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COMMENTARY

PRESYNAPTIC RECEPTOR SYSTEMS IN CATECHOLAMINERGIC TRANSMISSION

KLAUS STARKE, HANS D. TAUBE and EVELYN BOROWSKI
Institute of Pharmacology, University of Essen, Hufelandstrasse 55, D-4300 Essen, West Germany

At least three groups of receptors are essential in chemical neurotransmission (Fig. 1). Firstly, receptors on soma and dendrites of the innervating neurone determine the frequency of the impulses carried down to the axon terminals. Secondly, postsynaptic receptors recognize the transmitter and mediate the response of the innervated cell. While these classical receptors would suffice to make the system work, there is evidence that a third group is located on the nerve endings and serves to control the release per pulse and in some cases the synthesis of the transmitter. These presynaptic receptors have previously been inferred from electrophysiologic observations on non-catecholaminergic neurones [1 pp. 122 and 220, 2, 3 p. 495]. More recently, extensive, mainly biochemical research has led to the conclusion that noradrenergic and dopaminergic nerve endings are endowed with a variety of release- or synthesis-modulating receptors. Only receptors for substances naturally occurring in the body are discussed in this commentary. The emphasis will be on current studies and open questions. Therefore, much of the fundamental work from which present concepts proceeded has been omitted. For details, the reader should consult other reviews [4–13].

1. *Presynaptic receptors on noradrenergic neurones*

1.1. *Angiotensin receptors.* Angiotensin (II) at low concentrations (10^{-10} M and higher) increases the stimulation-evoked overflow* of noradrenaline from some, but not all tissues (Table 1). The effect is prevented by antagonists such as saralasin and hence probably mediated by specific presynaptic angiotensin receptors [17, 20]. The increase of overflow reflects an increase in the amount of transmitter released* per nerve impulse. In agreement with this view, angiotensin also enhances the stimulation-evoked overflow of dopamine-β-hydroxylase [56], a constituent of noradrenaline storage vesicles that is secreted along with noradrenaline in the process of exocytosis.

Angiotensin has been reported to inhibit the neuronal uptake of noradrenaline (e.g. [57]). If so, this might contribute to the increase of the stimulation-evoked overflow. However, research in several laboratories failed to confirm inhibition of uptake by reasonably low concentrations (up to 10^{-6} M; see [58]). A strong additional argument can be derived from the effect of angiotensin on noradrenaline metabolism. Part of the noradrenaline released upon stimulation is metabolised to 3,4-dihydroxyphenylglycol (DOPEG). The transformation probably takes place intraneuronally after re-uptake. Therefore, drugs such as cocaine which impair re-uptake diminish the stimulation-evoked overflow of DOPEG (but not basal outflow, which results from degradation of noradrenaline leaking directly from the granules into the neuronal cytoplasm [59]). Figure 2 demonstrates that in rabbit pulmonary artery the stimulation-evoked overflow of DOPEG is enhanced rather than reduced by angiotensin. On the other hand, it is virtually abolished by subsequent addition of cocaine. Either drug increases the stimulation-evoked overflow of normetanephrine, which mainly originates from extraneuronal *O*-methylation [61]. The results indicate that angiotensin-induced facilitation of release is not accompanied by any inhibition of noradrenaline uptake.

Angiotensin promotes the formation of noradrenaline from tyrosine or dopamine in some isolated tissues, possibly by stimulating the synthesis of tyrosine hydroxylase and dopamine-β-hydroxylase at the translational level [62–64]. The effect is not secondary to facilitation of release, since it occurs even in the absence of impulses. Conversely, facilitation of release

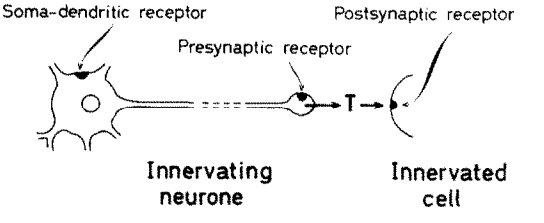

Fig. 1. Receptors involved in chemical neurotransmission. T, transmitter substance.

