Responses to agonists were much more sensitive to yohimbine (**22**) than to prazosin (**17**). The same type of receptor is likely to inhibit the firing of the noradrenergic cells of the locus ceruleus.[50] Thus, central (soma-dendritic) and peripheral (terminal) noradrenergic neurons contain inhibitory α_2 adrenoceptors.

Peripheral Postsynaptic α_2 Adrenoceptors

Vascular Smooth Muscle. The rather surprising discovery of a simultaneous occurrence of postsynaptic α_1 and α_2 adrenoceptors in vascular smooth muscle, both involved in drug-induced vasoconstriction, has definitely established the classification of α adrenoceptors into two distinct functional subtypes. Originally, it was demonstrated that in isolated strips of human palmar digital

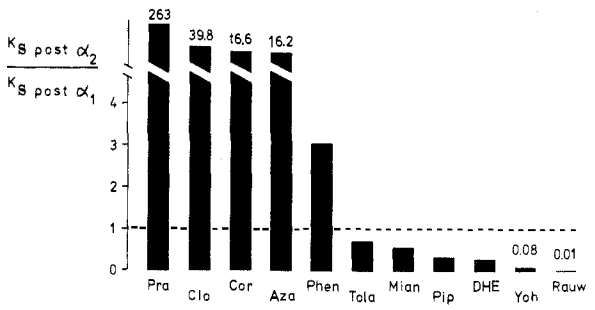

Figure 3. Selectivity of α-adrenoceptor antagonists for postsynaptic α_1 and α_2 adrenoceptors in the intact circulatory system of the pithed normotensive rat. The ratio K_B (post α_2)/K_B (post α_1) was calculated as an index of the preferential blocking activity at either α-adrenoreceptor site against (−)-phenylephrine (α_1) and B-HT 933 (α_2) induced vasoconstriction. $K_B = 10^{-pA_2}$. From left to right: prazosin, clozapine, corynanthine, azapetine, phentolamine, tolazoline, mianserin, piperoxan, dihydroergotamine, yohimbine, and rauwolscine. From ref 75.

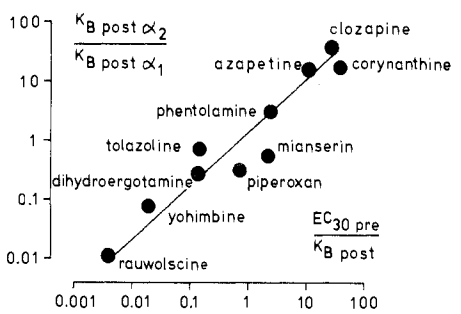

Figure 4. Relationship between the selectivity of α-adrenoceptor antagonists for postsynaptic α_1 and α_2 adrenoceptors in vascular smooth muscle of the pithed normotensive rat (also see Figure 3) and the selectivity of the blocking agents for presynaptic (α_2) and postsynaptic (α_1) adrenoceptors in the rabbit isolated pulmonary artery (see also Figure 2). From ref 75.

arteries the α_1-adrenoceptor blocker prazosin was unable to antagonize the contraction to norepinephrine, in contrast to human visceral arteries,[51,52] indicating a prazosin-resistant and a prazosin-sensitive vasoconstrictor α adrenoceptor in human vascular smooth muscle. The mixed α_1/α_2-adrenoceptor antagonist phentolamine (**27**) inhibited the contractile response to noradrenaline in both arterial preparations. Following these first observations, whole animal studies presented evidence favoring the existence of functional α_1 and α_2 adrenerceptors at postjunctional sites in the intact circulatory system of various animal species. By the use of more or less specific agonists and antagonists of α_1 and α_2 adrenoceptors, the diversification of postsynaptic α adrenoceptors into α_1 and α_2 subtypes has been substantiated in rats,[53-62] rabbits,[63-65]

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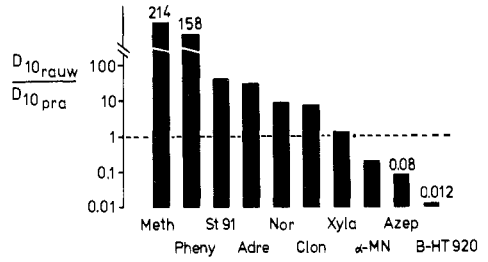

Figure 5. Antagonistic potency ratios of the α_2-adrenoceptor blocking drug rauwolscine (rauw) and the α_1-adrenoceptor antagonist prazosin (pra) against the pressor effect of various α-adrenoceptor agonists in pithed normotensive rats. D_{10} represents the doses of the antagonist causing a 10-fold shift of the agonist dose–pressor response curve. The ratio D_{10} (rauw)/D_{10} (pra) is a proposed measure of the α_1/α_2 selectivity of the agonists. From left to right: (±)-methoxamine, (−)-phenylephrine, St 91 (2-[[(2,6-diethylphenyl)imino]imidazolidine), (−)-epinephrine, (−)-norepinephrine, clonidine, xylazine, (−)-α-methylnorepinephrine, azepexole, and B-HT 920. Data from ref 76.

dogs,[66-70] and cats[53,71] 53,71 (see also ref 22, 72, 73). Recently, preliminary evidence for a postsynaptic α_2 adrenoceptor in the vasculature of the human forearm has been communicated.[74]

The remarkable convenience of separate stimulation of postsynaptic vasoconstrictor α adrenoceptors of either type, when appropriate agonists are used, has been applied to differentiate α-adrenoceptor antagonists. In pithed normotensive rats, α_1-adrenoceptor stimulation was achieved by (−)-phenylephrine (**1**), and the α_2 subtype was activated by azepexole (**6**). Quantitative analysis of the antagonism of the pressor effects of both selective agonists by the α-sympatholytic drugs resulted in the calculation of the ratio of K_B (post α_2)/K_B (post α_1) as a measure of the selectivity for either α-adrenoceptor site.[75] As visualized in Figure 3, the α-adrenoceptor antagonists covered a 20 000-fold range of activity ratios. The higher the column, the greater the affinity of the particular blocking drug for postsynaptic α_1 adrenoceptors in comparison with its affinity for postsynaptic α_2 adrenoceptors. The antagonists most selective for either type were prazosin (α_1) and rauwolscine (α_2). The selectivity ratios thus established very satisfactorily agree with the ratios found in the rabbit isolated pulmonary artery preparation (see Figure 2). The correlation is illustrated in Figure 4. Consequently, the same specificity of antagonists as previously established toward presynaptic α_2 adrenoceptors is generally applicable to postsynaptic (vascular) α_2 adrenoceptors.

