SUMMARY This report reviews a number of significant developments in the fields of noradrenergic neurotransmission and adrenergic receptors which suggest that, in addition to the classical postsynaptic adrenoceptors, there are also presynaptic adrenoceptors that help modulate the release of norepinephrine (NE) from peripheral as well as central noradrenergic nerve endings during nerve stimulation. In particular, stimulation of presynaptic \( \alpha \)-adrenoceptors reduces this release of transmitter and the reverse is observed after blockade of these receptors. Clearcut pharmacological differences exist between the postsynaptic \( \alpha \)-adrenoceptors that mediate the responses of certain organs and the presynaptic \( \alpha \)-adrenoceptors that modulate the NE release during nerve stimulation. Therefore, subclassification of \( \alpha \)-adrenoceptors into \( \alpha_1 \) and \( \alpha_2 \) subtypes is warranted but must be considered to be independent of the anatomical location of these receptors.

Some noradrenergic nerve endings have also been shown to possess \( \beta \)-adrenergic receptors, the stimulation of which increases the quantity of transmitter released by nerve impulses. Physiologically, these receptors could be activated by circulating epinephrine (E) and be involved in essential hypertension. A third type of catecholamine receptor found at the noradrenergic nerve ending is the inhibitory dopamine (DA) receptor, which might be of significance in the development of new antihypertensive agents. Application of these new concepts of noradrenergic neurotransmission and the subclassification of \( \alpha \)-adrenoceptors to the treatment of hypertension is presented. Clonidine, for example, appears to be a potent \( \alpha_2 \)-adrenoceptor agonist; the central receptor involved in its antihypertensive action is pharmacologically an \( \alpha_1 \)-type but located postsynaptically. Clonidine also induces activation of peripheral presynaptic \( \alpha_2 \)-adrenoceptors, which might contribute to its cardiovascular action.

The antihypertensive effects of \( \alpha \)-methyldopa are related to the formation of \( \alpha \)-methylnorepinephrine, a preferential \( \alpha_2 \)-adrenoceptor agonist, which can stimulate peripheral presynaptic \( \alpha_2 \)-adrenoceptors leading to a decrease of NE release and a reduction in sympathetic tone. Prazosin is a new antihypertensive agent the mechanism of action of which involves a selective blockade of postsynaptic \( \alpha_1 \)-adrenoceptors. This drug does not antagonize several effects of clonidine that are mediated via \( \alpha_2 \)-adrenoceptors. The mechanisms presently considered to account for the antihypertensive activity of \( \beta \)-adrenoceptor blocking agents are numerous. It is proposed that blockade of peripheral presynaptic facilitatory \( \beta \)-adrenoceptors could be of significance in the antihypertensive action of these drugs. (Hypertension 2: 372-382, 1980)

KEY WORDS • \( \alpha_1 \)-adrenoceptors • presynaptic \( \alpha \) and \( \beta \)-adrenoceptors • prazosin • clonidine • \( \beta \)-adrenoceptor antagonists • presynaptic dopamine receptors

MANY drugs used in the therapy of hypertension decrease blood pressure (BP) either by reducing the sympathetic drive to the cardiovascular system or by blocking the transduction of this signal into an effect at the end-organ level (i.e., blockade of the postsynaptic adrenoceptors). It is still a matter of discussion whether the effectiveness of these compounds is due to inhibition of a normal or an increased sympathetic drive in hypertensive patients, but it is a matter of fact that the high BP of many patients can be normalized and stabilized by drugs that effectively reduce sympathetic tone.

During recent years a number of significant developments have been made in the field of noradrenergic neurotransmission and adrenoceptors. Concepts such as modulation of transmitter release by presynaptic receptors and the subclassification of \( \alpha \)-adrenoceptors into \( \alpha_1 \) and \( \alpha_2 \)-subtypes will be discussed in this review and applied to the understanding of the mechanism of action of some antihypertensive
drugs. We will concentrate on the following groups of antihypertensive drugs:

1. Clonidine-type drugs, which may be considered to possess preferential agonist properties for \( \alpha_2 \)-adrenoceptors
2. \( \alpha \)-Methyldopa, which is the precursor of \( \alpha \)-methylnorepinephrine, a preferential \( \alpha_1 \)-adrenoceptor agonist
3. Prazosin, a selective \( \alpha_1 \)-adrenoceptor antagonist
4. \( \beta \)-Adrenoceptor blocking agents, and new findings on the mechanism of their antihypertensive action.