* The term "release" is used for the passage of noradrenaline or dopamine across the neuronal membrane into the extracellular space. Unless further defined it indicates secretion evoked by orthodromic action potentials, triggered for instance by electrical stimulation. "Overflow" describes the diffusion of noradrenaline, dopamine, or their metabolites from the tissue into the perfusion or incubation fluid. Release elicited by electrical stimulation gives rise to "stimulation-evoked overflow". Only the fraction of released transmitter that escapes uptake into extraneuronal cells or back into the neurone (and subsequent storage or degradation) appears in the overflow and can be measured. In most cases there is good evidence that effects of presynaptic modulators on the stimulation-evoked *overflow* are due to changes in *release* rather than changes of uptake or biotransformation.

Table 1. Effect of presynaptic agonists on transmitter release evoked by electrical stimulation of noradrenergic neurones

Species	Tissue	Angiotensin II	Muscarinic agonists	PGE_1, PGE_2	α-Adrenergic agonists	Dopaminergic agonists	β-Adrenergic agonists	Narcotic analgesics
Dog	Blood vessels	+ [14]	− [21]		− [33]			
Cat	Spleen	0 [15]	− [22]	− [26, 27]	− [34, 35]	− [48]	+ [35]	
	Nictitating membrane	0 [16]	−*	0 [28]	− [36]	− [36, 48]	+ [28]	− [52]
Rat	Brain cortex	0 [17]	0 [17]	− [17, 29]	− [6, 17, 37]	0 [17]	0 [17]	− [53, 54]
Mouse	Vas deferens	0 [18]			− [38]			− [18]
Rabbit	Heart	+ [19]	− [23]	− [26]	− [39, 40]			0 [55]
	Pulmonary artery	+ [17, 20]	− [17, 20]	− [17, 20]	− [17, 41, 42]	0 [17, 20]	0 [17, 20]	0 [20]
	Ear artery		− [24]	− [30]	− [43, 44]	− [43, 44]		
	Vas deferens	+ [18]						0 [18]
Guinea pig	Heart				− [43]	0 [43]	+ [49]	
	Vas deferens		− [25]	− [31]	− [45, 46]	0 [46]	+ [46]	
Man	Blood vessels			− [32]	− [32, 47]	− [47]	+ [50, 51]	

+ Increase, − decrease, 0 no change. Results of experiments in which the stimulation-evoked overflow of noradrenaline, or of labelled compounds after treatment with radioactive noradrenaline, was determined. Experiments in which drug concentrations or stimulation frequency seem inappropriate are not included. * S. Z. Langer, personal communication.