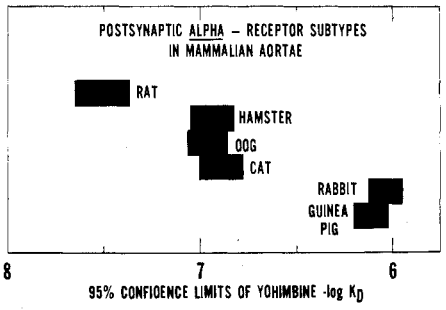

Figure 6. Mean −log K_B values and 95% confidence limits for yohimbine in aortas from six mammalian species. From ref 84.

In pithed rats, the antagonistic potencies of the selective α-adrenoceptor blocking agents prazosin (α_1) and rauwolscine (α_2) were assessed against various α-adrenoceptor agonists.[76] Doses of these antagonists that shifted the dose–response curves for an agonist 10-fold to the right (D_{10}) were calculated. The ratio D_{10} (rauwolscine)/D_{10} (prazosin), considered a measure of an agonist's α_1/α_2 selectivity ratio, varied greatly (Figure 5). Within the series of compounds tested, B-HT 920 (**5**) was selective for α_2 adrenoceptors and methoxamine (**2**) was selective for α_1 adrenoceptors.

The evidence for a functional constrictor α_2 adrenoceptor is largely based upon in vivo experiments. It has been rather difficult to detect and satisfactorily characterize postsynaptic vascular α_2 adrenoceptors in vitro. Although the results of a study by Moulds et al. with isolated strips of human vascular smooth muscle[51,52] have been taken as the first indications for the additional presence of vascular postsynaptic α_2 adrenoceptors, further in vitro investigations by these authors do not allow a firm classification of both subtypes in human digital arteries and metacarpal veins.[77,78] The authors concluded that the α adrenoceptors in human vessels are either different from other α_1 and α_2 adrenoceptors or are a mixed population of two or more types of receptors.

It is well documented that the α-adrenergic receptors of certain veins differ from those of most arteries and are not antagonized in a competitive way by prazosin.[79-81] The presence of both α_1 and α_2 adrenoceptors has been indicated on canine femoral and saphenous venous smooth-muscle cells.[82,83] However, the conclusion is complicated by the presence of noncompetitive antagonism.

With the aid of clonidine and yohimbine, the postsynaptic α adrenoceptors in isolated aortas from six mam-

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malian species have been divided into three classes.[84] As shown in Figure 6, the α adrenoceptors of the rat aorta possessed the highest affinity for yohimbine and clonidine. Markedly lower affinities were found for yohimbine and clonidine in guinea pig and rabbit aortas, whereas intermediate affinities were determined in aortas from hamster, cat, and dog. The affinities of both yohimbine and clonidine in rat aorta are exactly what one would expect for α_2 adrenoceptors. In fact, this receptor has many other characteristics of α_2 adrenoceptors.[85,86] However, the selective agonists of α_1 adrenoceptors, phenylephrine and methoxamine, and the α_1 antagonist prazosin are also potent in rat aorta.[87-89] Furthermore, in rat isolated aorta, prazosin has been found more potent in antagonizing clonidine than phenylephrine, and yohimbine was more potent in attenuating phenylephrine than clonidine.[90] It is therefore hardly possible to force the α adrenoceptors of the rat aorta into the classification of either α_1 or α_2.

The postsynaptic α receptor of the dog isolated basilar artery resembles an α_2 adrenoceptor.[91] Yohimbine inhibited the contractile responses to noradrenaline and clonidine competitively, whereas corynanthine (up to 10^{-6} M) and prazosin had no effect. However, phenylephrine also acted as a full agonist, and yohimbine attenuated the phenylephrine response in a noncompetitive manner.

Provided that highly selective agonists of α_2 adrenoceptors are being used, the dog saphenous vein represents an in vitro tissue where it is possible to demonstrate postsynaptic vasoconstrictor α_2 adrenoceptors unequivocally. Compounds M-7 (**8**)[92] and UK-14304 (**7**)[93] are postsynaptic α_2-adrenoceptor agonists in this vessel. The use of less selective agonists has led to inconclusive results.[94]

An interesting observation has been made in isolated perfused hindquarters of rats, where a vasoconstrictor effect of B-HT 920 (**5**) was only apparent following treatment of the animals with reserpine.[95,96] In fact, this is the first and, until now, only example reported that B-HT 920 produces a vasoconstriction in vitro. There is as yet no clear explanation for this finding.

We can summarize the available data on the in vitro vascular α_2 adrenoceptor, concisely outlined above, by stating that the demonstration of this class of α_2 adrenoceptor under in vitro conditions with a reasonable degree of success seems only possible when highly selective α_2 stimulants and tissues with a high proportion of α_2 adrenoceptors are being employed.

