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Presynaptic Regulation of the Release of Catecholamines

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I. Introduction and Historical Background

IT IS now well established that norepinephrine released in response to nerve impulses interacts with specific receptors (α- or β-adrenoceptors) that are located in the membrane of the postsynaptic cell and triggers the physiological response of the effector organ.

Until recently, noradrenergic nerve endings were thought to be concerned exclusively with the synthesis, storage, release, and inactivation of norepinephrine and there were no indications that specific receptors might also be present in the outer surface of the membrane of nerve endings. Nevertheless, more than 20 years ago it was reported by Brown and Gillespie (24) that phenoxybenzamine, an α-adrenoceptor blocking agent, enhances the overflow of norepinephrine elicited by nerve stimulation in the perfused cat spleen. This effect was initially considered to be due to the block of the α-adrenoceptors of the effector organ. When it was found that phenoxybenzamine inhibits neuronal (126, 133) as well as extraneuronal uptake of norepinephrine (69, 134, 135), it was postulated that the increase in transmitter overflow elicited by the α-adrenoceptor blocking agent was due to inhibition of the inactivation of released norepinephrine.

Agents like cocaine or desipramine that inhibit neuronal uptake of norepinephrine without blocking the α-adrenoceptors were tested on peripheral noradrenergic neurotransmission. These drugs produced little or no increase in the stimulation-evoked release of the neurotransmitter even at concentrations at which maximal inhibition of neuronal uptake of norepinephrine is obtained (21, 23, 60, 174). These results did not support the view that the increase in stimulation-evoked transmitter overflow observed in the presence of phenoxybenzamine was due to the inhibition of neuronal uptake of norepinephrine.

The possible significance of the inhibition by phenoxybenzamine of extraneuronal uptake of norepinephrine became apparent when studies on transmitter release carried out with ^{3}H-norepinephrine showed that a significant fraction of the labelled transmitter released by nerve stimulation was collected as ^{3}H-norepinephrine metabolites (63, 151, 154, 179, 201). Phenoxybenzamine prevents the metabolism of ^{3}H-norepinephrine released by nerve stimulation, but this effect does not fully account for the large increase in norepinephrine overflow observed in the presence of this drug (151, 188). Consequently, an actual increase in norepinephrine release by nerve stimulation occurred (151, 177).

Phenoxybenzamine and other α-adrenoceptor blocking agents like phentolamine produce an actual increase in the output of norepinephrine during nerve stimulation because these drugs enhance the stimulation-evoked release of the neurotransmitter in concentrations that do not inhibit either neuronal or extraneuronal uptake of norepinephrine (45, 73, 153, 247). In addition, De Potter et al. (52) and Cubeddu et al. (45) reported that the release of dopamine-β-hydroxylase was increased when neurotransmission in the perfused spleen was studied in the presence of phenoxybenzamine or phentolamine.

The increase in the stimulation-evoked release of norepinephrine observed in the presence of α-adrenoceptor blocking agents was obtained within the range of drug concentrations eliciting postsynaptic α-receptor blockade (45, 61, 63, 158). Both Häggendal (106, 107) and Hedqvist (110, 112) suggested the existence of a transsynaptic regulation for the release of norepinephrine whereby transmitter output would be controlled by the activity of the effector cell. The inverse relationship between end organ responses to nerve stimulation and transmitter overflow seen in the iris and vas deferens was compatible with this hypothesis (78, 79). Yet a causal relationship between the block of responses of the effector organ and the increase in transmitter release was excluded because the α-adrenoceptor blocking agents increased the overflow of norepinephrine from guinea-pig atria (164, 206), rabbit heart (254), and cat heart (76) preparations where the adrenoceptors that mediate the response of the effector organ are of the β-type.

These results led to the hypothesis that α-adrenoceptors are present on or in the surface of the membrane of noradrenergic nerve endings. According to this proposal presynaptic α-adrenoceptors are involved in the regulation of norepinephrine release through a negative feedback mechanism mediated by the neurotransmitter itself (for previous reviews see 153, 157, 158, 160–162, 247, 285, 296). During norepinephrine release elicited by nerve stimulation, once the transmitter reaches a threshold concentration in the synaptic cleft, it activates presynaptic α-adrenoceptors triggering a negative feedback mechanism that inhibits further release of the neurotransmitter (73, 152, 153, 230, 245, 246). In support of this hypothesis it was demonstrated that α-adrenoceptor agonists inhibit norepinephrine release elicited during nerve stimulation (147, 173, 176, 180, 244, 246, 249) while an increase in the stimulation-evoked release of norepinephrine is obtained in the presence of α-adrenoceptor blocking agents (45, 61, 73, 151, 175, 180, 188, 254). These effects are observed regardless of the α or β nature of the postsynaptic adrenoceptor of the effector cell.

Presynaptic inhibitory α-adrenoceptors regulate the calcium-dependent release of the neurotransmitter through a mechanism that operates most effectively for the low and intermediate range of frequencies of nerve stimulation (61, 63, 152).

There are presynaptic autoreceptors through which the neurotransmitter can regulate its own release not only for norepinephrine but also for other transmitters like acetylcholine, dopamine, GABA, and 5-hydroxytryptamine (159, 163).

In addition to the presynaptic autoreceptors involved in negative feedback mechanisms for different neurotransmitters, presynaptic receptors sensitive to endogenous compounds other than the neuron's own transmitter have been described. These presynaptic receptors can be acted upon by transmitters released from adjacent terminals or by various locally produced or blood-borne substances to modulate neurotransmission in the peripheral as well as in the central nervous system (157, 247).

The aim of this review is to analyze the physiological and pharmacological relevance of presynaptic autoreceptors and of other presynaptic receptor systems in the peripheral as well as in the central nervous system. In the context of this review the term presynaptic autoreceptors will be used for those receptors probably located in axon terminals that are involved in the regulation of the calcium-dependent release of a neurotransmitter by the transmitter itself. The term presynaptic receptors will be used for those receptors that are acted upon by other neurotransmitters or autacoids but not by the neuron's own transmitter.

II. Presynaptic Inhibitory α-Adrenoceptors and the Regulation of Noradrenergic Neurotransmission

A. Modulation of Noradrenergic Neurotransmission Mediated by Presynaptic α-Adrenoceptors

As already indicated in the INTRODUCTION, figure 1 shows schematically the involvement of presynaptic α-adrenoceptors in the negative feedback mechanism for the autoregulation of the release of norepinephrine during nerve stimulation.

In tissues in which the responses of the effector organ are mediated by postsynaptic α-adrenoceptors (like the spleen or the nictitating membrane), the increase in the stimulation-evoked release of norepinephrine obtained with α-adrenoceptor blocking agents is accompanied by a reduction in the postsynaptic responses to nerve stimulation (61, 63, 73, 80). When the increase of neurotransmitter release elicited by α-adrenoceptor blockade is

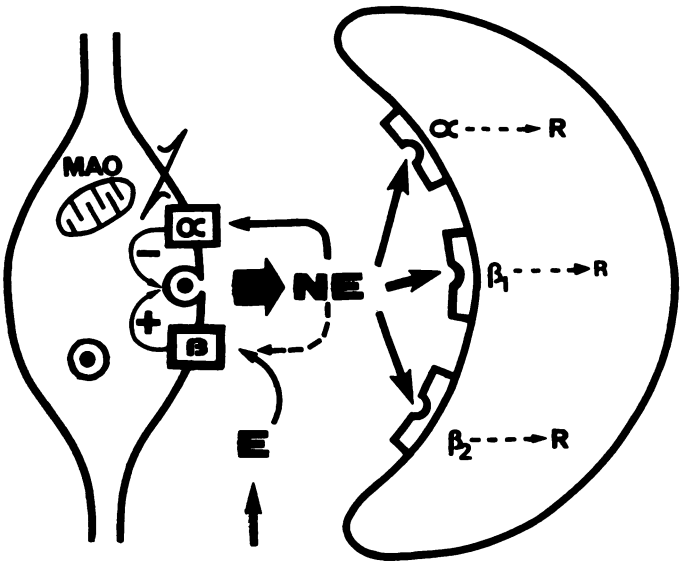

FIG. 1. Presynaptic α- and β-adrenoceptors on peripheral noradrenergic nerve terminals. Presynaptic inhibitory α-adrenoceptors are acted upon by released norepinephrine (NE) to inhibit the release of the neurotransmitter. Presynaptic facilitatory β-adrenoceptors are acted upon by circulating epinephrine (E) to enhance the release of the neurotransmitter. The postsynaptic adrenoceptors involved in the responses (R) of the effector cells are also shown. MAO, monoamine oxidase.

studied in tissues in which the postsynaptic responses are mediated by β-adrenoceptors, as in the heart, a potentiation of the responses to nerve stimulation is obtained (166). The positive chronotropic responses to accelerans nerve stimulation in guinea-pig atria are potentiated during exposure to a concentration of phentolamine that produces a 3-fold increase in the release of the neurotransmitter (166). Similar results were obtained under in vivo conditions: α-adrenoceptor blockade potentiates the positive chronotropic responses to cardioaccelerator nerve stimulation in the anaesthetized dog (30, 195, 304). In experiments in which the overflow of norepinephrine into the coronary sinus is determined together with heart rate changes in the spinal dog it was seen that the α-adrenoceptor agonist clonidine decreases norepinephrine overflow and the positive chronotropic effects to cardioaccelerator nerve stimulation (30, 304). Under these conditions the administration of phentolamine blocks the effects of clonidine and increases transmitter release as well as the cardioaccelerator responses to nerve stimulation (30). These results support the view that the negative feedback mechanism mediated by presynaptic α-adrenoceptors plays a physiological role in the regulation of the release of norepinephrine during nerve stimulation both under in vitro as well as under in vivo conditions.

The operation of the presynaptic negative feedback mechanism for norepinephrine release requires a threshold concentration of the transmitter released by nerve impulses in the synaptic gap (153). When the endogenous norepinephrine stores are depleted the effectiveness of phenoxybenzamine in enhancing the overflow of ^{3}H-norepinephrine during nerve stimulation is considerably reduced (71). Similar results were obtained in the perfused cat spleen by Cubeddu and Weiner (46), who measured the overflow of dopamine-β-hydroxylase (DBH) elicited by nerve stimulation. Pretreatment with reserpine completely depletes the endogenous norepinephrine stores without affecting the levels of DBH in the cat spleen (46). While phenoxybenzamine enhances 4-fold the release of DBH elicited by nerve stimulation in the untreated spleen (when norepinephrine is also released), the drug fails to enhance the stimulation-evoked release of DBH when the norepinephrine stores are depleted by pretreatment with reserpine (46). Consequently, the ability of α-adrenoceptor antagonists to increase the stimulation-evoked release of norepinephrine is dependent on the transmitter being released from nerves and stimulating presynaptic inhibitory α-adrenoceptors.

It follows from the negative feedback concept that α-adrenoceptor antagonists should have no effect on the overflow of norepinephrine resulting from a single stimulatory pulse (under these conditions no prior released norepinephrine is available to stimulate presynaptic α-adrenoceptors). With guinea-pig atria, Rand et al. (231) demonstrated that phenoxybenzamine did not affect the overflow of ^{3}H-norepinephrine in response to one pulse but increased that due to 2, 4, 8, and 16 pulses at a frequency of 1 Hz. Recently Kalsner (137) reported that, in the vas deferens, exposure to 33 μM phenoxybenzamine increased the tritium overflow to one pulse, and concluded that the α-adrenoceptor-mediated negative feedback concept for norepinephrine release should be reconsidered. It is possible that in these experiments the concentration of phenoxybenzamine may have been excessive since it also increased the basal outflow of tritium thus distorting the accurate estimation of the stimulation-evoked release of the labelled neurotransmitter. The effect of lower concentrations of phenoxybenzamine in this preparation was not reported (137). That the concentration of phenoxybenzamine used by Kalsner may have been excessive is suggested by results obtained in the mouse vas deferens. In this tissue the selective presynaptic antagonist yohimbine (100 nM) has no effect on ^{3}H-norepinephrine released to a single electrical pulse (202). This concentration of yohimbine did, however, increase both the overflow and the postsynaptic response to two pulses (202).