Modulation of Peripheral and Central Noradrenergic Neurotransmission Through Presynaptic \( \alpha \)-Adrenoceptors

During NE release elicited by the arrival of nerve impulses, the neurotransmitter interacts with specific receptors (\( \alpha \) or \( \beta \)-adrenergic type) located in the membrane of the postsynaptic cell to trigger a cell-specific response at the level of the effector organ. Until a few years ago, the role of noradrenergic nerve endings in neurotransmission was considered to be exclusively concerned with the synthesis, storage, release, and inactivation of NE, and there were no indications that receptors might also be present on or in the surface of the membrane of nerve terminals. During the last decade, evidence has accumulated in favor of the view that, in addition to the classical postsynaptic adrenoceptors, there are also presynaptic adrenoceptors of the \( \alpha \)-adrenergic type which are involved in the modulation of the release of NE from peripheral as well as from central noradrenergic nerve endings. In support of this view it is now well established that \( \alpha \)-adrenoceptor agonists inhibit NE release during nerve stimulation, while \( \alpha \)-adrenoceptor blocking agents enhance the stimulation-evoked release of the neurotransmitter. These results have been obtained both under \textit{in vitro} and \textit{in vivo} experimental conditions.

The effects of \( \alpha \)-adrenoceptor agonists and antagonists on NE release are frequency-dependent (i.e., they are most pronounced in the low and intermediate range of frequencies of nerve stimulation). In addition, the presynaptic modulation of NE release triggered by presynaptic \( \alpha \)-adrenoceptors is observed only for calcium-dependent mechanisms of transmitter release such as the release evoked by nerve stimulation or potassium depolarization. The calcium-independent NE release induced by tyramine is not subjected to modulation by presynaptic inhibitory \( \alpha \)-adrenoceptors.

These results support the hypothesis that \( \alpha \)-adrenoceptors located on or in the (outer) surface of noradrenergic nerve endings are involved in the regulation of the release of NE through a negative feedback mechanism mediated by the neurotransmitter itself (fig. 1). The presence of presynaptic inhibitory \( \alpha \)-adrenoceptors on noradrenergic nerve endings has been found to be independent of the predominant population of \( \alpha \) or \( \beta \)-postsynaptic adrenoceptor present on the effector cell.

Clearcut pharmacological differences have been shown to exist between the postsynaptic \( \alpha \)-adrenoceptors that mediate the response of the effector organ and the presynaptic inhibitory \( \alpha \)-adrenoceptors that modulate the release of NE during nerve stimulation. The presynaptic inhibitory \( \alpha \)-adrenoceptors are generally much more sensitive than the postsynaptic ones to activation by agonists like tramazoline or clonidine and to blockade by antagonists like yohimbine or piperoxan.

In contrast, the postsynaptic \( \alpha \)-adrenoceptors are much more sensitive than the presynaptic ones to activation by agonists like phenylephrine and methoxamine, and to blockade by antagonists like prazosin and WB 4101. Based on these pharmacological differences, the subclassification of \( \alpha \)-adrenoceptors into \( \alpha_1 \) and \( \alpha_2 \) subcategories was first proposed and subsequently extended. Since this first proposal, considerable evidence has accumulated to support the view that at least two pharmacologically distinct populations of \( \alpha \)-adrenoceptors exist.

While presynaptic receptors as such are defined by the function that they control (i.e., modulation of the stimulation-evoked release of NE), \( \alpha_2 \)-adrenoceptors are characterized and defined through the relative order of potencies for agonists and their susceptibility...
to certain antagonists. In fact, α-adrenoceptors can be found at sites other than noradrenergic nerve endings, as for example: 1) sympathetic ganglia (where they mediate hyperpolarization); 2) platelets (where they affect platelet aggregation); and 3) human fat cells (where they inhibit lipolysis). Consequently, the α-adrenoceptor should be subclassified according to its pharmacological characteristics, and independent of its anatomical location.