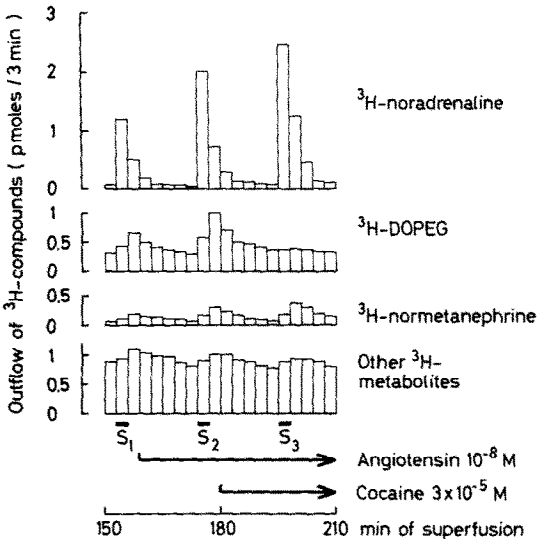

Fig. 2. Effect of angiotensin and cocaine on metabolism of [^{3}H]noradrenaline in rabbit pulmonary artery. Artery strips were preincubated with 10^{-6} M (−)[^{3}H]noradrenaline and then superfused with fresh physiological salt solution. The superfusate was collected in 3-min samples and analysed for [^{3}H]noradrenaline and ^{3}H-metabolites according to Graefe *et al.* [60]. The sympathetic nerves were stimulated by an electrical field three times for 3 min each at 4 Hz (S_1 – S_3; cf. [41]). From top to bottom: outflow in pmoles/3 min of [^{3}H]noradrenaline, [^{3}H]3,4-dihydroxyphenylglycol ([^{3}H]DOPEG), [^{3}H]normetanephrine, sum of other ^{3}H-metabolites (3,4-dihydroxymandelic acid, 3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxyphenylglycol). Means of three experiments. Standard errors were 1–16 per cent of corresponding means. In control experiments without angiotensin and cocaine, overflows elicited by S_1, S_2 and S_3 were similar.

is not due to enhanced biosynthesis, since the release of exogenous, previously stored noradrenaline is also increased (cf. Fig. 2). It is not known how far presynaptic receptors and biochemical events mediating the two effects are identical. Surprisingly, angiotensin fails to augment tyrosine hydroxylation in two tissues where it does facilitate release (rabbit coeliac artery and vas deferens [18, 62, 65]). If both are enhanced, the effects may cooperate. Increased biosynthesis may replenish the pool from which release is facilitated.

1.2. *Acetylcholine receptors.* Acetylcholine exerts two main effects on noradrenergic nerve endings. By activation of presynaptic nicotine receptors, it causes depolarization and a calcium-dependent release of noradrenaline. By activation of presynaptic muscarine receptors, it reduces the quantum secreted per nerve impulse. The nicotinic effect requires high concentrations which probably do not occur *in vivo* (e.g. threshold concentration in rabbit heart about 6×10^{-5} M [66]); for the muscarinic effect lower concentrations are sufficient (e.g. in rabbit heart about 6×10^{-8} M [23]). Muscarinic agonists depress the release of noradrenaline in most, but not all tissues (Table 1). Fozard and Muscholl [67] compared effects of nine muscarinic agonists on atrial tension development, ventricular rate, and noradrenaline release in the rabbit heart. They concluded that pre- and postsynaptic muscarine receptors are similar.

Some recent findings do not fit into this concept of two presynaptic cholinergic receptors with distinct functions. In perfused rabbit ear arteries, acetylcholine at 10^{-11}–10^{-10} M enhances both vasoconstriction and transmitter overflow evoked by sympathetic nerve stimulation, presumably through facilitation of release [24]. These concentrations are far below those needed for the muscarinic inhibitory and, of course, the nicotinic releasing effect. The increase is not affected by either atropine or hexamethonium. Similar results were obtained in rabbit atria [68]. In contrast, the same concentrations of acetylcholine had no effect in perfused rabbit hearts [8], rabbit pulmonary artery strips [20], and guinea pig atria [68]. More work is necessary to clarify the nature of this—apparently neither nicotinic nor muscarinic—facilitation.

1.3. *Prostaglandin receptors.* Prostaglandins of the E series diminish the per pulse release of noradrenaline in most, but not all tissues (Table 1). Few studies have been performed with other prostaglandins. In the rabbit pulmonary artery, $PGF_{2\alpha}$ and PGB_2 also reduce release, but only at high concentrations [20].