The evidence in favour of the presynaptic location of the inhibitory α-adrenoceptors involved in the regulation of noradrenergic neurotransmission can be summarized as follows: 1) The regulation of norepinephrine release is independent of the α or β type of the postsynaptic receptors that mediate the response of the effector organ (153, 157, 186, 247). 2) The increase in the stimulation-evoked release of norepinephrine obtained by α-adrenoceptor blocking agents like phentolamine is not affected by the atrophy of the postsynaptic effector cell as dem-

onstrated after duct ligation in the rat submaxillary gland (81). 3) α-Adrenoceptor blockade enhances ^{3}H-norepinephrine release induced by potassium depolarization from recently formed nerve endings in cultured rat superior cervical ganglia (286), i.e. under conditions in which there are no postsynaptic effector cells. 4) After degeneration of noradrenergic nerve endings in the rat heart by chemical sympathectomy with 6-hydroxydopamine there is a significant reduction in the specific binding of an α-adrenoceptor ligand (^{3}H-dihydroergocryptine) to rat heart ventricle membranes (267).

The magnitude of the reduction in the stimulation-evoked release of norepinephrine obtained with α-adrenoceptor agonists is more pronounced the lower the frequency of nerve stimulation (173). In fact, α-adrenoceptor agonists fail to reduce the output of norepinephrine elicited by high frequency nerve stimulation (11, 175). Contrary to these findings, Kalsner (138) found no relationship between the frequency of stimulation and the inhibition by exogenous norepinephrine of ^{3}H-norepinephrine overflow in the guinea-pig vas deferens. Confirmation of these unexpected results would indicate that one should be cautious in extrapolating from tissue to tissue with regard to the frequency range over which this presynaptic α-modulatory control mechanism operates. This frequency-dependent characteristic of the regulation mediated by presynaptic α-adrenoceptors is in contrast with the effects of neuron blocking agents like guanethidine or bretylium, which decrease the release of the neurotransmitter at both low and high frequencies of nerve stimulation (11). The inhibition of noradrenergic neurotransmission by α-adrenoceptor agonists of the phenylethylamine structure can only be demonstrated when neuronal uptake of norepinephrine is inhibited by cocaine or desipramine (66, 173). On the other hand, when transmitter release is reduced by α-adrenoceptor agonists that are imidazoline derivatives it is not necessary to inhibit neuronal uptake (66–68, 218). In fact, inhibition of neuronal uptake with cocaine or desipramine decreases the effectiveness of imidazoline derivatives like oxymetazoline or clonidine to inhibit noradrenergic neurotransmission in the peripheral (66, 270) and in the central nervous systems (220).

The regulation of norepinephrine release mediated by presynaptic α-adrenoceptors can only be demonstrated for the calcium-dependent processes of transmitter release like nerve stimulation and depolarization by either potassium or veratridine. The calcium-independent release of norepinephrine induced by tyramine is not modified by α-adrenoceptor agonists or antagonists.

It is possible that presynaptic α-adrenoceptor agonists inhibit the stimulation-evoked release of norepinephrine by reducing the availability of calcium for the excitation-secretion coupling involved in the exocytotic release of the neurotransmitter. Another possibility is that activation of presynaptic inhibitory α-adrenoceptors prevents the spreading of depolarization through the network of varicosities (259). According to this view, activation of presynaptic α-adrenoceptors would reduce neurotransmission by preventing the recruitment of varicosities for transmitter release (259). So far presynaptic inhibitory α-adrenoceptors have been reported to be present in all the peripheral tissues in which they have been explored. Recently, however, Kalsner and Chan (141), who used oxymetazoline as a selective α-adrenoceptor agonist, demonstrated a decrease in ^{3}H-norepinephrine overflow from radial but not from renal artery strips of cattle. Since phentolamine also failed to increase ^{3}H-norepinephrine overflow on stimulation of the renal arteries (141) one might conclude that presynaptic α-adrenoceptors may not be present in this preparation.

B. Possible Involvement of Cyclic Nucleotides in the Presynaptic Inhibition of Norepinephrine Release

The presence of a calcium-dependent presynaptic mechanism for the generation of cyclic GMP has been described in the rat pineal gland (217). This cyclic GMP-generating system appears to be linked to an α-adrenoceptor because the increase in cyclic GMP levels obtained by either norepinephrine or potassium is blocked by α-receptor blocking agents (217). Furthermore this effect of α-adrenoceptor agonists on cyclic GMP levels is lost after sympathetic denervation. In the rat pineal gland, there is evidence for a presynaptic α-adrenoceptor-mediated regulation of the potassium-evoked release of norepinephrine (218).

More recently Pelayo et al. (219) reported that exposure to dibutyryl cyclic GMP reduces the potassium-evoked release of ^{3}H-norepinephrine from the rat pineal, but fails to modify the release of the tritiated transmitter induced by tyramine. In addition, a decrease in the stimulation-evoked release of ^{3}H-norepinephrine was observed during exposure to an inhibitor of the cyclic GMP specific phosphodiesterase (219). Taken together, these results suggest that in the rat pineal gland cyclic GMP may be a link in the chain of events following activation of presynaptic α-adrenoceptors and leading to a decrease in the release of norepinephrine. The question is still open as to whether cyclic GMP is similarly involved in the presynaptic regulation of norepinephrine release in other tissues. In the perfused cat spleen and in the rat vas deferens analogs of cyclic GMP do not reduce the release of norepinephrine during nerve stimulation. Yet, analogs of cyclic GMP reduce the stimulation-evoked release of acetylcholine through a presynaptic effect that may be linked to the inhibitory presynaptic muscarinic receptors (306).

α-Adrenoceptor agonists of the imidazoline series reduce the tissue levels of cyclic AMP (241) and it was suggested that inhibition of neurotransmission through the activation of presynaptic inhibitory α-adrenoceptors may be linked to a decrease in cyclic AMP levels (300). Additional evidence is still required to clarify the role of

cyclic nucleotides in the presynaptic modulation of norepinephrine release.

C. Possible Involvement of the Membrane Na^+-K^+ ATPase in the Modulation of Norepinephrine Release through Presynaptic Inhibitory α-Adrenoceptors

The involvement of the Na^+-K^+-activated ATPase of the membrane in the mechanism of release of neurotransmitters has been reviewed recently (284). Under conditions in which the enzyme activity is inhibited, transmitter release occurs, while activation of the Na^+-K^+-ATPase leads to inhibition of transmitter release. It is therefore possible that inhibition by catecholamines of noradrenergic neurotransmission is related to the activation of the Na^+-K^+-ATPase of nerve terminals. In support of this view, catecholamines activate the enzyme in brain homogenates and in synaptosomes (94, 307) and α-adrenoceptor agonists activate the Na^+-K^+-ATPase prepared from the adrenal medulla (104). The stimulation of Na^+-K^+-ATPase activity elicited by α-adrenoceptor agonists in the rat submaxillary gland is abolished by sympathetic denervation (105). Further evidence for the neural origin of the effects of α-adrenoceptor agonists on the Na^+-K^+-ATPase activity was obtained after duct ligation in the rat submaxillary gland. The stimulation of Na^+-K^+-ATPase activity by α-adrenoceptor agonists was still present after duct ligation but this effect was abolished after sympathetic denervation of the salivary glands that underwent duct ligation (105).

Activation of the Na^+ pump by α-adrenoceptor agonists may reduce the release of norepinephrine by increasing the efflux of calcium from the nerve terminals. In support of this view, it was shown that α-adrenoceptor agonists enhanced the efflux rate of Ca^{++} in the adrenal medulla (105).

The presynaptic modulation of norepinephrine release during nerve stimulation is highly frequency-dependent. Since at high frequencies of nerve stimulation there is an increase in the intracellular Na^+ concentration, stimulation of the Na^+-K^+-activated ATPase can occur. The latter has been shown to inhibit transmitter release (283) and could explain why transmitter output per pulse may decrease at high frequencies of nerve stimulation. The decreased effectiveness of α-adrenoceptor agonists to inhibit norepinephrine release at high frequencies of stimulation may be related to the fact that the membrane ATPase is already in a stimulated state (284).

The molecular level and the mechanisms involved in the local control of norepinephrine release through presynaptic α-adrenoceptors is not yet entirely clarified. Activation of presynaptic α-adrenoceptors may produce a local hyperpolarization of varicosities that prevents the spread of impulse conduction in noradrenergic nerve endings (108, 259). The latter may be triggered by an increase in potassium conductance leading to a highly localized hyperpolarization and conduction block (259).

On the other hand, presynaptic inhibition of noradrenergic neurotransmission through α-adrenoceptors may be mediated through a depression of the electrosecretory coupling rather than by restricting the entry of nerve impulses into the more distal parts of the nerve terminals (i.e. depressing the recruitment of varicosities).

D. Differences between the Release-Regulating Presynaptic α-Adrenoceptors and the Postsynaptic α-Adrenoceptors That Mediate the Response of the Effector Organ

Although both the presynaptic and the postsynaptic α-adrenoceptors are stimulated by α-receptor agonists and blocked by α-receptor antagonists, considerable evidence has accumulated during recent years in favour of the view that the two receptors are not identical. Experimental evidence suggesting differences between presynaptic and postsynaptic α-adrenoceptors was first obtained in the perfused cat spleen (152). Dubocovich and Langer (61) reported that phenoxybenzamine is 30 to 100 times more potent in blocking the postsynaptic α-adrenoceptors than it is in blocking the presynaptic α-adrenoceptors. Cubeddu et al. (45) studied the stimulation-evoked overflow of DBH in the perfused cat spleen. They found that phenoxybenzamine was 30 to 100 times more potent in blocking the postsynaptic α-receptors than the presynaptic receptors. These authors found only a small difference in the potencies of phentolamine in blocking the presynaptic and the postsynaptic α-adrenoceptors in the perfused cat spleen (45).

These results led to the proposal for a subclassification of the α-adrenoceptors into α_1 and α_2 subcategories (153). Originally this proposal identified the α_1-adrenoceptor with the postsynaptic receptor that on the whole mediates excitatory responses, e.g. vasoconstriction, and the α_2-adrenoceptor with the presynaptic receptors that mediate an inhibitory effect (reduction of norepinephrine release during nerve stimulation).

Starke et al. (248) reported that the α-adrenoceptor blocking agent, yohimbine, is more potent in blocking the presynaptic α-adrenoceptor than in blocking postsynaptic α-adrenoceptors. These results further supported the view that there were differences between the presynaptic and the postsynaptic α-adrenoceptors in their affinity for agonists as well as for antagonists.

Differences between the presynaptic and postsynaptic α-adrenoceptors have also been demonstrated with the use of agonists (250). For instance, clonidine is more potent in reducing norepinephrine release during nerve stimulation than in stimulating the postsynaptic α-adrenoceptors (211, 253). In fact, in guinea-pig atria, concentrations as low as 10 pM clonidine can reduce significantly the stimulation-evoked release of ^{3}H-norepinephrine (211).

The pharmacological differences between α_1 and α_2 types of adrenoceptors are summarized in table 1. The main criterion for the subclassification of α-adrenocep-

tors is the relative order of potencies of α-adrenoceptor agonists and particularly of antagonists.

The affinity for the α_1 and α_2 adrenoceptors is similar when agonists like naphazoline, epinephrine, and norepinephrine are considered. On the other hand drugs like guanabenz, tramazoline, α-methyl-norepinephrine, clonidine, and oxymetazoline have a higher affinity for the α_2- than for the α_1-adrenoceptor (table 1). Phenylephrine and methoxamine belong to the other extreme of the spectrum, having a high affinity for the α_1-adrenoceptor and little or no affinity for the α_2-adrenoceptor. It is of interest to note that the neurotransmitter norepinephrine has equal affinity for both α_1- and α_2-adrenoceptors.

There are differences also in the relative affinities for α_1- and α_2-adrenoceptors when several antagonists are considered. Phentolamine has the same potency in blocking the α_1- and α_2-adrenoceptors. On the other hand, rauwolscine, yohimbine, piperoxane, and tolazoline are more potent in blocking the α_2-adrenoceptors when compared with the α_1-adrenoceptors (table 1). Prazosin has a high affinity for the blockade of α_1-adrenoceptors and in most species is practically devoid of α_2-adrenoceptor-blocking properties (28, 32, 56, 57, 204). Labetolol, which also blocks β-adrenoceptors, is a selective α_1-adrenoceptor blocking agent (table 1). Phenoxybenzamine, preferentially, blocks the α_1-adrenoceptors and only when the dose or the concentration of the drug is increased blockade of α_2-adrenoceptors is demonstrated (45, 61).