Use of receptor-binding techniques has provided substantial support for the subclassification of α-adrenoceptors into α1 and α2 subtypes in the peripheral as well as in the central nervous system. The α-adrenoceptor ligand H-dihydroergocryptine (H-DHE) labels both α1 and α2 adrenoceptors. On the other hand, the selective α1-adrenoceptor antagonist H-WB 4101 labels preferentially α1-adrenoceptors in the periphery and in the central nervous system. Figure 2 shows that the relative potencies of prazosin, phentolamine, and yohimbine in displacing the specific binding of H-WB 4101 in the rat heart correspond to their pharmacological affinities for α1 and α2-adrenoceptors.

Subclassification of α-adrenoceptors into α1 and α2 categories is helpful in understanding the overall pharmacological profile of α-adrenoceptor agonists and antagonists currently in clinical and experimental use. In addition, it opens new possibilities in the design and development of novel agonists and antagonists with high degrees of selectivity for either receptor as potentially useful agents for the treatment of hypertension.

Presynaptic Facilitatory β-Adrenoceptors and Noradrenergic Neurotransmission

Facilitation of the stimulation-evoked release of NE through presynaptic β-adrenoceptors was first reported under in vitro conditions in peripheral tissues from the guinea pig and the cat, and in the human oviduct and vasoconstrictor nerves. There is also in vivo evidence for the presence of presynaptic facilitatory β-adrenoceptors in the dog heart. The experimental evidence available so far favors the view that the presynaptic facilitatory β-adrenoceptors are of the β2 rather than β1 type. Low concentrations of epinephrine (E) and terbutaline are effective in increasing the stimulation-evoked release of NE. In addition, propranolol and butoxamine but not practolol can block these presynaptic β-adrenoceptors. It is likely that presynaptic β-adrenoceptors are mainly activated by circulating E to enhance noradrenergic neurotransmission since, when peripheral noradrenergic nerve endings are labelled with E instead of NE, propranolol becomes more effective in reducing transmitter release elicited by sympathetic nerve stimulation. Consequently, it is possible that E may participate in a positive feedback mechanism for the release of NE from peripheral noradrenergic nerve endings. Beta-adrenoceptor antagonists may thus act at this site to cause a decrease in transmitter release by blocking this positive feedback mechanism, the sensitivity of which could be increased in essential hypertension.

In contrast to the presynaptic inhibition through α-adrenoceptors, which is present in peripheral as well as in central noradrenergic nerve terminals, there is as yet no evidence for the presence of facilitatory presynaptic β-adrenoceptors in certain areas of the central nervous system involved in the regulation of cardiovascular function.

Presynaptic Inhibitory Dopamine Receptors and Noradrenergic Neurotransmission

A DA-sensitive presynaptic inhibitory receptor has been described for some peripheral noradrenergic nerve endings. Stimulation of presynaptic inhibitory DA receptors by agonists like DA, apomorphine, bromocriptine, or N,N-di-n-propyldopamine reduces the stimulation-evoked release of NE, and this effect, as in the case of the presynaptic α-adrenoceptor, is frequency-dependent. This reduction in the stimulation-evoked release of NE obtained by DA receptor agonists is unaffected by α-adrenoceptor blockade, while it is selectively antagonized by DA receptor blocking agents like chlorpromazine, pimozide, or sulpiride. These results indicate that presynaptic inhibitory DA receptors differ from presynaptic α-adrenoceptors, which can be acted upon by released NE (fig. 1).