Indirect evidence suggests that certain prostaglandins may exert a facilitatory presynaptic effect in some organs. In the hind paw of the dog, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ [69, 70] as well as PGA_2 and PGB_2 [71] enhance the vasoconstrictor response to sympathetic nerve stimulation, but at identical doses leave the response to intra-arterial noradrenaline unchanged (cf. [72]). The authors propose that in these cases the prostaglandins augment noradrenaline release. However, attempts to confirm such an effect by determination of the stimulation-evoked overflow of noradrenaline have hitherto been unsuccessful. In rabbit pulmonary artery $PGF_{2\alpha}$, a promising candidate for facilitation, caused pure inhibition [20]. Facilitation would raise interesting questions. Upon sympathetic nerve impulses, endogenous prostaglandins are formed and depress further release of noradrenaline (see 6.). Facilitation might occur when an exogenous prostaglandin with low intrinsic inhibitory activity competes with endogenous prostaglandins for their presynaptic receptors. Alternatively, prostaglandins might possess intrinsic facilitatory activity in some tissues. If so, what is the basis for opposite effects of one prostaglandin in different tissues?

1.4. *α-Adrenoceptors.* α-Receptors have been found on all noradrenergic neurones tested (Table 1). Their activation leads to a decrease of the amount of transmitter released per impulse. Presynaptic α-receptors resemble classical postsynaptic ones, since the order of presynaptic potency of several β-phenylethylamines agrees with their order of postsynaptic potency [34, 42, 46]. Yet the agreement is not perfect. It has been repeatedly shown that within a given tissue the relative potencies of agonists on pre- and postsynaptic α-receptors may differ. For instance, in perfused rabbit hearts low concentrations of phenylephrine cause an α-adrenergic increase of contractile force, but fail to inhibit noradrenaline release; in contrast, low concentrations of oxymetazoline or naphazoline are devoid of inotropic effects, but markedly depress release [39]. Similar results were obtained in rabbit pulmonary artery strips. Methoxamine and phenylephrine preferentially activate postsynaptic α-receptors and thereby elicit smooth muscle contrac-

tion. In contrast, oxymetazoline, clonidine, α-methylnoradrenaline and tramazoline preferentially activate presynaptic α-receptors. For noradrenaline, adrenaline and naphazoline post- and presynaptic potencies are similar [42]. Experiments in perfused rabbit ear arteries [73, 74] and pithed rats [75] further underscore the possibility that certain pre- and certain postsynaptic α-adrenoceptors differ in structure and, hence, affinity to drugs.

The significance of these findings is difficult to evaluate. It would no doubt be premature to consider presynaptic α-receptors as one structurally homogeneous group which can be confronted with postsynaptic α-receptors as the second homogeneous group. There are indications that postsynaptic α-receptors are not all of a single type [76, 77]. The same may be true for presynaptic α-receptors. It cannot be excluded at present that the differences between pre- and postsynaptic α-receptors of one tissue are no greater than the differences between postsynaptic α-receptors of various tissues. Available data suggest that perhaps agonists related to clonidine [42, 73, 74] and xylazine [75] have a general preference for the presynaptic site. Hopefully, studies on further tissues will reveal whether presynaptic α-receptors on the one hand, and postsynaptic α-receptors on the other hand, can indeed be considered as two major subclasses with respect to drug sensitivity.

1.5. *Dopamine receptors.* Dopamine acts as an agonist on postsynaptic α-adrenoceptors, being 1/10–1/100 as potent as noradrenaline [77]. On the other hand, it is approximately equipotent with noradrenaline in reducing the per pulse release of noradrenaline in some tissues [36, 43, 44, 47, 48]. This is not another example for differences between pre- and postsynaptic α-adrenoceptors. Rather, some noradrenergic neurones appear to possess a distinct set of presynaptic dopamine receptors, similar to the dopamine receptors in the central nervous system [78]. Like the latter, and unlike α-adrenoceptors, presynaptic dopamine receptors are activated by apomorphine and blocked by low doses of neuroleptic drugs such as chlorpromazine [36, 79]. Presynaptic dopamine receptors have been found on some, but not all noradrenergic neurones (Table 1). Activation of dopamine receptors on *dopaminergic* nerve terminals reduces tyrosine hydroxylase activity even after impulse flow is abolished (see 2.1.). It would be of interest to know whether dopaminergic agonists also slow transmitter biosynthesis in noradrenergic nerve endings.