WB 4101 is a preferential α_1-adrenoceptor blocking agent (204) that has been extensively used as a radioactive ligand to label α_1-adrenoceptors.

The relative order of potencies shown in table 1 represents an oversimplification because there are some tissue and species differences for the agonists as well as the antagonists (5, 32, 234). In addition, clonidine and other imidazolines can under certain experimental conditions act as α-adrenoceptor blocking agents rather than as agonists (129, 211).

The first proposal of the subclassification of α-adrenoceptors into α_1- and α_2-categories (153) was subsequently extended by other authors (18, 300, 301). As recently pointed out by Starke and Langer (251), presynaptic receptors are defined by the function that they control: modulation of transmitter release, while α_2-adrenoceptors are characterized and defined by their relative affinities for agonists and antagonists. Therefore, the term α_2-adrenoceptor should be used in the context of its pharmacological characteristics. The subclassification of α-adrenoceptors is therefore independent of anatomical location and it is based exclusively on the pharmacological characteristics (table 1). In fact α_2-adrenoceptors have been described at sites other than the noradrenergic nerve terminals. Table 2 summarizes the distribution and physiological effects involving α_1- and α_2-types of adrenoceptors. Receptors of the α_2-type involve neuronal as well as nonneuronal locations like platelets, fat cells, pancreatic islets, and vascular smooth muscle (table 2).

The pharmacological differences between presynaptic and postsynaptic α-adrenoceptors have important implications because the release-modulating presynaptic receptors might be activated or blocked selectively by administered agonists or antagonists to modify norepinephrine release with small or negligible effects on the corresponding postsynaptic α-receptors.

Prazosin, a selective α_1-adrenoceptor blocking agent, antagonizes effectively the pressor effects of phenylephrine but it is considerably less active against the pressor effects induced by exogenous norepinephrine. These paradoxical results are probably due to the presence of α_2-adrenoceptors on vascular smooth muscle (table 2). Evidence for the presence of postsynaptic α_2-adrenoceptors in vascular smooth muscle was obtained in the rat (54, 58) and dog (182).

More recently it was found that low doses of prazosin reduced markedly the responses to sympathetic nerve stimulation in the perfused hindleg of the dog while failing to antagonize the responses to exogenous norepinephrine in the same preparation (183). The contrast between effective blockade of responses to endogenously released norepinephrine and the inability of the α_1-selective antagonist prazosin to block responses to exogenous norepinephrine may be due to the fact that α_1-adrenoceptors on vascular smooth muscle may be located in close vicinity to the noradrenergic nerves while the α_2-adrenoceptors are mainly extrasynaptic and therefore stimulated by exogenous norepinephrine but not by the endogenously released neurotransmitter (185). The selectivity of prazosin in preferentially blocking responses to sympathetic nerve stimulation when compared with exogenous norepinephrine has also been observed in the

TABLE 1

*Relative orders of potency of agonists and antagonists for α_1- and α_2-adrenoceptors**

Relative Order of Potency of Agonists	
Guanabenz > tramazoline > clonidine > αCH_3 - norepinephrine > oxymetazoline	α_2
> naphazoline = epinephrine = norepinephrine >	$\alpha_2 = \alpha_1$
> phenylephrine > methoxamine	α_1
Relative Order of Potency of Antagonists	
rauwolscine > yohimbine ≫ piperoxan > tolazoline ≫	α_2
> phentolamine >	$\alpha_2 = \alpha_1$
> phenoxybenzamine ≫ WB 4101 >≫ labetolol = prazosin	α_1

* The results shown were obtained in noradrenergically innervated tissues of peripheral neuroeffector junctions of several species.

TABLE 2

*Distribution and physiological effects mediated by α_1- and α_2-adrenoceptors**

A. α_1-adrenoceptors
1. Postsynaptic in vascular smooth muscle (contraction)
2. Postsynaptic in the heart (positive inotropic)
3. Postsynaptic in the liver (glycogen phosphorylase activation)
4. Postsynaptic in CNS (stimulation)
B. Neuronal α_2-adrenoceptors
1. Presynaptic on peripheral and central NE nerve endings (inhibition of NE release)
2. Presynaptic on cholinergic neurons (inhibition of Ach release)
3. Presynaptic on 5HT neurons (inhibition of 5HT release)
4. Postsynaptic in the CNS (hypotension, bradycardia)
5. Sympathetic ganglia (hyperpolarization)
6. Somatodendritic autoreceptors in CNS (inhibition of firing in NE neurons)
C. Nonneuronal α_2-adrenoceptors
1. Platelets (aggregation)
2. Human fat cells (inhibition of lipolysis)
3. Pancreatic islets (inhibition of insulin secretion)
4. Vascular smooth muscle (contraction)

* Abbreviations used are: NE, norepinephrine; Ach, acetylcholine; 5HT, serotonin; CNS, central nervous system.

perfused cat spleen (184). In this preparation phentolamine, which blocks equally α_1- and α_2-adrenoceptors, antagonizes to the same extent the responses to nerve stimulation and to exogenous norepinephrine (184). When neuronal uptake is inhibited with cocaine, prazosin becomes more effective than in the absence of cocaine in blocking the responses to exogenous norepinephrine in the perfused cat spleen (184). In a recent study, Yamaguchi and Kopin (305) compared the effectiveness of different α-adrenoceptor blocking agents on the pressor responses and the changes in plasma norepinephrine levels upon spinal cord stimulation in the rat. These authors also suggested that in the rat it is the α_1-adrenoceptor subtype that predominates intrasynaptically (305). Figure 2 shows schematically the proposed locations of postsynaptic α_1- and α_2-adrenoceptors in vascular smooth muscle.

Receptor binding techniques have provided additional evidence in support of the subclassification of α-adrenoceptors into α_1- and α_2-categories. The mixed agonist/antagonist, dihydroergocryptine (DHE) was the first tritiated ligand to be widely used to study α-adrenoceptors. This ligand binds to both the α_1 and the α_2 types of adrenoceptor (303). The inhibition of the specific ^{3}H-DHE binding in the rat brain by prazosin or yohimbine follows a biphasic pattern (212) suggesting two populations of receptors with different affinities for the α_1-selective antagonist prazosin and the α_2-preferential antagonist yohimbine.

The relative porportions of α_1- and α_2-adrenoceptors in several tissues were estimated by Hoffman et al. (128) with the use of a computer model to analyse the inhibition of ^{3}H-DHE binding in these tissues by prazosin, phentolamine, and yohimbine. These authors concluded that the α-adrenoceptors in the rat liver were of the α_1-type while those in human platelets were of the α_2-type. In the rabbit uterus 37% of the α-adrenoceptors are α_1 and 63% are α_2 (128).

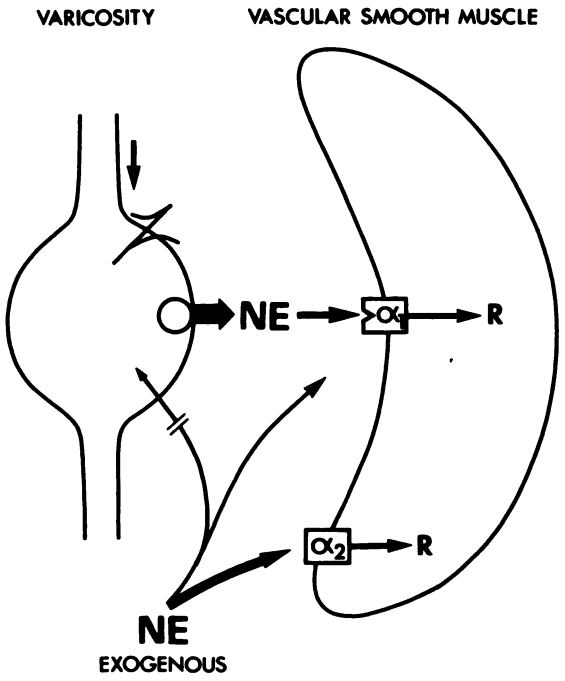

FIG. 2. Postsynaptic α_1- and α_2-adrenoceptors in vascular smooth muscle. Schematic representation of a vascular smooth muscle neuroeffector junction at the level of the small resistance vessels. Norepinephrine (NE) released by nerve impulses activates preferentially α_1-adrenoceptors of predominantly intrasynaptic location. Exogenously administered or circulating NE acts preferentially on extrasynaptic α_2-adrenoceptors to produce vasoconstriction. It is possible that neuronal uptake limits the access of exogenous NE to intrasynaptic α_1-adrenoceptors. Inhibition of neuronal uptake with cocaine increases the effectiveness of prazosin to block responses to exogenous NE.

More recently the two radiolabeled α_1-selective antagonists ^{3}H-WB 4101 and ^{3}H-prazosin have become available. The high affinity binding of ^{3}H-prazosin to α_1-adrenoceptors in the brain and the pattern of inhibition of binding by α-adrenoceptor antagonists are shown in table 3. Similarly, the pattern of displacement of ^{3}H-WB 4101 binding in the rat heart by α-adrenoceptor antagonists is

TABLE 3
*^{3}H-prazosin binding to α_1-adrenoceptors in rat cerebral cortex membranes**

A.	K_d, 0.28 ± 0.03 nM B_{max}, 193 ± 29 fmoles/mg of protein	
B.	Inhibiting drugs	IC_{50} (nM)
	1. Antagonists	
	Prazosin	2.8
	Phentolamine	85.0
	Yohimbine	2,100.0

* K_d (affinity constant) and B_{max} (maximal binding) were calculated from Scatchard analysis. The IC_{50} values are the concentrations of drug required to inhibit by 50% the binding of ^{3}H-prazosin at 0.5 nM. Data taken from C. Pimoule and S. Z. Langer (unpublished results).

compatible with the α_1-characteristics of the receptor labelled by ^{3}H-WB 4101 (225). A similar profile was obtained when the binding of ^{3}H-WB 4101 was studied in the rat vas deferens (298).

For studies of α_2-adrenoceptors the radioactive ligand most widely used is ^{3}H-clonidine. Table 4 shows the characteristics of the binding of ^{3}H-clonidine to α_2-adrenoceptors in the rat submaxillary gland. In this tissue ^{3}H-clonidine labels postsynaptic α_2-adrenoceptors: the binding of ^{3}H-clonidine in the rat submaxillary gland is reduced by more than 50% after duct ligation (C. Pimoule and S. Z. Langer, unpublished observations). In membranes of the guinea-pig ileum ^{3}H-clonidine appears to label α_2-adrenoceptors located on cholinergic neurons (272). In this tissue the binding of ^{3}H-clonidine is not affected by the administration of 6-hydroxydopamine (272).

Recent autoradiographic studies with ^{3}H-WB 4101 and ^{3}H-clonidine revealed that α_1- and α_2-adrenoceptors are distributed differently in the rat brain (308). While high densities of α_2-adrenoceptors are found in the limbic system and in the nucleus tractus solitarius, α_1-adrenoceptors are concentrated predominantly in the olfactory bulb and the dentate gyrus of the hippocampus (308).

In the central nervous system of the rat, ^{3}H-prazosin appears to label preferentially α_1-adrenoceptors (102). The specific binding of ^{3}H-prazosin is inhibited preferentially by prazosin, phenoxybenzamine, WB 4101, and indoramine, while yohimbine has a lower affinity for this site (102).

In the brain, the maximal binding of ^{3}H-WB 4101 plus that of ^{3}H-clonidine is equal to the maximal binding obtained with ^{3}H-DHE alone (101). These results suggest that ^{3}H-WB 4101 and ^{3}H-clonidine label two separate populations of α-adrenoceptors that have different regional distributions in the brain (101, 308), while ^{3}H-DHE appears to label both types of adrenoceptors (221).