![Figure 2. Displacement of H-WB 4101 specific binding in rat heart ventricle by alpha-adrenoceptor antagonists.](http://example.com/figure2.png)
Presynaptic inhibitory DA receptors on noradrenergic nerve terminals might be involved in the renal vasodilating and BP-lowering effects of DA receptor agonists.\textsuperscript{84-86} Figure 3 shows the inhibitory effects of the presynaptic DA agonist N,N-di-n-propyldopamine on the reductions in renal blood flow elicited by sympathetic nerve stimulation in anesthetized dogs. Consequently, presynaptic inhibitory DA receptors could be considered as target receptors for the development of selective agonists that might be useful antihypertensive agents.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Effect of close-arterial infusion of the presynaptic dopamine agonist N,N-di-n-propyldopamine (DPDA) on the reduction in renal blood flow induced by various frequencies of renal sympathetic nerve stimulation in anesthetized dogs (n = 3). Asterisk indicates a significant (p < 0.05: paired t test) inhibition of responses. Ordinate: Percentage reduction in renal blood flow, which was measured with an electromagnetic flow probe positioned on the left renal artery. Abscissa: Control: reductions in renal blood flow to renal sympathetic nerve stimulation (10 V, 1 msec, 0.5-4 Hz for 60 sec) under control conditions. DPDA = Antagonism of the effects of renal nerve stimulation by an intrarenal artery infusion of DPDA (6.25 µg/kg/min).}
\end{figure}

Antihypertensive and Other Pharmacological Properties of Clonidine, a Preferential \( \alpha \)-Adrenoceptor Agonist

Clonidine is an imidazoline that was originally designed as a nasal vasoconstrictor because of its ability to stimulate \( \alpha \)-adrenoceptors on vascular smooth muscle.\textsuperscript{87} The accidental discovery of its hypotensive and bradycardic effects may be considered as the starting point for the increasing attention devoted in recent years to the role of central \( \alpha \)-adrenoceptors in the control of cardiovascular function. Several excellent reviews on the pharmacology of clonidine have recently appeared.\textsuperscript{88,89}

When clonidine is administered intravenously to intact anesthetized animal preparations, it produces an initial BP rise followed by a longer lasting hypotensive phase.\textsuperscript{90} The initial hypertension results from stimulation of postsynaptic vascular \( \alpha \)-adrenoceptors for which clonidine, as well as structurally related imidazolines, has high affinity, even if it has been shown to have low efficacy and to behave as a partial agonist.\textsuperscript{91,92}

The generalized cardiovascular depression (hypotension, bradycardia, and decrease in cardiac output) produced by clonidine is compatible with an action on the central nervous system, because administration of low doses of clonidine into the cisterna magna or infused into the vertebral artery produces these cardiovascular effects without being preceded by a pressor response. Furthermore, this central action is confirmed by the findings that clonidine reduces the spontaneous discharges in sympathetic preganglionic fibers of splanchnic nerve and postganglionic fibers of cardiac nerves.

The central cardiovascular effects of clonidine are antagonized by \( \alpha \)-adrenoceptor blocking agents, and consequently they are due to activation of \( \alpha \)-adrenoceptors that appear to be localized postsynaptically. In support of this view, depletion of central endogenous catecholamines does not inhibit the clonidine-induced decrease in spontaneous discharge in the splanchnic sympathetic nerves of the cat.\textsuperscript{93} Furthermore, the hypotensive effects of clonidine are not affected by degeneration of central noradrenergic nerve terminals produced by administration of 6-hydroxydopamine.\textsuperscript{94,95} The central site of action of clonidine-induced cardiovascular effects has been proposed to be in the area of the nucleus tractus solitarii and in the medulla oblongata. At these sites, clonidine stimulates \( \alpha \)-adrenoceptors, which may be classified pharmacologically as \( \alpha \_1 \)-adrenoceptors, since its effects are preferentially blocked by \( \alpha \_2 \)-adrenoceptor antagonists.

Recent evidence suggests that clonidine reduces adrenaline turnover in some areas of the rat brain involved in cardiovascular control.\textsuperscript{96} Other studies have indicated that clonidine might possibly act by stimulating \( \alpha \_2 \)-presynaptic autoreceptors present on adrenaline and/or noradrenaline nerve terminals.\textsuperscript{97} These findings might be relevant to the cardiovascular effects of this drug.