1.6. *β-Adrenoceptors.* β-Adrenergic agonists increase the per pulse release of noradrenaline in some, but not all tissues (Table 1). The facilitation is mediated by β-receptors, since it is antagonized by propranolol [35, 51]. Stjärne and Brundin [51] found that in human blood vessels selective β_1-receptor agonists did not enhance release whereas the β_2-receptor agonists terbutaline and salbutamol did. Moreover, the facilitatory effect of isoprenaline was not changed by the β_1 selective blocking agent practolol, but was counteracted by a β_2 selective antagonist. The authors concluded that the presynaptic receptors are of the β_2 type. On the other hand, Dahlöf *et al.* [80] suggested that in cat hind limb blood vessels the presynaptic receptors are β_1, since they were blocked by the β_1 selective blocking agent metoprolol. Interestingly, both facilitatory β- and inhibitory α-adrenoceptors may also occur on the chromaffin cells of the adrenal medulla [81–83].

1.7. *Morphine receptors.* Narcotic analgesics reduce the stimulation-evoked overflow of noradrenaline from some, but not all tissues, probably by inhibition of release. Cerebral noradrenergic neurones (of the rat) are among the sensitive ones (Table 1). The effect is mediated by specific morphine receptors, since it is stereospecific and prevented by narcotic antagonists. For some analgesics such as pethidine inhibition of release is difficult to demonstrate [54], because even at low concentrations they impair neuronal uptake of noradrenaline and thereby tend to *increase* the stimulation-evoked overflow [55]. The block of uptake is unrelated to morphine receptors. Morphine promotes the biosynthesis of prostaglandins [84]. It might be supposed that the inhibition of release is mediated by prostaglandins. However, inhibition persists after prostaglandin formation has been blocked by indometacin*.

Presynaptic opiate receptors are considered here because recent investigations indicate that narcotic analgesics are exogenous agonists acting on receptors meant for endogenous substances just as nicotine and muscarine are agonists related to acetylcholine. Two endogenous morphine receptor ligands have been isolated from the brain and identified as pentapeptides (methionine-enkephalin and leucine-enkephalin [85]). Figure 3 shows that methionine-enkephalin shares with morphine the ability to inhibit release from central noradrenergic neurones. The effect of enkephalin is antagonized by naloxone [86].

2. *Presynaptic receptors on dopaminergic neurones*

The lack of peripheral dopaminergic neurones has hampered studies on this transmitter. Presynaptic effects on central *noradrenergic* neurones always have a counterpart in effects on postganglionic sympathetic

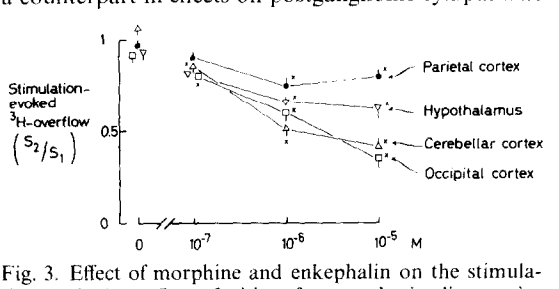

Fig. 3. Effect of morphine and enkephalin on the stimulation-evoked overflow of tritium from rat brain slices preincubated with [^{3}H]noradrenaline. Slices from various regions were preincubated with 10^{-7} M (−)[^{3}H]noradrenaline and then superfused with fresh physiological salt solution. The superfusate was collected in 5-min samples. The slices were stimulated by an electrical field twice for 2 min each at 3 Hz (S_1, S_2; cf. [53]). Morphine (●) or methionine-enkephalin (□ ▽ △) were added 20 min before S_2 at concentrations indicated on the abscissa. Ordinate, ratio between the overflow of tritiated compounds evoked by S_2 and that evoked by S_1. Stimulation-evoked overflow of tritium reflects noradrenaline release [53]. Each point is the mean ± S.E.M. of 8–34 experiments. Significant differences from controls: $^{\times}P < 0.02$ to < 0.001.