E. Localisation of α_1- and α_2-Adrenoceptors by Binding Studies

In peripheral as well as in central structures the presynaptic α-adrenoceptors that modulate the release of norepinephrine are of the α_2-type. The presynaptic location of the release-modulating α_2-adrenoceptors was recently demonstrated in the rat heart. Story et al. (267) used the ventricle because it has a rich noradrenergic innervation with postsynaptic β_1-adrenoceptors mediating the physiological responses of the effector organ. Two weeks after chemical sympathectomy with 6-hydroxydopamine there was a significant decrease in the maximal binding of ^{3}H-DHE in the rat heart, indicating that some of the α_2-adrenoceptors labelled by ^{3}H-DHE are associated with noradrenergic nerve endings (267).

Chemical denervation with 6-hydroxydopamine does not reduce the binding of ^{3}H-WB 4101 in the rat heart (225). In this tissue ^{3}H-WB 4101 labels α_1-adrenoceptors (225).

In the central nervous system no decrease of ^{3}H-WB 4101 or ^{3}H-clonidine binding was observed after chemical denervation with 6-hydroxydopamine (242, 277). It is possible that both ^{3}H-WB 4101 and ^{3}H-clonidine label α_1- and α_2-adrenoceptors localised postsynaptically in the central nervous system. Since the typical standard errors of the maximal binding for the α-adrenoceptor ligands in these experiments are in the order of 10% to 20%, decreases of considerable magnitude are required after denervation before they can be detected as significant changes by the techniques currently available. The problem is further complicated by the development of denervation supersensitivity, which increases the maximal binding at the postsynaptic level.

In the rat submaxillary gland ^{3}H-clonidine labels α_2-adrenoceptors that are located postsynaptically. In this tissue surgical sympathetic denervation results in a 50% increase in B_{max} and a significant decrease in the K_d value (223). Surprisingly enough, Pimoule et al. (223) found the changes in K_d and B_{max} of ^{3}H-clonidine binding already 24 and 48 hr after superior cervical ganglionectomy (i.e. at the time when the postjunctional component of supersensitivity has not yet developed). This early increase in B_{max} of ^{3}H-clonidine binding after short-term denervation is observed at a time when the binding parameters for ^{3}H-quinuclidinylbenzilate (^{3}H-QNB) remain unchanged

TABLE 4
*^{3}H-clonidine binding to α_2-adrenoceptors in rat submaxillary gland**

A.	K_d, 2.63 ± 0.29 nM B_{max}, 36.3 ± 2.2 fmoles/mg of protein	
B.	Inhibiting drugs	IC_{50} (nM)
	1. Agonists	
	p-Aminoclonidine	1.0
	Clonidine	1.5
	Methoxamine	3,400.0
	2. Antagonists	
	Rauwolscine	250.0
	WB 4101	2,000.0

* K_d (affinity constant) and B_{max} (maximal binding) were calculated from Scatchard analysis. The IC_{50} values are the concentrations of drug required to inhibit by 50% the binding of ^{3}H-clonidine at 1 nM. Data taken from C. Pimoule, M. S. Briley, and S. Z. Langer (unpublished results).

(223). These puzzling effects of short-term denervation on ^{3}H-clonidine binding may occur in the brain and could obscure the significance of the results so far reported for ^{3}H-clonidine binding in the central nervous system after 6-hydroxydopamine administration. Further and extensive studies are required to clarify the significance of changes in the binding parameters of α-adrenoceptor ligands after surgical or chemical denervation.

Additional evidence for the presynaptic location of the α-adrenoceptor that modulates norepinephrine release was obtained in cultured rat superior cervical ganglia. It was shown that in recently formed nerve endings from cultured superior cervical ganglia phenoxybenzamine enhances the potassium-evoked release of ^{3}H-norepinephrine (286). Under these conditions, blockade of α-receptors increased the stimulation-evoked release of norepinephrine in the absence of a postsynaptic effector cell.

F. Influence of Neuronal Uptake of Norepinephrine on the Negative Feedback Mechanism Mediated by Presynaptic α-Adrenoceptors

The inactivation of norepinephrine released by nerve stimulation is carried out by neuronal uptake of the transmitter across the membrane of the nerve terminals (134, 154, 276). This active transport mechanism for norepinephrine effectively reduces the concentration of the released transmitter in the synaptic cleft. Neuronal uptake of norepinephrine can thus regulate the fraction of the transmitter released by stimulation that is available to activate presynaptic α-adrenoceptors (153). When neuronal uptake of norepinephrine is inhibited by cocaine a higher fraction of the transmitter released by nerve stimulation becomes available for the activation of the presynaptic inhibitory α-adrenoceptors (45, 63, 154, 174). Consequently, inhibition of neuronal uptake by cocaine should lead to enhanced feedback inhibition by the higher concentration of norepinephrine achieved in the vicinity of the nerve endings (153, 157).

One of the practical implications of the effects of inhibition of neuronal uptake on noradrenergic neurotransmission is the determination of the relative potencies of agonists on presynaptic and postsynaptic α-adrenoceptors. Several catecholamines in addition to norepinephrine inhibit the stimulation-evoked release of the neurotransmitter (66). Yet exposure of tissues prelabelled with ^{3}H-norepinephrine to catecholamines like norepinephrine, epinephrine, or α-methylnorepinephrine results in a pronounced increase in the basal outflow of radioactivity, which makes it very difficult to determine accurately the overflow of the labelled transmitter induced by nerve stimulation or by potassium (72, 147). Consequently, when the effects of catecholamines that are α-adrenoceptor agonists were studied on transmitter release, neuronal uptake of norepinephrine was inhibited either by cocaine or by desipramine. α-Adrenoceptor agonists like clonidine, oxymetazoline, and other imidazolines have no affinity for the carrier of neuronal uptake of norepinephrine and therefore they do not modify the basal outflow of the transmitter and can be studied in the absence of drugs that inhibit neuronal uptake (180, 218, 219).

When the inhibition of noradrenergic neurotransmission elicited by clonidine or oxymetazoline was compared in the presence and in the absence of neuronal uptake inhibition it was found that α-adrenoceptor agonists of the imidazoline series are less effective in reducing norepinephrine release when neuronal uptake is inhibited with cocaine, desipramine, or amphetamine (68, 220). This is in sharp contrast with the observation that cocaine and desipramine potentiate the inhibition by catecholamines of norepinephrine release.

The fact that clonidine and other imidazolines are less effective in reducing the stimulation-evoked release of norepinephrine when neuronal uptake is inhibited should draw attention to the need to analyse with caution the relative potencies of α-adrenoceptor agonists on presynaptic α-adrenoceptors because some of these studies were carried out under conditions in which neuronal uptake was inhibited by either cocaine or desipramine.

The physiological importance of neuronal uptake in regulating the concentration of norepinephrine in the synaptic cleft is inversely related to the width of the synaptic gap; the narrower the gap the more important is neuronal uptake in regulating the concentration of the neurotransmitter. It appears that the width of the synaptic cleft is also important for the negative feedback mechanism that regulates norepinephrine release. The analysis of results obtained in different tissues with known synaptic gaps shows that the magnitude of the increase in transmitter release elicited by nerve stimulation in the presence of phentolamine was the more pronounced the smaller the width of the synaptic gap of the tissue (175). It appears that in organs with narrow neuromuscular clefts, the presynaptic feedback inhibition for norepinephrine release during nerve stimulation plays a more important role as a regulatory mechanism than in tissues with wide synaptic gaps. This relationship is supported by the results of Kalsner and Chan (38, 140) with renal and facial artery strips from cattle. They found that phentolamine and phenoxybenzamine produce small increases in ^{3}H-norepinephrine overflow (1.13- to 2.88-fold) in these large vessels. The results are comparable to those reported previously with large cat and rat vessels (1.81- to 1.98-fold increases) (175). By using rabbit ear arteries and guinea-pig atria, Rand et al. (230) found that exogenous norepinephrine decreases transmitter release to the same extent in these two tissues while phenoxybenzamine produces a much greater increase in release from guinea-pig atria (8-fold) than from the rabbit ear artery (only 2.5-fold). Yet, one should not conclude from these experiments that the negative feedback control of norepinephrine release is of less importance in blood vessels than in other tissues. Studies of ^{3}H-norepinephrine release have been restricted to the larger blood

vessels and the situation may be different in the smaller resistance vessels.

G. Presence of Presynaptic Inhibitory α-Adrenoceptors in the Central Nervous System

As in the peripheral nervous system, the central noradrenergic neurons have receptors on their cell bodies and dendrites that are involved in the generation and modulation of action potentials. The presynaptic receptors, possibly located on axon terminals, would modulate the calcium-dependent release of neurotransmitters. The situation in the central nervous system is very complex because, in addition to the existence of different types of synapses, there are also many nerve endings that do not make typical synaptic contacts (17). Consequently, one should be very cautious in applying the criteria employed in the peripheral nervous system to study modulation of transmitter release through presynaptic receptors in the central nervous system.

The use of transmitter release models from brain slices in areas in which one is dealing predominantly with nerve terminals is desirable (occipital cortex for norepinephrine, striatum for dopamine). In addition, it is essential to demonstrate the calcium-dependence of the depolarization-induced release of the transmitter (either potassium or electrical stimulation). While short interneurons may be present in slice preparations, the use of synaptosomal preparations for transmitter release studies has the advantage of dealing predominantly with effects at the level of nerve terminals. In most cases the postsynaptic membrane is still present in synaptosomal preparations and there are also terminals that release various other transmitters at the time the depolarizing stimuli are applied. In spite of these technical difficulties transmitter release studies in synaptosomal preparations have yielded results that are similar to those obtained in brain slices, thus supporting the presence of presynaptic α-adrenoceptors modulating release of norepinephrine in the central nervous system (157, 220, 247, 274).

In vivo studies on norepinephrine release in the peripheral nervous system support the view that presynaptic inhibitory α-adrenoceptors modulate the stimulation-evoked release of the neurotransmitter (30, 304). Similar results under in vivo conditions in the central nervous system are not only difficult to obtain but also difficult to interpret. The study of drug-induced changes in the outflow of transmitters under in vivo conditions with the use of the push-pull cannula is complicated by the influence of neuronal loops and transsynaptic regulatory mechanisms involving postsynaptic receptors. Drugs can also act on somatodendritic receptors (36) leading to changes in the rate of firing of the catecholaminergic neurons in these in vivo studies.

In spite of all these difficulties, the evidence available supports the view that there are presynaptic inhibitory α-adrenoceptors on the noradrenergic nerve endings of several brain regions (for reviews see 157, 247). As already demonstrated in the peripheral nervous system α-adrenoceptor agonists decrease, while α-adrenoceptor antagonists increase the action potential-evoked release of ^{3}H-norepinephrine from several brain regions. The relative potencies of agonists and antagonists for the release-regulating α-adrenoceptors in the central nervous system appear to be similar to those shown in table 1 for the peripheral sympathetic system. Thus it has been found that clonidine and oxymetazoline but not methoxamine reduce the potassium-evoked release of ^{3}H-norepinephrine from slices of the rat occipital cortex (59). On the other hand, yohimbine and phentolamine but not prazosin or WB 4101 increase the potassium-evoked ^{3}H-norepinephrine overflow from rat occipital cortex slices (59, 90). Consequently, it appears that the presynaptic α-adrenoceptors in the central nervous system are of the α_2-type with respect to their pharmacological characteristics. Figure 3 shows schematically the location of presynaptic and somatodendritic α_2-adrenoceptors in a central noradrenergic neuron.