Fat Cells. Evidence has been presented that the inhibition of lipolysis by α-adrenoceptor agonists in human and hamster adipose tissue is mediated by α_2 adrenoceptors.[97-99] Based on the inhibition of theophylline-induced lipolysis, the relative order of activity of various α-adrenoceptor agonists was clonidine > epinephrine > phenylephrine > methoxamine. The order of potency of antagonists for the human α adrenoceptor of adipocytes was yohimbine (**22**) > piperoxan (**28**) > phenoxybenzamine (**30**) ≥ prazosin (**17**).

Pancreatic Islets. The release of immunoreactive insulin (IRI) from mammalian pancreatic islets is inhibited by α-adrenergic stimulation.[100] Phentolamine, as well as yohimbine, markedly increased plasma IRI and inhibited epinephrine-induced hyperglycemia in fasted mice that was enhanced by phenoxybenzamine and prazosin.[101] These results indicate that the α adrenoceptors responsible for the plasma IRI levels resemble α_2 adrenoceptors.

Platelets. Out of many α-adrenergic agonists tested, only epinephrine, norepinephrine, and α-methylnorepinephrine have been reported to induce primary platelet aggregation and inhibition of adenylate cyclase, whereas other phenylethylamine derivatives, such as phenylephrine and methoxamine, but also all imidazoli(di)ne derivatives, such as clonidine and tramazoline, hardly cause platelet aggregation or reduce adenylate cyclase activity. These latter drugs, however, can potentiate this response to other agonists (e.g., ADP) and generally behave as partial agonists. They can act as antagonists of adrenaline-induced aggregation. In contrast to prazosin, yohimbine and phentolamine inhibit epinephrine-induced platelet aggregation.[102-108]

The α adrenoceptors of platelets appear quite similar to the α_2 receptor with regard to binding affinities of various α-adrenergic agonists. They are, however, different from that found in other tissues inasmuch as only some catecholamines act as agonists, whereas other potent α_2-adrenoceptor stimulants act as antagonists. It should be added that α_1-adrenoceptors have also been suggested on human, but not on rabbit, platelets.[106,109] These α_1 adrenoceptors have no significant role in the response to epinephrine, which is mediated solely by the α_2 adrenoceptors.

It has recently been shown for human platelets that the clonidine analogue UK-14304 (**7**) is a full agonist, in contrast to clonidine itself.[109] This result is intriguing, espe-

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cially since UK-14 304, but not clonidine, is a full agonist of (presynaptic) α_2 adrenoceptors in the rat heart.[110] It may be worthwhile to explore M-7 (8) and B-HT 920 (5) for the ability to cause platelet aggregation in view of their pronounced intrinsic activity with respect to α_2 adrenoceptors.

Melanocytes. Skin color in lizards (*Anolis carolinensis*) and frogs (*Rana pipiens*) is influenced both by melanocyte-stimulating hormone (MSH) and catecholamines. MSH-induced darkening of the skin can be inhibited or reversed by drugs with α-adrenoceptor stimulating activity. This action is thought to be mediated by α adrenoceptors on the melanophore.[111-113] The α adrenoceptor on melanocytes inhibitory to dispersion of granules has been defined as the α_2 subtype.[17,113,114] α-Methylnorepinephrine was 10 times more potent than norepinephrine, and methyldopamine had a 30- to 100-fold greater potency than dopamine.[17,113] Clonidine was found to mimic catecholamine action, and yohimbine antagonized the effect of clonidine, whereas prazosin had negligible blocking activity.

Central Nervous System

A variety of effects can be initiated within the central nervous system by activation and/or blockade of α_2 adrenoceptors. Due to the complexity of the central nervous system, the details of most of the mechanisms and of the synaptic location of the α_2 adrenoceptors are poorly understood. For this reason, a separate section is devoted to central nervous system α_2 adrenergic effects.

Clonidine and other α-adrenoceptor stimulants decrease the turnover of norepinephrine in the spinal cord and brain of rats and also decelerate the rate of synthesis.[115-119] The reduced norepinephrine turnover is most likely due to a negative feedback in noradrenergic neurons involving presynaptic α_2 adrenoceptors. Yohimbine (22) piperoxan (28), and tolazoline (29) are effective blockers, whereas phenoxybenzamine (30) weakly interfered and prazosin (17) not at all interfered with this effect.

The principle of presynaptic α_2-adrenoceptor-mediated modulation of norepinephrine release in the central nervous system has been demonstrated by various authors.[120-127] Depolarization of the nerve terminal membrane was achieved by electrical-field stimulation of elevated K^+ concentrations of isolated brain tissue or synaptosomes preincubated with the tritium-labeled transmitter. It has been found that clonidine and oxymetazoline, but not methoxamine, reduced K^+-evoked release and that yohimbine and phentolamine, but not prazosin or WB-4101 (20), increased the K^+-evoked release of [^{3}H]-norepinephrine from slices of the rat occipital cortex.[128,129] Consequently, cerebral noradrenergic neurons may possess somadendritic (see above) and presynaptic α_2 adrenoceptors.

Centrally mediated hypotension and bradycardia can be elicited by clonidine and related drugs, as well as by α-Me-Dopa. An inhibition of peripheral sympathetic tone is then brought about by stimulation of central α adrenoceptors. The basis for the formulation of clonidine's and α-Me-Dopa's mode of action need not to be detailed here, since the principles have been reviewed extensively.[130-134] There is ample experimental evidence for the view that the central hypotension (bradycardia) induced by clonidine and related drugs is due to stimulation of α_2 adrenoceptors.[17,135,136] The selective α_2-adrenoceptor antagonists yohimbine (22) and rauwolscine (23) are very effective blockers of the central hypotensive effect of clonidine. Much higher doses of corynanthine (18) and prazosin (17) are needed to reduce clonidine's central hypotension.[135,137] Furthermore, preferential agonists of α_2 adrenoceptors, such as B-HT 933 (azepexole, 6), B-HT 920 (5), and UK-14 304 (7), are the most potent centrally acting hypotensive drugs.[138-141] On the other hand, for directly acting agonists of α_1 adrenoceptors that are lipophilic enough to penetrate into the central nervous system, like cirazoline (3) and St 587 (4), a central hypotensive effect is lacking.[110,142,143] The

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location of central hypotensive α_2 adrenoceptors relative to the synapse is as yet not properly understood. Some aspects of the synaptic location of these central α_2 adrenoceptors will be touched upon in the following paragraphs.