* H. D. Taube, H. Montel and K. Starke, unpublished.

neurones; the analogy supports the view that the modulators act directly on central noradrenaline-containing nerve terminals rather than on non-noradrenergic fibres which then influence the noradrenergic ones (see 3.). For central *dopaminergic* neurones such analogies do not exist. The question whether a drug affects dopamine release or biosynthesis directly (via receptors on the dopaminergic neurone) or indirectly (other neurones being intercalated) remains more difficult to answer.

2.1. *Dopamine receptors.* Dopamine receptors on dopaminergic nerve endings were considered by Farnebo and Hamberger [6, 37] when they found that apomorphine reduces the stimulation-evoked overflow of tritium from rat neostriatal slices preincubated with [^{3}H]dopamine, presumably by depressing release per pulse from the nigro-striatal dopaminergic fibres (see, however, [10 p. 106]). Activation of presynaptic dopamine receptors seems to have a second consequence, namely inhibition of tyrosine hydroxylation and thereby of dopamine synthesis. The inhibition of biosynthesis is not secondary to diminished impulse-evoked release, since dopaminergic agonists reduce striatal tyrosine hydroxylation even when there is no impulse flow, as for instance after the nigro-striatal axons have been cut [87], or after impulse traffic has been suppressed by γ-butyrolacton [88], or in striatal synaptosomes [78, 89] or slices [90, 91]. Conversely, inhibition of release is not secondary to reduction in synthesis, since release of exogenous, previously stored dopamine is also depressed [37] and since drug effects on release and synthesis have a different time-course [91]. Apparently, the decreases of biosynthesis and release are largely independent.

Mechanisms involved in presynaptic dopaminergic inhibition of tyrosine hydroxylation are the subject of intensive investigation. In agreement with a receptor-mediated effect, the inhibition is reversed by neuroleptic drugs [87, 89, 91]. Activation of presynaptic dopamine receptors appears to lead to an alteration in the kinetics of tyrosine hydroxylase, above all to a large increase of the enzyme's affinity for the end-product inhibitor, dopamine [92]. In other words, presynaptic, receptor-mediated inhibition of tyrosine hydroxylation might be due to greater sensitivity of the enzyme to end-product inhibition by intraneuronal dopamine. If so, how does receptor activation trigger the change in physical properties of tyrosine hydroxylase? Many effects of dopamine are thought to be mediated by an adenylate cyclase. However, cyclic AMP stimulates rather than inhibits striatal tyrosine hydroxylase and decreases rather than increases its sensitivity to dopamine [93, 94]. Therefore, the possibility that activation of a presynaptic adenylate cyclase is responsible for the effect of dopaminergic agonists can probably be ruled out. An alternative is that activation of presynaptic dopamine receptors increases the calcium permeability of the neuronal membrane so that more calcium enters into the cytoplasm; calcium inhibits striatal tyrosine hydroxylase and increases its affinity for dopamine [92]. On the other hand, a role of presynaptic adenylate cyclase in further factors contributing to the complex regulation of tyrosine hydroxylase activity seems quite possible [94, 95].

Pre- and postsynaptic dopamine receptors may differ in their sensitivity to drugs. It cannot be excluded that low doses of apomorphine preferentially activate the presynaptic receptor [96, 97].

2.2. *Other receptors.* Dopaminergic nerve endings appear to possess both nicotine and muscarine receptors. Activation of nicotine receptors elicits release of dopamine [98, 99]; activation of muscarine receptors reduces release evoked by electrical stimulation [100]. Muscarine receptors of noradrenergic nerve endings are more sensitive to acetylcholine than nicotine receptors (see 1.2.). For dopaminergic terminals differential sensitivity has not been observed; in rat striatal slices, 10^{-6} M acetylcholine is required for muscarinic inhibition, 10^{-7} M being ineffective [100]; on the other hand, 10^{-6} M acetylcholine also induces release via nicotine receptors [99]. Finally, dopaminergic neurones resemble noradrenergic ones in that release is depressed by prostaglandins E_1 and E_2 [10 p. 107, 29] as well as by morphine (release evoked by high potassium [101]), pointing to presynaptic prostaglandin and opiate receptors, respectively.