In vivo studies in which the turnover of norepinephrine and epinephrine were determined in several areas of the

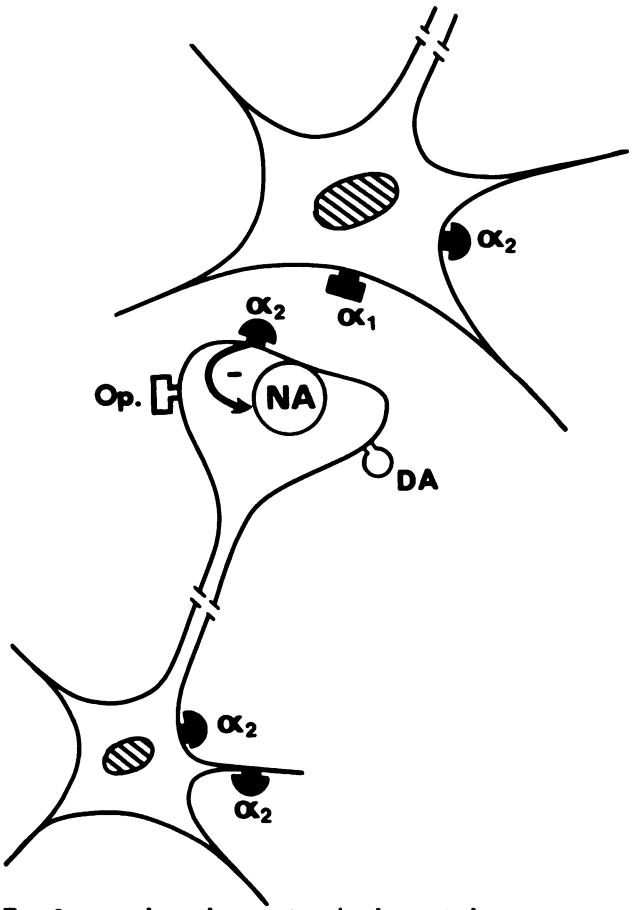

FIG. 3. α_1- and α_2-adrenoceptors in the central nervous system. Schematic representation of a central noradrenergic neuron (NA). Somatodendritic inhibitory α_2-adrenoceptors are present in addition to the presynaptic inhibitory α_2-adrenoceptors on noradrenergic nere terminals. Postsynaptic adrenoceptors are of the α_1- as well as of the α_2-type. In addition, the figure shows the presynaptic inhibitory opiate (Op) and dopamine (DA) receptors on central noradrenergic nerve terminals.

rat brain show that the administration of clonidine reduces the turnover of both catecholamines (237). This is antagonized by the preferential α_2-adrenoceptor blocking agent yohimbine while it remains unaffected by the α_1-selective antagonist prazosin. There is evidence originating from receptor binding studies that indicates that there are both α_1- and α_2-type adrenoceptors in the central nervous system and that both types of α-adrenoceptors might be located postsynaptically (212, 277). As discussed below, the antihypertensive and bradycardic effects of clonidine are mediated predominantly through the activation of α_2-adrenoceptors in the central nervous system. The evidence available indicates that these α_2-adrenoceptors are located postsynaptically (127, 148, 149). The decrease by clonidine of the turnover of norepinephrine and epinephrine in the rat brain might be due to the activation of α_2-adrenoceptors located either presynaptically or postsynaptically (178, 237). Anden et al. (4) have provided biochemical and behavioral evidence for the presence of different α-adrenoceptor subtypes in the central nervous system.

H. Development of Subsensitivity of the Presynaptic Adrenoceptors

The development of subsensitivity and supersensitivity is a well established phenomenon for the classical postsynaptic receptors that mediate responses in the peripheral and in the central nervous systems. While subsensitivity is associated with chronic stimulation of these receptors, the development of postsynaptic supersensitivity is usually linked to chronic blockade of the receptors or an impairment of the process of neurotransmission (155, 276).

Changes in the sensitivity of the presynaptic α-adrenoceptors involved in the regulation of norepinephrine release have been reported recently. Subsensitivity of the presynaptic α-adrenoceptors was seen in the cat nictitating membrane 18 hr after surgical denervation at a time when the postsynaptic changes in sensitivity are not yet developed (150, 170, 180). The subsensitivity of presynaptic α-adrenoceptors appears to be due to exposure of the nerve ending to the transmitter leaking from degenerating nerve endings at the onset of the degeneration contraction (150, 180, 187).

The sensitivity of the presynaptic α-adrenoceptor can be reduced after exposure in vitro to an effective concentration of an α-adrenoceptor agonist. In the cat spleen, perfused with cocaine to inhibit neuronal uptake, a short-lasting subsensitivity of both the presynaptic and the postsynaptic α-adrenoceptor can be demonstrated after a 60-min exposure to 0.6 μM norepinephrine (171). As discussed below, it is possible that after chronic treatment with clonidine some degree of subsensitivity may develop in the presynaptic α-adrenoceptors. The hypertensive crisis that results from the sudden interruption of the chronic administration of clonidine may result at least partially from an increased release of norepinephrine from sympathetic nerves (156, 158, 181). Tricyclic antidepressants like imipramine, desipramine, and amitryptiline are potent inhibitors of neuronal uptake of norepinephrine. Since inhibition of neuronal uptake increases the concentration of the neurotransmitter in the synaptic gap, it is possible that chronic inhibition of neuronal uptake of norepinephrine may lead to subsensitivity of presynaptic α-adrenoceptors due to a long-lasting increase in the concentration of norepinephrine in the synaptic cleft (153, 158, 168, 171). Therefore, chronic administration of tricyclic antidepressants that inhibit neuronal uptake of norepinephrine may result in an increase in the neuronally mediated release of the transmitter due to the development of subsensitivity of the presynaptic inhibitory α-adrenoceptors. This hypothesis might explain the latency that is required for the appearance of the clinical antidepressant effects of these compounds; a certain time is required for the development of subsensitivity of the presynaptic α-adrenoreceptors that regulate the release of norepinephrine. In support of this hypothesis, Crews and Smith (42, 43) reported that after chronic but not after the acute administration of desipramine there is an increase in the stimulation-evoked release of norepinephrine from the rat heart. Similar results have been reported in the central nervous system after the chronic administration of tricyclic antidepressants (210). The development of postsynaptic subsensitivity of central adrenoceptors after the chronic administration of different types of antidepressants has been reported (282). In addition, chronic treatment with antidepressant drugs reduces the number of specific β-adrenoceptor binding sites and this effect is not observed in rats treated with 6-hydroxydopamine (302). Since subsensitivity of presynaptic α-adrenoceptors has been shown to develop in parallel with subsensitivity of postsynaptic α-adrenoceptors in the cat spleen (171), it is likely that the subsensitivity of postsynaptic central β-adrenoceptors reported to develop after chronic treatment with antidepressants (12, 226, 236) occurs also for the presynaptic α-adrenoceptor that regulates the stimulation-evoked release of norepinephrine. There is no evidence to indicate that chronic antidepressant treatments produce changes in either the β_2- or the α_1-adrenoceptor in the central nervous system. An increase in the neurally mediated release of norepinephrine in the central nervous system resulting either from blockade or from subsensitivity of presynaptic α-adrenoceptors might represent a common mechanism of action for the antidepressant effects of several drugs (158, 167, 168). Such mechanism of action would be compatible with the catecholamine hypothesis of affective disorders (238).

I. Physiological and Pharmacological Significance of the Negative Feedback Mechanism Mediated by Presynaptic α-Adrenoceptors

If the negative feedback mechanism mediated by presynaptic α-adrenoceptors plays a physiological role in the

regulation of neurotransmission, the enhancement in norepinephrine release observed in the presence of α-adrenoceptor blocking agents should be reflected in an increase in the response of the effector organ to nerve stimulation. For the tissues in which the postsynaptic responses are mediated through α-adrenoceptors like blood vessels, spleen, or nictitating membrane, the responses to nerve stimulation are reduced by α-adrenoceptor antagonists. Nevertheless, with yohimbine, which is more selective in blocking the presynaptic α-adrenoceptors (table 1), an increase in both transmitter overflow and responses to nerve stimulation in the rabbit pulmonary artery can be observed in the low range of concentrations (248). In tissues in which the postsynaptic response is mediated through β-adrenoceptors, exposure to α-adrenoceptor blocking agents should enhance the responses to nerve stimulation as a result of the increase in transmitter release. In support of this view a significant increase in the positive chronotropic response to accelerans nerve stimulation was obtained in guinea-pig atria in the presence of concentrations of phentolamine that enhanced significantly the release of ^{3}H-norepinephrine during nerve stimulation (166). Similar results were obtained under in vivo experimental conditions; clonidine reduced the positive chronotropic responses to cardioaccelerator nerve stimulation (11, 30) while α-adrenoceptor blocking agents potentiated the positive chronotropic effects of cardioaccelerator nerve stimulation (195, 304).

The relationship between the increase in stimulation-evoked release of norepinephrine and the enhancement in the positive chronotropic responses to nerve stimulation obtained in the presence of α-adrenoceptor blocking agents supports the view that a negative feedback mechanism mediated by presynaptic α-adrenoceptors operates under physiological conditions of noradrenergic neurotransmission.

The presence of presynaptic α-adrenoceptors in human vasoconstrictor nerves has been demonstrated (260, 264). In experiments on isolated perfused biopsy specimens of human peripheral arteries and veins, Stjärne and coworkers (263, 264) found a decrease in the stimulation-evoked release of ^{3}H-norepinephrine in the presence of α-adrenoceptor agonists and an increase in the overflow of the labelled transmitter during exposure to α-adrenoceptor blocking agents.

The pharmacological relevance of the presynaptic inhibitory α-adrenoceptors stems from the fact that α-adrenoceptor agonists as well as α-adrenoceptor antagonists can no longer be analysed for their overall pharmacological effects as a function of the simple activation or blockade of the classical postsynaptic adrenoceptors. In view of the fact that most effector organs are constantly activated through norepinephrine released by tonic impulses, the net effect of the activation of α-adrenoceptors will result from the algebraic sum of reducing norepinephrine release presynaptically and activating directly postsynaptic adrenoceptors.

Since presynaptic and postsynaptic α-adrenoceptors differ in their affinity for agonists as well as for antagonists, it follows that the presynaptic receptors regulating transmitter release can be activated or blocked selectively by administering agonists or antagonists to modify neurotransmission with negligible effects on the corresponding postsynaptic receptor. Conversely, selective activation or blockade of postsynaptic α-adrenoceptors can be achieved with little or no effects on norepinephrine release during nerve stimulation. These pharmacological differences between presynaptic and postsynaptic α-adrenoceptors offers an attractive challenge in drug discovery because of the therapeutic potential of selective α_2-adrenoceptor agonists or antagonists. Selective α_1-adrenoceptor antagonists like prazosin are used effectively in the treatment of hypertension (169).

An analysis of the distribution of α_1- and α_2-adrenoceptors (table 2) points to the different target receptors that can be stimulated or blocked by α-adrenoceptor agonists or antagonists. In view of the fact that the subclassification and characterization of α_1- and α_2-adrenoceptors are rather recent developments, it is likely that in the coming years more α-adrenoceptors (peripheral and central) will be defined pharmacologically either as α_1 or as α_2.

As shown schematically in figure 2, in the central nervous system there is evidence for the presence of soma-dendritic inhibitory α-adrenoceptors in the locus coeruleus. These receptors have the pharmacological characteristics of the α_2-adrenoceptors (36).

III. Presynaptic Facilitatory β-Adrenoceptors in Peripheral Noradrenergic Nerve Endings

Facilitation of the stimulation-evoked release of norepinephrine through presynaptic β-adrenoceptors was first proposed in 1974 (165). Further support for the presence of presynaptic β-adrenoceptors was obtained from experiments in which exposure to low concentrations of isoproterenol facilitated the release of norepinephrine during low frequency nerve stimulation in several noradrenergically innervated organs: guinea-pig atria, cat thoracic aorta, calf muscle, and perfused spleen, and rat pineal gland and portal vein (1, 37, 47–49, 219, 297). An increase by isoprenaline and a decrease by sotalol in the stimulation-evoked release of norepinephrine were reported under in vivo conditions in the anaesthetized dog (304). The presence of presynaptic facilitatory β-adrenoceptors was also reported in the human oviduct (120) and in human vasoconstrictor nerves (260–263). In addition, Weinstock et al. (291) demonstrated that presynaptic β-adrenoceptors are present in recently formed noradrenergic nerve endings when rat superior cervical ganglia are cultured (i.e. in the absence of postsynaptic structures).

The increase in the stimulation-evoked release of norepinephrine obtained in the presence of isoproterenol is antagonized by preincubation with 0.1 μM propranolol (1, 37, 49, 219). A small but statistically significant de-

crease in transmitter release elicited by nerve stimulation was obtained with propranolol in isolated guinea-pig atria (1), in the perfused cat spleen (37), in the perfused calf muscle of the cat pretreated with phenoxybenzamine (47), and in the isolated portal vein of spontaneously hypertensive rats (49). On the other hand, exposure to propranolol does not per se reduce the stimulation-evoked release of ^{3}H-norepinephrine from human omental arteries and veins (260) or from the rat pineal gland (219).