Stimulation of α adrenoceptors within the central nervous system leads to behavioral depression of laboratory animals.[132,133,141] In fact, sedation constitutes a prominent side effect in the antihypertensive therapy with centrally acting α-adrenergic hypotensive drugs. With respect to the clonidine-induced sedation, the involvement of α_2 adrenoceptors has been advocated. The relative potency of α-adrenoceptor agonists corresponds with that observed for peripheral (presynaptic) α_2 adrenoceptors.[144,145] In addition, selective antagonists of α_2 adrenoceptors profoundly interfere with the sedative action of clonidine, in full contrast to blockers of α_1 adrenoceptors.[135,145-148] It has been proposed that inhibitory presynaptic α_2 adrenoceptors represent the sedative α adrenoceptors (see below).

Similar populations of central α_2 adrenoceptors presumably exert suppression of conditioned avoidance behavior[149] and of self-stimulation.[150,151]

After stimulation of each auditory canal with a fine wire, mice show a pinna reflex.[152] Clonidine (**11**), guanfacine (**12**), and guanabenz (**9**) were potent inhibitors of the reflex, while methoxamine (**2**) was only partially effective even after central injection. Yohimbine (**22**) and piperoxan (**28**) were effective in antagonizing the inhibitory effects of the agonists, but prazosin (**17**) was ineffective.[153] The results suggest that α_2 adrenoceptors participate.

Apart from the central α_2 adrenoceptors discussed above, populations of α adrenoceptors, which most likely are to be classified as α_2 adrenoceptors, have been identified controlling temperature regulation,[154] salivation,[155] ACTH release,[156] and anticonvulsant effects.[157]

Eye

Topical application of the selective α_2-adrenoceptor agonists azepexole (B-HT 933, **6**) and B-HT 920 (**5**) to the eyes of conscious rabbits resulted into a marked and dose-dependent ocular hypotensive response with neither macroscopic ocular side effects nor an effect on the pupil size.[158] The decrease in ocular pressure brought about by the drugs was antagonized by yohimbine (**22**). The results indicate the presence of α_2 adrenoceptors in the eye involved in the reduction of intraocular pressure. No data are available with respect to a pre- or a postsynaptic location of these α_2 adrenoceptors.

Table I. Drug Competition at [^{3}H]Clonidine Binding Sites in Rat Brain Membranes

drug	K_i,[a] nM
(−)-phenylephrine	270
(−)-norepinephrine	17
α-methylnorepinephrine	7.7
clonidine	5.7, 3.6*
naphazoline	5.7
tramazoline	4.2
oxymetazoline	1.9
phentolamine	22, 18*
piperoxan	95
rauwolscine	149*
yohimbine	150, 149*
tolazoline	180
WB 4101	200
prazosin	4 500*
corynanthine	15 800*

[a] From ref 135 (asterisked) and 167.

Radioligand Binding

The results of binding experiments with α adrenoceptors support the concept of α_1 and α_2 subtypes.[159-162] The mixed agonist/antagonist [^{3}H]dihydroergocryptine was the first ligand used to study α adrenoceptors. Initially, the two binding sites detected for this radioligand were interpreted as agonist and antagonist α-receptor sites.[163,164] However, subsequent studies made it more likely that [^{3}H]dihydroergocryptine labels α_1 and α_2 adrenoceptors with equal affinity.[160,165,166] The inhibition of the specific [^{3}H]dihydroergocryptine binding to rat brain membranes by prazosin and yohimbine follows a biphasic pattern.[165] At present, tritium-labeled clonidine is widely used to identify α_2 adrenoceptors. Specific high-affinity binding to α_2 adrenoceptors has been extensively reported in brain[167,168] and various peripheral tissues,[159,160,166] e.g., kidney,[169] heart,[170] ileum,[171] platelets,[172,173] liver,[174] fat

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cells,[175] salivary glands,[176] uterus,[177] and vessles.[178] Table I lists some affinity constants of nonradioactive compounds competing for the [^{3}H]clonidine binding sites in rat brain membranes satisfying the α_2 classification.

p-Amino[^{3}H]clonidine has also been an excellent probe for the study of α_2 adrenoceptors, and it binds with a greater affinity than [^{3}H]clonidine to these sites.[179] The pharmacologically and structurally related drugs guanfacine (**12**) and lofexidine occupy the same α_2-adrenoceptor population as [^{3}H]clonidine.[180,181] Due to the greater pharmacological specificity of yohimbine and rauwolscine over dihydroergocryptine, the former two drugs have been characterized as very useful radioligands for a direct labeling of α_2 adrenoceptors.[173,178,182,183]

Affinities of agonists and antagonists for the [^{3}H]clonidine binding sites in various tissues have been compiled by Starke.[22] The rank order of K_i values generally corresponds in the different tissues. However, as noted by Starke[22] many discrepancies exist between the absolute K_i values. It is a general observation already pointed at in the very first binding experiments with [^{3}H]clonidine[184] that agonists possess higher affinities for the [^{3}H]clonidine site than antagonists (see also Table I). There are observations in favor of the existence of at least two conformational states of the α_2 adrenoceptor, which are differentiated by high or low affinity for agonists. [^{3}H]Clonidine appears to bind only to the high-affinity state of the α_2 adrenoceptor.[185,186] [^{3}H]Yohimbine and [^{3}H]rauwolscine have been proposed to label both the high- and the low-affinity states of the α_2 adrenoceptor.[182,183] Modulation of agonist binding to α_2 adrenoceptors will be summarized in the following paragraphs.