As already discussed, presynaptic inhibitory \( \alpha \_2 \)-adrenoceptors are present in peripheral and central noradrenergic nerve endings, and clonidine is very potent in reducing noradrenergic neurotransmission.\textsuperscript{98} Impairment of peripheral noradrenergic transmission by clonidine, more pronounced for low frequencies of nerve stimulation, was reported for heart rate responses in rats.\textsuperscript{99,100} Clonidine also decreases the positive chronotropic effects elicited by cardioaccelerator nerve stimulation in rabbits, cats, and dogs. This effect was found to be accompanied by a reduction in NE output in the dog.\textsuperscript{101-103} Figure 4 shows the effects of clonidine on the chronotropic responses and on transmitter release elicited by stimulation of the cardioaccelerator nerve in spinal
vagotomized dogs. The reduction of NE release by clonidine paralleled its effects on the positive chronotropic effects to nerve stimulation. Both these effects of clonidine were antagonized by the administration of phentolamine (fig. 4). This peripheral effect of clonidine on presynaptic $\alpha_2$-adrenoceptors appears to be of functional significance, because in intact dogs very small doses of clonidine injected into the artery perfusing the sino-atrial node region produce a negative chronotropic effect which is antagonized by a dose of phentolamine not affecting BP (fig. 5). These results support the view that these effects of clonidine on peripheral presynaptic $\alpha_2$-adrenoceptors are as pronounced as the centrally mediated inhibition of sympathetic tone to the heart.

If clonidine exhibits similar activity at vascular presynaptic $\alpha_2$-adrenoceptors, particularly during chronic treatment, this mechanism could significantly contribute to its antihypertensive effects. However, it is more difficult to assess this possibility under experimental in vivo conditions because of the postsynaptic vasoconstrictor effect of clonidine.

Future synthesis of compounds that do not cross the blood-brain barrier, act selectively on presynaptic $\alpha_2$-adrenoceptors, and are devoid of vasoconstrictor effects may provide suitable experimental tools to assess the role of peripheral presynaptic $\alpha_2$-adrenoceptors in the inhibition of noradrenergic neurotransmission as a potential mechanism for novel antihypertensive agents. Such drugs might lack the undesirable central effects of clonidine.

Involvement of $\alpha_2$-adrenoceptors in the production of sedation and dry mouth by clonidine has been suggested by many pharmacological studies. In chicks, for example, the sleep-inducing action of clonidine is antagonized by $\alpha_2$-adrenoceptor blocking agents with a preferential action on $\alpha_2$-adrenoceptors but not by prazosin. In cats, clonidine was shown to reduce submaxillary salivation, evoked by peripheral parasympathetic nerve stimulation, through activation of presynaptic $\alpha_2$-adrenoceptors that inhibit cholinergic transmission.

Potentially dangerous side effects in patients treated with clonidine, seen with abrupt withdrawal of treatment, are "rebound" hypertension and tachycardia that may be associated with anxiety, headache, vomiting, and accompanied by increased catecholamine excretion. The mechanism of this syndrome is not yet fully understood, although it may be due to a clonidine-induced change in the sensitivity of $\alpha_2$-adrenoceptors both in the periphery and the central nervous system.
Stimulation of Alpha-Adrenoceptors by $\alpha$-Methylnorepinephrine: Possible Relevance to the Antihypertensive Effects of Alpha-Methyldopa

Alpha-methyldopa (AMD) has been used successfully in the treatment of hypertensive disease for nearly 20 years. Recently, two reviews on the pharmacology and site of action of this drug have appeared. Initially, the biochemical effect of AMD in inhibiting L-amino acid decarboxylase was thought to be causally related to the hypotensive action of the drug, but this hypothesis was proven incorrect. In fact, studies by Henning demonstrated that decarboxylation of AMD is a prerequisite for the hypotensive effect.

While AMD lowers BP when administered after a decarboxylase inhibitor with poor penetration into the central nervous system (MK 485), hypotension was abolished when AMD was given following decarboxylase inhibition in both peripheral tissues and in the central nervous system by using Ro 4-46002. In addition, pretreatment of rats with inhibitors of dopamine $\beta$-hydroxylase (FLA-63 or disulfiram) blocks the hypotensive action of AMD. Thus, the formation of $\alpha$-methylnorepinephrine within the central nervous system is necessary to mediate the hypotensive effect of AMD. That the site of action of AMD was within the central nervous system had been suggested by earlier pharmacological studies where intravertebral artery infusion of low doses of AMD lowered BP more effectively than via the intravenous route.