3. *Presynaptic receptors—a working hypothesis*

Many endogenous substances are able to modify the release per pulse and in some cases the biosynthesis of catecholamine transmitters. There is no doubt that the modulation is mediated by specific receptor systems; each is activated or blocked by structurally related drugs only. The receptors have been called prejunctional or presynaptic in order to distinguish them from those of the soma-dendritic part of the neurone and from those of the postsynaptic cell (Fig. 1). It is evident that the release- and synthesis-modulating receptors are not soma-dendritic receptors, since many experiments leading to their detection were performed on preparations devoid of nerve cell bodies and dendrites. On the other hand, the distinction between pre- and postsynaptic location is much less certain, in particular, as has been pointed out, for dopaminergic fibres. The presynaptic (as opposed to postsynaptic) location is a working hypothesis. What is its basis?

A working hypothesis should explain the observations as simply as possible. The most obvious site for a release- or synthesis-modulating agent to act is the releasing or synthesizing cell. Any view that the primary action takes place elsewhere requires additional assumptions, namely that a second signal is created at the primary site, and that the nerve ending can perceive the second, unknown signal. Economy favours the presynaptic receptor hypothesis.

Neurones with different morphologic and biochemical environment respond to presynaptic modulators in the same way. For instance, α-adrenergic agonists inhibit release from noradrenergic neurones supplying various smooth muscle organs, cardiac muscle, and brain areas. It cannot be excluded that in all these tissues the modulators primarily act upon some element outside the noradrenergic fibres. However, a direct action on the one ingredient common to the tissues, the nerve terminals themselves, appears less strained.

The soma and dendrites of postganglionic sympathetic neurones possess a host of receptor systems [102].

Moreover, there is evidence for dopamine receptors on central dopaminergic cell bodies and for α-adrenoceptors on central noradrenergic cell bodies [103]. Maybe the receptors are restricted to the soma-dendritic part. However, if a nerve cell has the ability to construct receptors and post-receptor reaction chains for its soma-dendritic region, it can easily do the same for its terminals. From a more general point of view the morphologic demonstration of axo-axonic synapses and the electrophysiologic phenomenon of presynaptic inhibition make the assumption of presynaptic receptors inevitable.

A working hypothesis should be amenable to trial. One type of experiment would be to search for presynaptic receptors on postganglionic sympathetic neurones grown in organ culture which contain no postsynaptic element [104]. The model might help to clarify whether the attribute "presynaptic" describes the location of release- and synthesis-modulating receptors correctly.

4. *Mechanism of modulation of release*

The mechanisms of presynaptic modulation of release are not known. Current thinking emphasizes alterations of the availability of calcium for release, since calcium is considered to be rate-limiting in electro-secretory coupling. Drugs might modify the influx of calcium from the extracellular space, or its efflux, or its distribution between intraneuronal compartments. However, the evidence briefly outlined below is suggestive rather than conclusive. Moreover, the steps leading to the presumed alteration of calcium availability remain uncertain.