Localization of α_2 Adrenoceptors

Several experimental observations provide strong indications that α_2 adrenoceptors inhibiting norepinephrine release are presynaptic in a topographic sense. Accordingly, the inhibitory mechanism can be demonstrated in various synapses endowed with either α or β adrenoceptors at the target organs. Furthermore, the principle of regulation of norepinephrine release is not affected by atrophy or absence of the postsynaptic effector cells.[10,11]

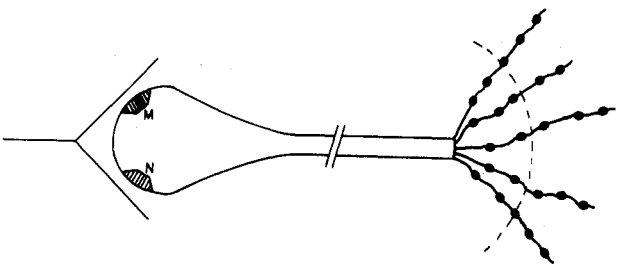

Figure 7. Sympathetic ganglion with nicotinic (N) and muscarinic (M) receptors on the cell body and postganglionic nerve terminating in the vascular wall. It is suggested that upon stimulation of the ganglionic nicotinic receptors, the neurotransmitter norepinephrine is released in the synapses of the varicosities more proximal to the nerve terminal endowed with predominantly α_1 adrenoceptors. Activation of the muscarinic receptors may give rise to a stimulus reaching the varicosities more distant to the nerve ending containing postsynaptic α_2 adrenoceptors. From ref 194.

A direct labeling of presynaptic α_2 adrenoceptors by means of suitable radioligands has met with but limited success. This is in sharp contrast to a direct identification of α_2-adrenoceptor binding sites at postsynaptic locations in the periphery as well as in the central nervous system (see above). Destruction of norepinephrine neurons with 6-hydroxydopamine did not reduce the number of [^{3}H]-clonidine binding sites but rather increased it,[160,167,171,185,186] except in the rat heart, where a significant decrease in maximal binding of [^{3}H]dihydroergocryptine was observed.[170] These results indicate that the majority of the binding sites are at postsynaptic locations.

Neonatal 6-hydroxydopamine treatment of rats showed that in animals aged 7–14 days there was a 20% decrease in the number of α_2 adrenoceptors, but that in rats 45–50 days old this number was increased.[187] Surgical denervation (frontal lobotomy) of rat cerebral cortex resulted in a very small decrease in α_2-adrenoceptor binding capacity.[188] Consequently, presynaptic α_2 adrenoceptors at noradrenergic nerve terminals in the central nervous system represent only a minor portion of the total α_2-adrenoceptor population. However, such a qualitatively minor population of presynaptic α_2 adrenoceptors may still have an important functionality. In addition, loss of presynaptic α_2-adrenoceptor sites may be overcome due to the development of denervation supersensitivity, which increases the maximal binding at the postsynaptic level.[10,11,187,189-191]

Binding as well as functional studies have established the occurrence of nonneuronal α_2 adrenoceptors at postsynaptic sites in platelets, fat cells, and pancreatic islets (see above). Recent experiments have provided some additional information on the anatomical localization of postsynaptic α_2 adrenoceptors in vascular smooth muscle. A differential effectiveness of α-adrenoceptor blocking agents at inhibiting the pressor responses to spinal-cord

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stimulation and intravenously administered norepinephrine in pithed rats has been noticed.[192] It has also been found that pressor responses elicited by sympathetic nerve stimulation in the dog were markedly antagonized by prazosin and that in the same species rauwolscine rendered the pressor effects of intravenous norepinephrine sensitive to prazosin blockade.[68-70] Norepinephrine release through ganglionic stimulation with the nicotinic agonist 1,1-dimethyl-4-phenylpiperazine iodide (DMPP) in adrenalectomized rats also stimulated only α_1 adrenoceptors, no pressor component via α_2-adrenoceptors being detectable.[193] These data support the concept that postsynaptic vasoconstrictor α_1 adrenoceptors are part of the synapse and that the corresponding α_2 adrenoceptors have a predominant extrasynaptic location. However, when the indirectly acting α-sympathomimetic agent tyramine was used, indications for postsynaptic vasopressor α_2 adrenoceptors activated by neurons were still obtained.[194] It has been made plausible that these α_2 adrenoceptors are activated via ganglionic muscarinic receptors.[194] As an alternative hypothesis for the extrasynaptic location of vascular α_2 adrenoceptors, it has been suggested that activation of ganglionic nicotinic receptors leads to stimulation of the nearest varicosities endowed with α_1 adrenoceptors. However, activation of ganglionic muscarinic receptors may lead to additional release of neurotransmitter in the more distant varicosities containing α_2 adrenoceptors (Figure 7).

The α_2 adrenoceptors in the pontomedullary region of the brain are presumably the main sites of action of clonidine, α-Me-Dopa, and related drugs in initiating cardiovascular depression. As discussed above, stimulation brings about an increase in vagal tone, as well as a decrease in peripheral sympathetic nervous activity, blood pressure, and heart rate. Although it is difficult to define precisely a single neuron or brain region as the sole and major target of these drugs, the nucleus of the solitary tract (NTS) seems an important site of action.[130-133,195] High densities of α_2 adrenoceptors are identified in this nucleus.[196,197] Local administration of α-adrenoceptor agonists into the NTS elicited a decrease in arterial pressure.[198-200] However, it is quite disappointing that the pharmacological data presented do not allow a classification of the depressor α adrenoceptors in the NTS in terms of α_1 or α_2 subtypes. For example, clonidine is but moderately active and oxymetazoline is even without effect. Additionally, both yohimbine and prazosin are effective antagonists.