It would appear that it is the direct action of $\alpha$-methylnorepinephrine that mediates the central hypotensive effect of AMD rather than the displacement and loss of endogenous NE from central structures, because there is no correlation between the time-course of effects of AMD on BP and on brain NE levels after infusion of the drug into the vertebral artery of cats. Further arguments against the false transmitter theory in the mechanism of action of AMD have been discussed previously by Henning.

The suggestion that the hypotension was induced by stimulation of central adrenoceptors through one of the metabolites of AMD was first made by Hoyer and Van Zwieten largely on the basis of results obtained with other sympathomimetic compounds such as clonidine and amphetamine. Later studies verified this suggestion when it was found that $\alpha$-methylnorepinephrine administered directly into the central nervous system lowered BP and that this effect was antagonized by $\alpha$-adrenoceptor blocking drugs. Recent evidence, however, suggests that the 3-O-methylated metabolites of AMD might participate in the antihypertensive effect in the rat especially after chronic dosing.
peripheral in origin, mediated either by the peripheral postsynaptic β-adrenoceptor stimulation and/or by impairment of peripheral sympathetic neuronal function through the stimulation of presynaptic α₂-adrenoceptors by α-methylnorepinephrine. 

Relevance of the Alpha₂-Adrenoceptor Selectivity of the Antagonist Prazosin for the Antihypertensive Profile of the Drug

Prazosin can be considered the first member of a new class of antihypertensive drugs having the outstanding pharmacological property of preferentially blocking peripheral α₁-adrenoceptors. It is this effect that appears to be responsible for the hypotensive activity of this compound in several models of hypertension. Considerable evidence has accumulated now against the view initially advanced that a direct vasodilating activity participates in the antihypertensive effect of prazosin. Both pharmacological and receptor binding studies favor the view that prazosin is a highly selective postsynaptic α₁-adrenoceptor blocking agent. As shown in figure 2, prazosin is very potent in displacing the specific, high affinity binding of °H-WB 4101, a preferential α₁-adrenoceptor antagonist.

Blockade of presynaptic α₂-adrenoceptors increases the stimulation-evoked release of NE, which may counteract the blockade of postsynaptic α₁-adrenoceptors at the level of the vascular bed. It is possible that the effectiveness of prazosin in the chronic treatment of hypertension is at least partly due to the fact that it lacks α₂-adrenoceptor blocking properties. Classical α₁-adrenoceptor antagonists, by blocking α₁-receptors, increase the neuronal release of NE and thereby reduce their potential antihypertensive effects.

Most drugs that decrease BP through a peripheral mechanism of action trigger a number of reflexes at the cardiovascular level, leading to tachycardia and an increase in cardiac output. Alpha-adrenoceptor antagonists like phentolamine, which block both α₁ and α₂-adrenoceptors and direct vasodilators such as hydralazine, increase basal heart rate in the conscious dog, but this effect is not observed with prazosin. The absence of tachycardia when prazosin is administered to man represents a therapeutic advantage. The fact that prazosin has a very low or negligible affinity for the blockade of presynaptic α₂-adrenoceptors in the heart may contribute to this effect. To explain the lack of tachycardia in response to the BP fall produced by prazosin, however, other mechanisms must be invoked such as changes in baroreceptor sensitivity and absence of right atrial pressure increases.

The selectivity of prazosin in blocking α₁-adrenoceptors may also explain why this drug does not increase renin release when administered in doses that decrease BP.
Experiments in dogs have shown that chronic propranolol therapy reduces the pressor responses to carotid occlusion, while short-term therapy is without effect. These results could be related to an increased baroreceptor sensitivity or due to central nervous system effects of β-adrenoceptor blocking agents.