In the presence of concentrations of propranolol higher than 1 μM, a reduction in the release of norepinephrine during nerve stimulation is observed in several tissues. However, this effect is not related to the β-adrenoceptor blocking properties of the drug but rather to the local anaesthetic and membrane-stabilizing effects of propranolol (13, 132).

In the anaesthetized dog an infusion of isoproterenol increases the release of norepinephrine elicited by right cardioaccelerator nerve stimulation at low frequencies (304), while the administration of the β-adrenoceptor blocking agent, sotalol, significantly reduces the release of norepinephrine at stimulation frequencies between 1 and 5 Hz.

As already shown for the presynaptic α-adrenoceptor (258), the presynaptic β-adrenoceptor is also stereospecific. The increase in stimulation-evoked norepinephrine release observed with (−)-isoproterenol was not obtained when (+)-isoproterenol was substituted for (−)-isoproterenol in the perfusion medium of the cat spleen (37). Dahlöf et al. (49) found that *dl*- but not *d*-propranolol reduced the stimulation-evoked release of ^{3}H-norepinephrine from the isolated portal vein of spontaneously hypertensive rats. It is therefore surprising that Kalsner (139) found that both *l*- and *d*-propranolol blocked the facilitation of noradrenergic neurotransmission produced by isoprenaline in isolated guinea-pig atria. Since Kalsner (139) used only one concentration of the isomers of propranolol, these results await confirmation through full concentration-effect curves with both *l*- and *d*-propranolol.

The experimental evidence available so far suggests that the presynaptic facilitatory β-adrenoceptors might be of the β_2-type rather than of the β_1-type. In experiments carried out on human vasoconstrictor nerves it was found that terbutaline and salbutamol enhanced the release of ^{3}H-norepinephrine elicited by nerve stimulation, while the β_1-agonist, H110/38, was without effect (261). In the same preparation, it was seen that low concentrations of epinephrine enhanced the stimulation-evoked release of ^{3}H-norepinephrine (260). More recently, it was found that terbutaline enhances the potassium-evoked release of ^{3}H-norepinephrine from the rat pineal gland (219).

It is possible that presynaptic facilitatory β-adrenoceptors are mainly activated by circulating epinephrine to enhance noradrenergic neurotransmission (fig. 1). When peripheral noradrenergic nerve terminals are labelled with epinephrine instead of norepinephrine, propranolol becomes more effective in reducing transmitter release elicited by sympathetic nerve stimulation (103, 229). Therefore, it is possible that epinephrine may participate in a positive feedback mechanism for the release of norepinephrine from peripheral noradrenergic nerve endings. β-adrenoceptor antagonists may thus act at this site to cause a decrease in transmitter output by blocking the positive feedback mechanism mediated by presynaptic facilitatory β-adrenoceptors. The sensitivity of this positive feedback mechanism could be increased in essential hypertension, and blockade of presynaptic β-adrenoceptors by antagonists may contribute to their hypotensive effects.

In the calf muscle of the cat, the presynaptic β-adrenoceptors might be of the β_1-type because they are blocked by metoprolol, a selective β_1-adrenoceptor blocking agent (47). These results may reflect species and/or tissue differences. In addition, the possibility should be considered that the presynaptic β-adrenoceptors that mediate the facilitation of transmitter release during low frequency nerve stimulation might differ from the classical β_1- and β_2-postsynaptic adrenoceptors. As the presynaptic and the postsynaptic α-adrenoceptors differ in their affinity for agonists and for antagonists (table 1) the presynaptic β-adrenoceptors might themselves also differ from the classical postsynaptic β-adrenoceptors.

In contrast to the presynaptic inhibition mediated through α_2-adrenoceptors that is present in peripheral as well as in central noradrenergic nerve terminals (157, 186, 247, 285), there is as yet no evidence for the presence of facilitatory presynaptic β-adrenoceptors in areas of the central nervous system containing noradrenergic nerve endings. Nevertheless, it is of interest that dibutyryl cyclic AMP produces a concentration-dependent increase in the release of ^{3}H-norepinephrine elicited by electrical stimulation in slices of the rat occipital cortex (F. Pelayo, M. L. Dubocovich, and S. Z. Langer, unpublished observations).

IV. Presynaptic Inhibitory Dopamine Receptors in Peripheral Noradrenergic Nerve Endings

The inhibition by dopamine of the stimulation-evoked release of ^{3}H-norepinephrine in the perfused cat spleen was first reported in 1973 (152). Since then, several authors reported the presence of a dopamine-sensitive presynaptic inhibitory receptor in peripheral noradrenergic nerve terminals under in vitro (64, 72, 89, 130, 172, 198) and also under in vivo experimental conditions (196, 197, 203).

Stimulation of presynaptic inhibitory dopamine receptors by agonists like dopamine, apomorphine, bromocriptine, pergolide, or di-n-propyldopamine reduces the stimulation-evoked release of norepinephrine and this effect is accompanied by a decrease in the end organ responses to nerve stimulation. The inhibition of noradrenergic

neurotransmission elicited by dopamine receptor agonists is unaffected by α-adrenoceptor blocking agents (64, 72) while it is selectively antagonized by dopamine receptor blocking agents like chlorpromazine, pimozide, or sulpiride. Consequently, the presynaptic inhibitory dopamine receptors differ from the presynaptic α_2-adrenoceptors, which can be acted upon by released norepinephrine.

Kalsner and Chan (141) reported that norepinephrine does not reduce the stimulation-evoked release of ^{3}H-norepinephrine from renal arteries while dopamine effectively reduces transmitter release. In these arteries dopamine decreases ^{3}H-norepinephrine release more at low than at high frequencies of stimulation (141). Since blockade of presynaptic inhibitory dopamine receptors does not per se increase the release of norepinephrine during nerve stimulation, it appears unlikely that presynaptic dopamine receptors play a physiological role in noradrenergic neurotransmission (64, 172). Consistent with this view are the recent results of Kalsner and Chan (141), who found that dopamine receptor antagonists like pimozide and metoclopramide blocked the inhibitory effect of dopamine on ^{3}H-norepinephrine release from renal arteries but did not by themselves increase the stimulation-induced release of the neurotransmitter.

It appears that the presynaptic inhibitory dopamine receptors on noradrenergic nerve endings differ from the postsynaptic dopamine receptors that mediate vasodilatation in some vascular beds. Sulpiride blocks preferentially presynaptic inhibitory dopamine receptors while bulbocapnine antagonizes selectively the postsynaptic vascular dopamine receptor (R. Massingham, N. B. Shepperson, and S. Z. Langer, unpublished observations). In analogy with the nomenclature adopted for α-adrenoceptors, it is suggested that the postsynaptic dopamine vascular receptor be referred to as DA_1 and that the presynaptic inhibitory dopamine receptor on peripheral noradrenergic nerve endings be referred to as DA_2.

Presynaptic inhibitory dopamine receptors appear to be involved in the blood-pressure-lowering and bradycardic effects of dopamine receptor agonists (172, 197, 203). The renal vasodilating effects of dopamine agonists are mainly due to the activation of the postsynaptic vascular dopamine receptor.

Presynaptic inhibitory dopamine receptors can be considered as targets for the development of selective agonists that might be useful antihypertensive agents (64, 172, 203).

In the central nervous system, in experiments where cocaine was employed to inhibit neuronal uptake of norepinephrine, Taube et al. (274) showed that dopamine does not inhibit noradrenergic neurotransmission. It was therefore concluded that presynaptic inhibitory dopamine receptors were not present in central noradrenergic nerve endings (274). However when similar experiments were carried out on the rabbit hypothalamus, in the absence of cocaine, two dopamine receptor agonists, apomorphine and pergolide, reduced the stimulation-evoked release of ^{3}H-norepinephrine (90) and these effects were not affected by yohimbine but were blocked by sulpiride, a dopamine receptor blocking agent that blocks preferentially the DA_2 type of receptor (144). It therefore appears that presynaptic inhibitory dopamine receptors might also be present on noradrenergic nerve terminals in the central nervous system (fig. 2). Inhibition of neuronal uptake with cocaine or desipramine appears to interact with these central presynaptic dopamine receptors in a way similar to that reported for the presynaptic effects of clonidine (90, 220).

The presynaptic inhibitory effects of dopamine agonists on noradrenergic neurotransmission are more pronounced at low frequencies of stimulation both in the peripheral as well as in the central nervous system.

V. Presynaptic Inhibitory Muscarinic Receptors in Peripheral Noradrenergic Nerve Endings

The inhibition by muscarinic cholinoceptor agonists of noradrenergic neurotransmission was reported in the rabbit heart (82, 192), in the chicken heart (75), and in the guinea-pig heart (189). The reduction in the stimulation-evoked release of norepinephrine by muscarinic cholinoceptor agonists is blocked by atropine and other muscarinic receptor antagonists (214). It appears that activation of presynaptic inhibitory muscarinic cholinoceptors reduces transmitter release by decreasing the availability of calcium for the excitation-secretion coupling of norepinephrine (215).

Acetylcholine also decreases the stimulation-evoked release of norepinephrine from vascular tissues (3, 70, 257, 279, 280) through the activation of presynaptic inhibitory muscarinic cholinoceptors.

In the heart presynaptic inhibitory muscarinic cholinoceptors may play a physiological role in noradrenergic neurotransmission (215), because stimulation of the vagus nerves reduces the output of norepinephrine elicited by the stimultaneous stimulation of the postganglionic sympathetic nerves, presumably through the effects of released acetylcholine acting on presynaptic inhibitory muscarinic cholinoceptors on noradrenergic nerve terminals (190, 193).

Presynaptic inhibitory muscarinic receptors appear also to be present on noradrenergic nerve endings of the central nervous system. Muscarinic receptor agonists reduce the release of ^{3}H-norepinephrine elicited by potassium from hypothalamic and cerebellar slices (295). In addition, a decrease in norepinephrine release by acetylcholine was reported in the cat cerebral cortex under in vivo conditions (232).

In contrast to the presynaptic inhibitory α-adrenoceptors and dopamine receptors, which differ pharmacologically from the corresponding postsynaptic receptors, it appears that presynaptic inhibitory muscarinic receptors on noradrenergic nerve endings are identical with the postsynaptic muscarinic receptors in the heart (214).

VI. Presynaptic Inhibitory Opiate Receptors in Peripheral and Central Noradrenergic Nerve Endings

The first observation of the inhibition by morphine of noradrenergic neurotransmission in the cat nictitating membrane was reported by Trendelenburg in 1957 (275). This effect was subsequently shown to be mediated via opiate receptors (26, 65, 123, 124).

The inhibition of noradrenergic neurotransmission in the peripheral nervous system by opiate receptor agonists is, however, restricted to only a few neuroeffector junctions, for instance, the mouse vas deferens (121, 122) and the cat nictitating membrane (65, 123).

The inhibition by morphine of norepinephrine release elicited by nerve stimulation in the cat nictitating membrane is blocked by naloxone and is more pronounced at low frequencies of stimulation. The presynaptic inhibitory opiate receptor in the cat nictitating membrane differs from the presynaptic inhibitory α_2-adrenoceptor, since blockade of presynaptic α-adrenoceptors with phentolamine does not affect the inhibitory effects of morphine on noradrenergic neurotransmission (65).

Phenoxybenzamine in concentrations up to 1 μM does not affect the presynaptic inhibitory effects of methionine-enkephalin on noradrenergic transmission in the cat nictitating membrane. Yet, in the presence of 10 μM phenoxybenzamine the inhibition of norepinephrine release by methionine enkephalin is blocked (65). These effects of the rather high concentration of phenoxybenzamine may be related to the interaction of this blocking agent with opiate receptors (243).

Both methionine-enkephalin and leucine-enkephalin reduce the stimulation-evoked release of ^{3}H-norepinephrine from the isolated cat nictitating membrane (65). The naturally occurring pentapeptides are about 100 times more potent than morphine in inhibiting noradrenergic neurotransmission (65). The enkephalins also reduce norepinephrine release from the mouse vas deferens and this effect is blocked by naloxone (290).

There is indirect evidence in the guinea-pig ileum for the release of endogenous opiate ligands, which in turn inhibit the release of acetylcholine (289). There is as yet no evidence for the presence of the naturally occurring opiate peptides either in mouse vas deferens or in the cat nictitating membrane.