The question of whether the central cardiovascular depressant α_2 adrenoceptors are located at the terminals of noradrenergic neurons (presynaptic) or on the cell bodies or dendrites of noradrenergically innervated neurons (postsynaptic) cannot be answered with certainty due to methodological limitations. The deceleration of central norepinephrine turnover by clonidine and its reversal by yohimbine (see above) suggest an inhibition of norepinephrine release through presynaptic α_2 adrenoceptors. On the other hand, after depletion of norepinephrine by high doses of reserpine and by 6-hydroxydopamine and subsequent inhibition of synthesis, clonidine still reduced sympathetic nervous activity, and its vagally mediated bradycardia was also preserved.[201-204] Consequently, central endogenous transmitter norepinephrine is apparently not required for the central cardiovascular response to clonidine, indicating that the α_2 adrenoceptors are located at postsynaptic sites. These receptors do not have a noradrenergic input, since α adrenoceptor antagonists are virtually inactive at the central level and the elimination of endogenous transmitter by 6-hydroxydopamine treatment only moderately and transiently affects systemic arterial pressure. The participation of an as yet unknown transmitter has been considered.[133,201] However, no indications whatsoever are available to support this.

More conclusive material seems to be present to favor the view that the central α_2 adrenoceptors initiating sedation of α-adrenoceptor stimulants are inhibitory presynaptic α_2 adrenoceptors at noradrenergic neurons. It has been reported that after depletion of catecholamine stores alone or combined with destruction of noradrenergic neurons by 6-hydroxydopamine, clonidine no longer induces sedation but causes behavioral excitation.[205-207] Under the latter conditions, a selective agonist of α_2 adrenoceptors, such as B-HT 920 (5), proved without effect.[207]

Mechanisms

Electrical stimulation induced depolarization of the neuronal membrane leads to activation of voltage-sensitive calcium channels, resulting in an influx of calcium ions into the axoplasm which in some way provokes transmitter (e.g., norepinephrine) release by an exocytotic process.[208-211] Several mechanisms by which presynaptic α_2 adrenoceptors are thought to modulate this transmitter release have been proposed. It has been documented that the prejunctional α_2-adrenoceptor-mediated regulation mechanism is only operating on those release pathways that depend on the availability of extracellular calcium ions. K^+, veratrine, and electrical, but not tyramine, induced norepinephrine release is modulated by α_2-adrenoceptor agonists and antagonists.[7,8,11,123,212] As a consequence

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thereof, it has been suggested that the presynaptic α_2 adrenoceptor modifies norepinephrine release by regulating the influx of extracellular calcium ions. Thus, presynaptic α_2-adrenoceptor activation will inhibit the transmembrane inward current of calcium ions via potential-sensitive permeability channels.[213-216]

Stjärne[217,218] has proposed that inhibition of noradrenaline release is achieved by hyperpolarization of the axons, resulting in depression of impulse propagation and of recruitment of varicosities. Activation of presynaptic α_2 adrenoceptors would induce an increase in the K^+ permeability leading to an intraterminal conduction block in neighboring strings of varicosities.

Cyclic nucleotides have been implicated in the mechanism of norepinephrine release controlled by presynaptic α_2 adrenoceptors. Experimental evidence supporting the involvement of cyclic AMP or cyclic GMP is limited and rather conflicting (see, for example, ref 10 and 219–223). Additional data are needed to judge a role of cyclic nucleotides in the presynaptic modulation of norepinephrine release via α_2 adrenoceptors.

Up to now, the only known intracellular signal generated by stimulation of α_2 adrenoceptors, occurring presynaptically in adrenergic and cholinergic nerve endings and postsynaptically in a variety of tissues, was a fall in the cyclic AMP concentration. As shown in many tissues and cell types, this decreased concentration is due to α_2-adrenergic inhibition of adenylate cyclase.[224-226]

The pieces of evidence linking prejunctional α_2-adrenoceptor-mediated control of norepinephrine release with (Na^+,K^+)ATPase have very recently been critically reviewed.[227] The stimulation of α_2 adrenoceptors at the membrane of the nerve ending would increase ATPase activity. This would reduce the release of transmitter by increasing the efflux of calcium from the nerve terminals.[9,228] The participation of an α_2 adrenoceptor in the (Na^+,K^+)ATPase stimulating pathway is, however, by no means proven.

It is obvious from the foregoing that there are a number of intriguing possibilities to explain the steps linking presynaptic α_2-adrenoceptor activation and transmitter release. All mechanisms require further experimental support.

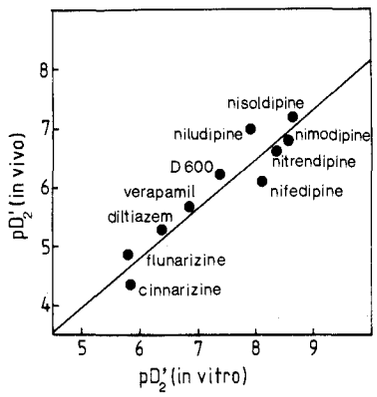

Figure 8. Relationship between the inhibitory activities of various calcium entry blockers on K^+-induced contractions of rabbit isolated thoracic aorta strips, pD_2' (in vitro), and on α_2-adrenoceptor-mediated vasopressor responses in pithed normotensive rats, pD_2' (in vivo). Data from ref 236. The significance of this relationship supports the hypothesis that a transmembrane influx of calcium ions is a prerequisite for the vasoconstriction brought about by stimulation of α_2 adrenoceptors.