Intracerebroventricular injection of propranolol leads to BP reduction; consequently, it was proposed that blockade of central β-adrenoceptors might be involved in the antihypertensive effects of this compound. Yet relatively large doses of propranolol were employed in these studies, and leakage into the periphery could contribute to the observed effects. Lewis and Haeseler demonstrated that the intravenous administration of propranolol to conscious rabbits reduces the splanchic nerve discharge as well as the BP. Similar decreases in splanchic nerve discharges were reported in cats treated with propranolol or pindolol administered centrally. In conscious rabbits, intravenous administration of propranolol reduces BP but has no effect on resting renal sympathetic nerve discharge, although it does reduce the threshold of the renal baroreflex.

Drugs like practolol and sotalol penetrate poorly into the central nervous system, yet these β-adrenoceptor blocking agents are effective antihypertensive drugs in man. The question of a central effect of β-receptor blocking agents remains open, but it is of interest to note that side effects like sedation and vivid dreams are observed particularly with many nonselective β-adrenoceptor antagonists.

Recent studies have shown that prolonged treatment of spontaneously hypertensive rats with β-adrenoceptor blocking agents reduces the responses of the portal vein to electrical stimulation without affecting the sensitivity to exogenous NE. The reduced release of NE per nerve impulse could be related to the blockade of the presynaptic facilitatory β-adrenoceptors on noradrenergic nerve terminals. Since E is more effective than NE in enhancing transmitter release through the activation of presynaptic facilitatory β-adrenoceptors, it is possible that circulating E as well as E released from noradrenergic nerve endings as a cotransmitter with NE may be the physiological stimulus for presynaptic β2-adrenoceptors. Recent studies indicate that the plasma levels of circulating E are significantly increased in hypertensive patients. In addition, it is well known that stress triggers an increase in plasma E levels. It is therefore possible that circulating E can be incorporated into noradrenergic nerve endings for storage and subsequent release. The increase in the responsiveness of certain cardiovascular effector tissues in hypertensive patients may be due to activation of this presynaptic β-adrenoceptor-mediated positive feedback loop by circulating or neurally released E. Under these conditions, a decrease in NE released from peripheral noradrenergic nerve endings due to the blockade of presynaptic facilitatory β-adrenoceptors could contribute to the antihypertensive effects of β-adrenoceptor antagonists.

Conclusions

Our understanding of the mechanism of action of several antihypertensive drugs has been improved by recent developments concerning presynaptic regulation of norepinephrine release and through the subclassification of α-adrenoceptors into α1 and α2-subcategories.

Most of the antihypertensive effects of clonidine and α-methyldopa are mediated through the activation of α2-adrenoceptors. On the other hand, the selective blockade of α1-adrenoceptors by prazosin may explain the effectiveness of this drug in the treatment of hypertension and partly the lack of tachycardia as a side effect. It is possible that blockade of presynaptic facilitatory β-adrenoceptors may contribute to the antihypertensive effects of β-adrenoceptor antagonists.

Finally, it is suggested that presynaptic inhibitory α2-adrenoceptors and presynaptic dopamine receptors might become important target receptors in the development of novel, selective agonists with potential antihypertensive properties.

References

9. Wikberg JES: The pharmacological classification of adrenergic α1 and α2 receptors and their mechanisms of action. Acta Physiol Scand (suppl 468); 1, 1979


76. De Jong W, Nijkamp FP, Buhus B: Role of noradrenaline and serotonin in the central control of blood pressure in normoten-


Day MD, Roach AG: β-adrenergic receptors in the central nervous system of the cat concerned with the control of arterial blood pressure and heart rate. Nature 242: 30, 1973

Reid JL, Lewis PJ, Myers MG, Dollery CT: Cardiovascular effects of intracerebroventricular d-, l- and d,l-propranolol in conscious rabbit. J Pharmacol Exp Ther 188: 394, 1974


Garvey HL, Ram N: Centrally induced hypotensive effects of β-adrenergic blocking drugs. Europ J Pharmacol 33: 283, 1975


Recent developments in noradrenergic neurotransmission and its relevance to the mechanism of action of certain antihypertensive agents.

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