Presynaptic inhibitory opiate receptors are also present on noradrenergic nerve endings of the central nervous system (fig. 2) (6, 273). The initial report of inhibition of dopamine release from the rat striatrum by opiate receptor agonists (194) was, however, not confirmed (6). Although the number of opiate receptor binding sites in the rat striatum is decreased after lesions of the nigrostriatal pathway (224), the stimulation-evoked release of ^{3}H-dopamine is not inhibited by either morphine or β-endorphin (6).

When chronic morphine administration to rats is stopped the presynaptic inhibition of norepinephrine release from the occipital cortex elicited by α_2-adrenoceptor agonists like clonidine or by presynaptic opiate agonists like morphine is not affected (H. G. Jenkins, M. L. Dubocovich, and S. Z. Langer, unpublished observations). The fact that clonidine retains its presynaptic inhibitory effects after the chronic administration of morphine is of interest because clonidine has been used successfully in the treatment of the opiate withdrawal syndrome in man (98).

VII. Presynaptic Inhibition of Noradrenergic Neurotransmission by Prostaglandins

Prostaglandins of the E series inhibit the stimulation-evoked release of norepinephrine from several noradrenergically innervated tissues (62, 112, 113, 115–117). This effect is, however, not observed in the perfused dog spleen (50) or in the cat nictitating membrane (M. A. Enero and S. Z. Langer, unpublished observations). Since release of prostaglandins of the E series is associated with sympathetic nerve stimulation in some tissues (51, 95), it was suggested that endogenously released prostaglandins were involved in a negative feedback mechanism that regulated the release of norepinephrine during nerve stimulation (111, 114). Evidence in support of this hypothesis was obtained initially in the rabbit heart (235, 292). In some preparations the nerve stimulation-induced output of prostaglandins tends to increase with the duration of the experiment, perhaps reflecting a deterioration of the tissues (62, 80, 131). In addition, inhibition of the synthesis of prostaglandins by drugs like indomethacin or meclofenamate enhance moderately (85, 86, 118, 252) or not at all (62, 131) the stimulation-evoked release of norepinephrine.

Although a physiological role of endogenously released prostaglandins in modulating noradrenergic neurotransmission is still disputed, the fact remains that in many neuroeffector junctions exogenous prostaglandins of the E series reduce the stimulation-evoked release of norepinephrine through a presynaptic effect. Consequently, it is possible that in some tissues prostaglandins of the E series may play a physiological role in the transsynaptic modulation of norepinephrine release.

The presynaptic inhibition of noradrenergic neurotransmission elicited by prostaglandins is independent of the feedback mechanism mediated by presynaptic α-adrenoceptors. The effects of α-adrenoceptor agonists or α-adrenoceptor antagonists on noradrenergic neurotransmission are essentially unaffected by the inhibition of the synthesis of prostaglandins (62, 252).

In the central nervous system, prostaglandin E_1 and E_2 inhibit the release of ^{3}H-norepinephrine from slices of the rat brain cortex elicited either by electrical or by potassium induced depolarization (274; F. Pelayo, M. L. Dubocovich, and S. Z. Langer, unpublished observations).

VIII. Other Presynaptic Receptors on Peripheral Noradrenergic Nerve Endings

A. In the isolated nerve-muscle preparation of the cat nictitating membrane, exogenous GABA in concentrations up to 100 μM fails to modify the spontaneous outflow or the stimulation-evoked release of labelled norepinephrine (7). Yet in slices of the rat occipital cortex prelabelled with ^{3}H-norepinephrine, exogenous GABA produces a concentration-dependent increase in the stimulation-evoked release of the labelled neurotransmitter (7). This facilitatory effect of GABA on central noradrenergic neurotransmission is not blocked by either bicuculline or picrotoxin (7). Under these conditions, exogenous GABA fails to enhance the calcium-independent release of ^{3}H-norepinephrine elicited by tyramine in slices of the rat occipital cortex (7). The nature of the GABA receptor mediating the central presynaptic facilitation of norepinephrine release remains to be elucidated. In studies on the posterior hypothalamus of the cat with a push-pull cannula it was reported that GABA increases the release of norepinephrine (222). GABA was also reported to increase the turnover of norepinephrine in several regions of the brain (20).

B. Adenosine and adenine nucleotides have been found to inhibit peripheral noradrenergic neurotransmission in various tissues of the rat, rabbit, and dog (74, 83, 119, 268, 281). The inhibition by adenosine is more pronounced at low frequencies of stimulation (88). Adenosine does not inhibit noradrenergic neurotransmission in the cat nictitating membrane (200), spleen (213), and heart (287). It appears that, in contrast to other species, the cat may lack presynaptic inhibitory adenosine receptors on peripheral noradrenergic nerve terminals.

It is well established that nerve activity is accompanied by the release of purines (25, 87, 199, 293). In general the purines recovered after nerve stimulation are adenosine and its catabolites, inosine and hypoxanthine. It has been suggested that the purine nucleosides found after nerve stimulation reflect the release of intact ATP, which is then rapidly metabolized (269). The release of purines may also originate after the intracellular breakdown of ATP.

ATP is present in the catecholamine granules of the adrenal medulla and also of peripheral nerves. While the release of ATP in parallel with catecholamines has been demonstrated in the adrenal medulla (55), the evidence for exocytotic release of ATP from nerve endings is far less convincing (265). In fact, it is well known that contraction of smooth muscle leads to purine release that is of postsynaptic origin (87, 199).

The presynaptic inhibitory effects of adenosine are not mediated through prostaglandins or through presynaptic α-adrenoceptors (88).

Theophylline, which blocks the receptors mediating the effects of adenosine, antagonizes the presynaptic inhibition by adenosine of noradrenergic neurotransmission, and increases per se the stimulation-evoked release of the neurotransmitter. It is therefore possible that the facilitation of the release of norepinephrine observed with theophylline and other methylxanthines could reflect antagonism of adenosine rather than inhibition of phosphodiesterase (84).

Since nerve activity is associated with the release of adenine compounds and their metabolites (predominantly from postsynaptic structures) it is possible that adenosine may be involved in a transsynaptic physiological modulation of the release of norepinephrine in the peripheral nervous system. The question whether adenosine modulates noradrenergic neurotransmission in the central nervous system as it does in the periphery awaits clarification (88).

C. The presence of presynaptic inhibitory 5-HT receptors on the noradrenergic nerve terminals of vascular tissues has been reported (208). Presynaptic inhibitory histamine receptors may also be present on some noradrenergic nerve terminals of the peripheral sympathetic system (209). So far there is no evidence for interactions between either serotonin or histamine on norepinephrine release in the central nervous system.

D. Presynaptic facilitatory angiotensin receptors have been described in peripheral noradrenergic nerve terminals of several tissues in the rabbit and the dog (29, 92, 256, 309, 310). In the rabbit heart low concentrations of angiotensin II (1 and 10 nM) can produce up to 4-fold increases of ^{3}H-norepinephrine release during nerve stimulation (92).

Recently it was reported that presynaptic facilitatory angiotensin receptors are also present in the rabbit hypothalamus (91). The facilitation of the potassium-evoked release of ^{3}H-norepinephrine in the rabbit hypothalamus is blocked by low concentrations of saralasin (91). Captopril, which inhibits the angiotensin converting enzyme, may reduce sympathetic tone through the decrease in the circulating levels and the local formation of angiotensin II. This effect, by reducing norepinephrine output may contribute to the antihypertensive effects of captopril and in general for other drugs that inhibit angiotensin converting enzyme.

Facilitatory presynaptic angiotensin receptors apparently are not present in tissues of the rat or the cat. These results stress once again the tissue and species variation in presynaptic modulation of transmitter release. One should therefore avoid extrapolating and generalizing from studies of presynaptic modulation of transmitter release carried out in a given tissue and only in a single species.

IX. Negative Feedback Regulation of the Release of Dopamine through Presynaptic Inhibitory Dopamine Receptors

The first suggestion for the presence of presynaptic inhibitory dopamine receptors on the dopaminergic nerve endings of the rat striatum was based on the inhibition

by apomorphine and the enhancement by chlorpromazine of the stimulation-evoked release of ^{3}H-dopamine (77). However, subsequent studies failed to reproduce these results (53, 240) and the whole question of the presence of presynaptic dopamine receptors that modulate the release of the transmitter was challenged (227, 228). It was suggested that, in contrast to the noradrenergic system, where presynaptic α_2-adrenoceptors inhibit the release of norepinephrine, in the dopaminergic system, presynaptic dopamine receptors inhibit the synthesis but not the release of the neurotransmitter (228).

There is considerable evidence that dopamine receptors possible located presynaptically are involved in the regulation of the biosynthesis of dopamine (145, 146, 288). Agonists acting on presynaptic dopamine receptors like apomorphine, piribedil, and bromocriptine decrease the synthesis of the neurotransmitter and this effect is blocked by neuroleptics of both the butyrophenone or the phenothiazine type.

Convincing experiments for the presence of presynaptic inhibitory dopamine receptors that regulate the release of the transmitter through a negative feedback mechanism were reported in superfused slices of the rabbit caudate (255). As already demonstrated for the noradrenergic neurons, the presynaptic modulation of dopamine release in the rabbit caudate nucleus operates for the calcium-dependent release of dopamine elicited by electrical stimulation but not for the calcium-independent release elicited by either amphetamine or tyramine (142). Results in favour of the presynaptic location of dopamine receptors modulating the release of ^{3}H-dopamine in the rabbit caudate nucleus were obtained recently by Jackisch et al. (136). These authors found that the inhibition by apomorphine and the enhancement by haloperidol of the release of ^{3}H-dopamine evoked by potassium are not affected in the presence of tetrodotoxin, suggesting that interneurons are not mediating the effects of these drugs. The stereoselectivity of the presynaptic dopamine receptors in the rabbit caudate nucleus was recently shown for the antagonists butaclamol and sulpiride (9).

There is as yet not enough information as to whether the presynaptic inhibitory dopamine receptors are similar to or different from the postsynaptic dopamine receptors. It appears, however, that the presynaptic inhibitory receptors might be of the DA_2 type (144) because sulpiride blocks selectively the inhibitory effects of apomorphine on ^{3}H-dopamine release in the rabbit caudate nucleus (142). Recent results indicate that presynaptic inhibitory autoreceptors for dopamine are also present in the cat caudate nucleus (10).

Evidence in support of the presence of presynaptic inhibitory dopamine autoreceptors regulating the release of the neurotransmitter has also been obtained under in vivo conditions (2, 16, 191).

In the dopaminergic neuron, transmitter release can also be elicited from dendrites and this process is also calcium-dependent (8, 93). While it is possible that dopamine released from dendrites can act on inhibitory dopamine autoreceptors on the dopaminergic cell body, it is not yet clear as to whether the dendritic release of dopamine can modify the resting or stimulation-evoked release of GABA in the substantia nigra.

A question that may be of therapeutic relevance concerns the possible changes in sensitivity of presynaptic inhibitory dopamine autoreceptors under conditions of chronic administration of neuroleptics that are extensively used in the treatment of schizophrenia.

Receptor binding studies with radioactive ligands have not yet clarified the location of dopamine receptors modulating transmitter release and synthesis in the rat striatum. A decrease in ^{3}H-apomorphine binding after degeneration of dopaminergic nerve terminals with 6-hydroxydopamine has been reported by Nagy et al. (216). On the other hand, Creese and Snyder (41) reported an increase in ^{3}H-apomorphine binding under similar experimental conditions. The binding of ^{3}H-spiroperidol increases after chemical denervation of the rat striatum with 6-hydroxydopamine (40, 41).

X. Other Presynaptic Receptor Systems on Central Dopaminergic Nerve Endings

A. As already discussed, the reported inhibition of the stimulation-evoked ^{3}H-dopamine release from the striatum by opiate receptor agonists (35, 194) was not confirmed in subsequent studies (6). It therefore appears that presynaptic opiate receptors modulate the release of norepinephrine but not that of dopamine in the central nervous system. Recent experiments in which the effects of opiate agonists on the release of dopamine were studied in the cat under in vivo conditions failed to demonstrate an inhibition of release with morphine or other opiate receptor agonists (J. Glowinski and M. F. Giorguieff, personal communication). In fact these authors find an increase in dopamine release by opiate receptor agonists.