It has already been briefly mentioned that α_2 adrenoceptors in general may be coupled to inhibition of adenylate cyclase (see above). Stimulation of nonneuronal α_2 adrenoceptors located on cell membranes of platelets, pancreatic islets, adipocytes, and neuroblastoma × glioma hybrid cells particularly respond with an inhibition of cyclic AMP accumulation (see also ref 229 and references quoted therein). This process is independent of calcium ions. In contrast, indications have recently been presented that extracellular calcium ions are required for the vasoconstriction in vivo initiated by activation of α_2 adrenoceptors.[230,231] This hypothesis has been formulated on the basis of the pronounced inhibitory action of Na_2-EDTA and numerous calcium-entry blockers on vasopressor responses to postsynaptic α_2-adrenoceptor activation in vivo. In vitro studies seem to confirm this principle.[232-235] A correlation between the inhibitory activities of calcium antagonists on vascular smooth-muscle constriction in vitro (rabbit aorta) after K^+ depolarization and in vivo (pithed rat) after the stimulation of vascular α_2 adrenoceptors has been derived (Figure 8).[236] This relationship suggests a similar type of interaction for the calcium-entry blockers and further supports the hypothesis that extracellular calcium ions play a role in triggering the vasocontriction induced by α_2-adrenoceptor stimulation.

Measurements of radioligand binding to α_2 adrenoceptors have been made in order to achieve an understanding of the mechanism of action of the receptors. This approach has so far been fruitfully applied to α_2 adrenoceptors that

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inhibit adenylate cyclase. Guanyl nucleotides and Na^+ ions have been reported to reduce high-affinity binding of agonists to α_2 adrenoceptors in brain[237-239] and platelet membranes.[240,241] The divalent cations Ca^{2+}, Mg^{2+}, and Mn^{2+} reversed the effects on binding of guanyl nucleotides and Na^+.[237] Ni^{2+}, Mn^{2+}, Mg^{2+}, Ba^{2+}, and Sr^{2+} potentiated [^{3}H]clonidine binding to α_2 adrenoceptors.[242] Na^+ ions and guanyl nucleotides convert a large fraction of the α_2 adrenoceptors into a low-affinity state. The divalent cations are necessary to form a high-affinity state of an agonist–receptor complex. An explanation of the effect of guanyl nucleotides is that agonists promote the association of the α_2 adrenoceptor with a regulatory membrane component. This complex is destabilized by guanyl nucleotides.[243,244] More direct evidence in favor of this explanation is indicated by the larger sedimentation coefficient (14.6 S) of the agonist-labeled α_2 adrenoceptor over the antagonist-labeled receptor (12.9 S) solubilized from human platelets.[245]

Targets for Drugs

The physiological role of presynaptic α_2 adrenoceptors may be threefold:[11] (1) Presynaptic α_2 adrenoceptors may serve as targets for circulating catecholamines. (2) Presynaptic α_2-adrenoceptors may function as targets for transmitters secreted from neighboring axon terminals. Accordingly, presynaptic interactions between the sympathetic and the parasympathetic nervous system have been demonstrated, which may supplement the classical postsynaptic antagonism between these two parts of the autonomic nervous system. (3) Presynaptic α_2 adrenoceptors may manifest themselves as autoreceptors for the endogenous neurotransmitter norepinephrine, thereby inhibiting its further release. Few details are as yet known about the actual physiological role of presynaptic α_2 adrenoceptors in vivo. Most experiments aiming at the demonstration of operating presynaptic mechanisms have been performed in vitro or in vivo under electrical stimulation. The physiological meaning of the autoinhibition of norepinephrine release in vivo has been criticized [246-248] (see also ref 11). A functional role of presynaptic α_2 adrenoceptors in noradrenergic transmission has been suggested in conscious rats,[249,250] but this has not been confirmed in conscious rabbits[251] and man.[252] However, the fragmentary investigations carried out so far are insufficient for one to decide upon a definite acceptance or rejection of the concept.

The physiological role of the postsynaptic α_2 adrenoceptors can only be the subject of mere speculation. In case they significantly contribute to peripheral resistance, selective blockade would result into a decrease in arterial pressure. Furthermore, the very attractive blood pressure lowering activity of the so-called calcium-entry blockers[253,254] can at least partly been explained with the aid of vascular α_2 adrenoceptors. Calcium slow channel blockers inhibit the transmembrane influx of calcium, which is required for the vasoconstrictor process of α_2-adrenoceptor stimulation. In view of the beneficial effects of calcium antagonists in those forms of angina that involve coronary spasm and in certain peripheral vasospastic disorders, such as Raynaud's syndrome, the involvement of vascular α_2 adrenoceptors can be speculated upon. The recent observation that vasoconstriction via postsynaptic α_2 adrenoceptors is influenced by inhibition of the formation of angiotensin II by captopril,[255] as well as by adrenalectomy,[256] is in agreement with the characterization of these α_2 adrenoceptors as hormone receptors. As discussed above, vascular α_2 adrenoceptors are probably not under direct noradrenergic control, so that a modulation of their response by blood-born substances is very conceivable.

Whatever the significance of pre- and postsynaptic α_2 adrenoceptors may be, a number of drug-induced effects, which are recognized as of potential therapeutic benefit, are presumed to be initiated by pre- or postsynaptic α_2 adrenoceptors.

Stimulation of central α_2 adrenoceptors by suitable drugs leads to hypotension and bradycardia. Clonidine and α-Me-Dopa, presumably via α-methylnorepinephrine, are the prototypes of these centrally acting antihypertensive drugs. Being an α-adrenoceptor stimulant, clonidine also activates presynaptic cardiac α_2 adrenoceptors. It is very likely that this peripheral effect contributes to the overall bradycardia of this drug.[257,258] The participation of (presynaptic) α_2 adrenoceptors in the production of sedation by clonidine and related drugs has been established, and activation of presynaptic α_2 adrenoceptors inhibiting cholinergic transmission is probably the explanation for the occurrence of dry mouth. So far, a separation between the sedative and the hypotensive properties of centrally acting α_2-adrenoceptor agonists has not been successfully achieved in therapy.

Clonidine and some related drugs suppress symptoms of opiate withdrawal.[259] This action is possibly due to a stimulation of central presynaptic α_2 adrenoceptors, which result in the inhibition of the firing of the locus ceruleus. The α_2 adrenoceptors also appear to play a role in the

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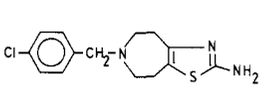
withdrawal syndrome following cessation of long-term antihypertensive treatment with clonidine.[260,261] This phenomenon may be related to the development of a clonidine-induced subsensitivity of the central and the peripheral α_2 adrenoceptors playing a role in the mechanism of action of this drug. However, in spite of this desensitization of α_2 adrenoceptors as suggested, there is generally no tolerance against the therapeutic effects of clonidine (hypotension, bradycardia).

A very attractive therapeutic application of α_2-adrenoceptor agonists may be offered by their profound effect on intraocular pressure.[158] Macroscopic ocular side effects or an effect on the pupil size is possibly related to α_1 adrenoceptor stimulation. Thus, selective α_2 adrenoceptor stimulants may represent a group of new antiglaucomatous agents. Studies in glaucaumatous patients have to establish their place in therapy.

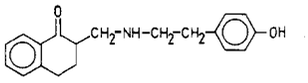
Some ideas have been developed that depression may be based in some way on a reduced noradrenergic transmission in the central nervous system.[262] Consequently, α_2-adrenoceptor antagonists might have a beneficial effect in depressive illness, since they facilitate neurotransmission. Some selective antagonists of α_2 adrenoceptors are presently being tested clinically for this purpose.

Central presynaptic α_2 adrenoceptors have also been considered to be involved in the mechanism of action of tricyclic antidepressants.[10] The chronic inhibition of neuronal uptake of noradrenaline would induce a subsensitivity of these presynaptic α_2 adrenoceptors, ultimately leading to enhanced release of the transmitter.

Under physiological conditions, the net effect of an α-adrenoceptor stimulant will be the sum of presynaptic (inhibition of transmitter release) and postsynaptic (activation of the target organ) actions, since most organs are constantly receiving a noradrenergic input. Obviously, the same applies to α-adrenoceptor antagonists. The relative proportion of functional postsynaptic α_2 adrenoceptors will then determine to what extent presynaptic (α_2) and postsynaptic (α_1/α_2) effects can be distinguished. In addition, possible central effects affecting the activity of the peripheral nervous system can be expected. Although the general characteristics of pre- and postsynaptic α_2 adrenoceptors are the same (see, e.g., Figure 2), there exist but few observations indicating a possibility to discriminate between pre- and postsynaptic α_2 adrenoceptors. Within a series of 2,5-disubstituted clonidine analogues, some derivatives appeared to distinguish between cardiac presynaptic and vascular postsynaptic α_2 adrenoceptors.[263] B-HT 958 (31) preferentially stimulates cardiac presynaptic α_2 adrenoceptors. Much higher doses are needed to provoke vasoconstriction via postsynaptic α_2 adrenoceptors.[264] Differences in receptor numbers can also be seriously considered an explanation. In addition, the α-adrenoceptor antagonist BE 2254 (32) has been reported to differ in potency at pre- and postsynaptic α_2 adrenoceptors.[265]



31 (B-HT 958)



32 (BE 2254, HEAT)

If indeed selective agonist and antagonists of pre- and postsynaptic α_2-adrenoceptors can be found, such compounds would offer an attractive challenge in drug discovery because of their therapeutic potential in interfering with pre- and/or postsynaptic α_2-adrenoceptors.

Conclusions

The subdivision of α adrenoceptors into pre- and postsynaptic vs. α_1 and α_2 subtypes is an example of the result of careful molecular pharmacological analysis. After an initial period of confusion, the classification of α adrenoceptors is now well accepted. The α_2 adrenoceptor, present at both pre- and postsynaptic sites, has been identified in various organs and tissue structures. A physiological role of these receptors seems likely, although such a role remains to be established in more detail and with more certainty. The extension of the α_1/α_2 adrenoceptor concept has allowed a more detailed understanding of the mode of action of centrally acting antihypertensive drugs, of which clonidine is the generally recognized prototype. Radioligand binding studies have allowed the quantification of affinities of various drugs and experimental compounds for the α_2 adrenoceptor. Recently, particular attention has been paid to the precise location of the postsynaptic α_2 adrenoceptor with respect to the synapse. Another question that has aroused a great deal of interest is the involvement of calcium fluxes in the process of vasoconstriction mediated by postsynaptic α_1 and α_2 adrenoceptors. Whereas the stimulation of α_1 adrenoceptors seems to induce depolarization and the release of calcium ions from intracellular stores, the excitation of postsynaptic α_2 adrenoceptors in vascular smooth muscle appears to open specific membrane channels via which extracellular calcium ions can enter the cell.

As a whole, more precise localization and subdivision of receptors have invariably led to the development of selective agonists and antagonists. Well-known examples of such a development are the subdivision of cholinergic receptors (nicotinic, muscarinic), β adrenoceptors (β_1/β_2), histamine (H_1/H_2), and serotonin (5-HT_1/5-HT_2) receptors. In all of these cases the introduction of selective agonists and antagonists has led to clinically useful drugs. A similar development has already been initiated with respect to the α adrenoceptors. Prazosin is a selective α_1 adrenoceptor blocking agent; clonidine and guanfacine are rather selective α_2-adrenoceptor agonists. A further development of drugs with a preference for either pre- or postsynaptic α_2 adrenoceptors would seem principally possible. Such an issue appears a fascinating challenge in drug design, which once met with success might prove highly rewarding both from theoretical and medical viewpoints.

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