B. Nicotine enhances the release of ^{3}H-dopamine from rat striatal slices and this effect is blocked by hexamethonium (294). Exogenous acetylcholine increases the outflow of newly synthetized ^{3}H-dopamine and this effect appears to be partly sensitive to pempidine and mecamylamine (19, 96, 97). There is also a muscarinic facilitatory effect on the release of dopamine from the striatum because the enhancement of ^{3}H-dopamine release induced by oxotremorine is blocked by atropine (96). The i.v. administration of oxotremorine enhances the outflow of dopamine into push-pull cannula superfusates of the cat caudate nucleus (15, 191).

C. Exogenous GABA facilitates the stimulation-evoked release of ^{3}H-dopamine from the rat striatum (266). These in vitro effects are similar in their characteristics to the facilitation by GABA of the release of ^{3}H-norepinephrine from the rat occipital cortex (7). Yet, in the substantia nigra GABA has an inhibitory effect on

the firing of the dopaminergic neurons and this effect is blocked by iontophoretically applied picrotoxin (44). In addition, the systemic administration of picrotoxin or bicuculline enhances the outflow of endogenous dopamine as well as that of recently synthesized ^{3}H-dopamine in superfusates of the cat caudate nucleus (15, 39). This difference between in vitro and in vivo studies on the interactions between neurotransmitters points to the complexity of the neuronal networks and synapses in the central nervous system and the role of interneurons in these interactions. A recent review by Bartholini (14) discusses the interactions of the striatal dopaminergic, cholinergic, and gabaergic neurons.

D. There is as yet very little information about interactions between other neurotransmitters and the stimulation-evoked release of dopamine. The possible interactions of serotonin, substance P, and some amino acids on dopaminergic neurotransmission require additional studies.

The involvement of presynaptic receptor mechanisms in local neurotransmitter interactions in the central nervous system continues to be an area of growing interest.

XI. Possible Involvement of α_2-Adrenoceptors in the Presynaptic Modulation of the Release of Epinephrine in the Central Nervous System

In the superfused rat nucleus tractus solitarius prelabelled with ^{3}H-epinephrine, clonidine reduces the potassium-evoked release of the labelled neurotransmitter while yohimbine facilitates this release (237). In support of the view that α_2-adrenoceptors modulate the release of epinephrine in the central nervous system, it was demonstrated under in vivo conditions that clonidine reduces and yohimbine increases the turnover of endogenous epinephrine in the rat hypothalamus in the cell groups A_1 and A_2 (237). While these studies do not prove the presynaptic location of the α_2-adrenoceptor involved in the modulation of the release of epinephrine, it is possible that the effects of α_2-adrenoceptor agonists on epinephrine release in the central nervous system are relevant to their cardiovascular effects.

When studied in the presence of cocaine, epinephrine is more potent than norepinephrine in reducing the action potential-evoked release of ^{3}H-norepinephrine in the rabbit hypothalamus (A. M. Galzin, M. L. Dubocovich, and S. Z. Langer, unpublished observations). The interactions between epinephrine and norepinephrine at the level of transmitter release in the central nervous system may be of physiological as well as pharmacological importance.

XII. Possible Therapeutic Potential of Presynaptic Receptors

Presynaptic receptors could be considered as potential targets for the development of selective agonists or antagonists. Such agents could either reduce or enhance the release of the neurotransmitter while having small or negligible effects on the corresponding postsynaptic receptors. Yet, when one examines table 2 it is clear that even an α_2-selective adrenoceptor agonist is likely to have postsynaptic effects, particularly at the sites where postsynaptic α_2-adrenoceptors are known to be present.

It is possible that presynaptic receptors are involved in the mechanism of action of the following drugs.

A. Clonidine is an imidazoline that was originally designed as a nasal vasoconstrictor because of its ability to stimulate α-adrenoceptors on vascular smooth muscle (99). The accidental discovery of its antihypertensive and bradycardic effects has started a new chapter on the role of central α-adrenoceptors in the control of cardiovascular function. The reader is referred to several comprehensive reviews on the pharmacology of clonidine (148, 239, 278).

The central receptor involved in the antihypertensive and bradycardic effects of clonidine can be defined pharmacologically as an α_2-adrenoceptor and it appears to be located postsynaptically (127). Clonidine also activates presynaptic inhibitory α_2-adrenoceptors on central and peripheral noradrenergic nerve endings thus inhibiting norepinephrine release (181). These peripheral presynaptic effects are likely to contribute to the bradycardic effects of clonidine (34). The presynaptic cardiac effects of clonidine are longer lasting than its postsynaptic effects on vascular smooth muscle (31).

Clonidine has also been used successfully to antagonize the acute opiate withdrawal symptoms in man (98). This beneficial effect of clonidine appears to be related to the inhibition of central noradrenergic firing by acting on somatodendritic and presynaptic inhibitory α_2-adrenoceptors to reduce the output of norepinephrine (fig. 2).

B. The antihypertensive effects of α-methyldopa are related to the formation of α-methyl norepinephrine, a preferential α_2-adrenoceptor agonist in the central nervous system (125). In the periphery, α-methylnorepinephrine can also stimulate peripheral presynaptic α_2-adrenoceptors leading to a decrease in norepinephrine release and a reduction of sympathetic tone (169).

C. Prazosin is a new antihypertensive agent, the mechanism of action of which involves a selective blockade of postsynaptic α_1-adrenoceptors. The absence of tachycardia when prazosin is administered to man represents a therapeutic advantage (22). The selectivitiy of prazosin in blocking α_1-adrenoceptors may also explain why this drug does not increase renin release when administered in doses that decrease blood pressure (143, 205). The absence of blockade of presynaptic α_2-adrenoceptors in the heart may explain the lack of tachycardia in response to the fall in blood pressure produced by prazosin. Yet other mechanisms can be involved in the absence of tachycardia, such as changes in baroreceptor sensitivity (27) and absence of right atrial pressure increases. The selective blockade by prazosin of vascular responses elic-

ited by neuronally released norepinephrine may explain the effectiveness of this drug in reducing peripheral resistance and blood pressure.

D. β-Adrenoceptor blocking agents are extensively used in the treatment of hypertension (207). It is possible that blockade of presynaptic facilitatory β-adrenoceptors may contribute to the antihypertensive effects of these drugs by decreasing the release of norepinephrine from peripheral noradrenergic nerve endings.

E. The antidepressant effects of mianserin could be partly related to the fact that this drug blocks presynaptic α_2-adrenoceptors in the central nervous system thus increasing the release of norepinephrine. Central presynaptic α_2-adrenoceptors might also be involved in the mechanism of action of tricyclic antidepressants. The chronic administration of these drugs, which inhibit neuronal uptake of norepinephrine, leads to the development of subsensitivity of the release-modulating presynaptic α_2-adrenoceptors. Under these conditions neuronal release of norepinephrine in the central nervous system would be enhanced. The time required for the development of subsensitivity of presynaptic α_2-adrenoceptors during treatment with tricyclic antidepressants may explain the lag period required for the antidepressant effects of these drugs in man.

F. Low doses of apomorphine have been reported to improve the psychotic symptoms in schizophrenic patients (271). These results could be partly related to the activation by apomorphine of the presynaptic inhibitory dopamine autoreceptors leading to a decrease in the synthesis and release of dopamine.

It is also possible that presynaptic receptors might be involved in the production of side effects during treatment with certain drugs. One such example is the rebound hypertension after acute withdrawal after chronic administration of clonidine. The rebound hypertension and tachycardia are accompanied by increased catecholamine excretion (109, 233, 299). While the mechanism of this syndrome is not yet fully understood, it may be due to a clonidine-induced subsensitivity of α_2-adrenoceptors both in the periphery and in the central nervous system.

The involvement of α_2-adrenoceptors in the production of sedation and dry mouth by clonidine is suggested by many pharmacological studies. In chicks, the sleep-inducing effect of clonidine is antagonized only by preferential α_2-adrenoceptor blocking agents and it remains unaffected by prazosin (33). This effect of clonidine may involve either presynaptic or postsynaptic central α_2-adrenoceptors. Clonidine reduces submaxillary salivation evoked by peripheral parasympathetic stimulation in the cat (100). This effect is probably mediated through the activation of presynaptic α_2-adrenoceptors that inhibit cholinergic transmission.

The orthostatic hypotension after treatment with L-dopa and dopamine receptor agonists like bromocriptine may be related to the activation of presynaptic inhibitory dopamine receptors on peripheral noradrenergic nerve endings.

It is possible that the growing interest in presynaptic receptors may lead to the development of selective presynaptic receptor agonists or antagonists with new and useful therapeutic properties.

XIII. Summary

During norepinephrine release elicited by the arrival of nerve impulses, the neurotransmitter interacts with specific receptors (α_1-, β_1-, or β_2-adrenoceptors) located in the membrane of the postsynaptic cell to trigger the response of the effector organ. Until a few years ago, it was thought that the role of noradrenergic nerve terminals in neurotransmission is concerned exclusively with the synthesis, storage, release, and inactivation of norepinephrine and there were no indications that receptors might also be present in the presynaptic membrane.

During the last decade, evidence has accumulated in favour of the view that, in addition to the classical postsynaptic adrenoceptors that mediate the responses of the effector organ, there are also receptors located on the noradrenergic nerve terminals. These presynaptic receptors are involved in the modulation of the calcium-dependent, action-potential-evoked release of norepinephrine in the peripheral as well as in the central nervous system.

Presynaptic inhibitory α-adrenoceptors are involved in the regulation of the release of norepinephrine through a negative feedback mechanism mediated by the neurone's own transmitter. α-Adrenoceptor agonists inhibit the release of norepinephrine during nerve stimulation, while α-adrenoceptor blocking agents enhance the stimulation-evoked release of the neurotransmitter. These results have been obtained both in vitro and in vivo.

There are pharmacological differences between the postsynaptic α-adrenoceptors that mediate the response of the effector organ and the presynaptic inhibitory α-adrenoceptors that modulate the release of norepinephrine during nerve stimulation. The subclassification of α-adrenoceptors into α_1- and α_2-types is based on differences in relative affinities for a range of α-adrenoceptor agonist and antagonist drugs. The term α_1-adrenoceptor is used for a receptor that is preferentially stimulated by phenylephrine and blocked by prazosin, whereas α_2-adrenoceptor is reserved for those preferentially stimulated by guanabenz or clonidine and blocked by rauwolscine or yohimbine.

The presynaptic inhibitory α-adrenoceptors in the peripheral and in the central nervous system have the pharmacological characteristics of the α_2-adrenoceptors.

Presynaptic inhibitory autoreceptors appear to be involved in the modulation of the release of dopamine and of epinephrine in the central nervous system. A short negative feedback mechanism similar to that for norepinephrine appears to regulate the stimulation-evoked

release of dopamine and epinephrine in central neurons.

In addition to presynaptic autoreceptors through which the transmitter can modulate its own release, a real mosaic of receptors is present on noradrenergic nerve endings. These presynaptic receptors can be stimulated by blood-borne substances, by other neurotransmitters released from neighbouring nerve terminals, or by locally formed endogenous compounds like adenosine or prostaglandins to modulate transmitter release.

Several presynaptic receptors are linked to the inhibition of norepinephrine release during nerve stimulation: a) muscarinic receptors, b) dopamine receptors, c) opiate receptors, d) adenosine receptors, and e) prostaglandins of the E series. Presynaptic receptors involved in the facilitation of the stimulation-evoked release of norepinephrine include β-adrenoceptors and angiotensin II receptors.

Local transmitter interactions through presynaptic receptors are probably involved in the modulation of noradrenergic and dopaminergic neurotransmission in the central nervous system. Opiate receptor agonists inhibit the stimulation-evoked release of norepinephrine but not of dopamine. GABA facilitates the stimulation-evoked release of both norepinephrine and dopamine.

Many drugs currently in use belong to the category of classical postsynaptic receptor agonists or antagonists. Most of these agents have different degrees of affinities for the corresponding presynaptic release-modulating receptor. The overall pharmacological and therapeutic effects of these drugs under acute as well as under chronic administration depend on their presynaptic as well as their postsynaptic effects.

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