(1) Several presynaptic modulators have been shown to affect calcium-dependent modes of release only, such as release evoked by electrical stimulation, high extracellular potassium concentrations, or nicotinic agonists, but not the calcium-independent small basal release or release evoked by the indirectly acting sympathomimetic amine tyramine (Table 2). However, selective inhibition of calcium-dependent secretion does not necessarily imply that the inhibitors reduce the amount of calcium available for electro-secretory coupling. They may just as well slow down another step in the calcium-mediated process which then becomes rate-limiting.—Dopamine release evoked by electrical stimulation as well as that evoked by high potassium can be modulated via presynaptic dopamine receptors (Table 2). This might suggest a dopaminergic *decrease* of intraneuronal calcium. On the other hand, in order to account for the presynaptic receptor-mediated inhibition of tyrosine hydroxylation a dopaminergic *increase* of intraneuronal calcium has been postulated [92]. This is another apparent paradox encountered in attempts to elucidate mechanisms controlling dopaminergic transmission (see 2.1.).

(2) Muscarinic agonists and prostaglandins cause more pronounced inhibition, the lower the external calcium concentration. An increase in calcium shifts presynaptic dose–inhibition curves to the right [105, 108]. The results are compatible with the view that the inhibitors reduce the availability of calcium for electro-secretory coupling; this reduction would be overcome by a rise of extracellular calcium. On the other hand, the interaction may be a functional antagonism [109] which does not allow us to draw conclusions concerning modes of action.

(3) The effect of most presynaptic modulators has been shown to decline with increasing frequency of stimulation. This is in accord with the calcium availability hypothesis if one assumes that during high frequency stimulation intraneuronal calcium rises to high levels [22, 110, 111] so that the "release receptors" for calcium become saturated. If so, a drug-induced change in calcium will markedly affect release at low frequency (when intraneuronal calcium is subsaturating), but negligibly affect release at high frequency (saturating intraneuronal calcium concentration). However, at present relations between frequency, intraneuronal calcium and release are hypothetical. Many unknown factors make conclusions from the frequency-dependence of presynaptic modulation hazardous.

An increase of cyclic AMP in noradrenergic nerve endings has been proposed as possible mode of

Table 2. Effect of presynaptic agonists on transmitter release evoked by different stimuli

Transmitter	Presynaptic agonist	Effect on basal release*	Effect on release evoked by: Electrical stimulation	High potassium	Nicotinic agonists	Tyramine
Noradrenaline	Angiotensin II	0 [19]	+†			0 [19]
	Muscarinic agonists	0 [21, 23]	−†	− [8, 105]	− [66]	0 [21, 23]
	PGE_1, PGE_2	0 [27]	−†	− [45, 106]	− [106]	0 [26, 106]
	α-Adrenergic agonists	0‡ [36, 39, 40]	−†	− [45, 107]		0 [107]
	Narcotic analgesics	0 [53, 54]	−†	− [86]		
Dopamine	Dopaminergic agonists		− [6, 37]	− [91]§		
	Muscarinic agonists		− [100]	− [100]	− [98]	

+ Increase, − decrease, 0 no change. "No change" refers to tissues where release by electrical stimulation or high potassium is sensitive to the respective agonists. * Release in the absence of electrical stimulation or releasing agents. † For references see Table 1. ‡ Many β-phenylethylamines release noradrenaline, perhaps by displacing intraneuronal transmitter. The effect is unrelated to presynaptic α-receptors; when it is prevented e.g. by cocaine, presynaptic α-adrenergic inhibition persists. § Indirect evidence; the dopamine receptor blocking agent fluphenazine enhances release.

β-adrenergic facilitation [28, 49]. In agreement with this idea, phosphodiesterase inhibitors and exogenous cyclic nucleotides enhance the stimulation-evoked overflow of both noradrenaline and dopamine-β-hydroxylase, though the increase is small [112, 113]. Of course further criteria have to be satisfied in order to establish this mechanism. An adenylate cyclase should be demonstrated in noradrenergic terminals which should respond to β-receptor agonists. Moreover, the increase in cyclic AMP should precede facilitation of release. These criteria are difficult to obtain in the case of nerves supplying a large tissue mass. Studies on noradrenergic cell bodies would be an alternative. It should be noted, however, that it is uncertain whether the adenylate cyclase of postganglionic sympathetic cell bodies is activated by β-adrenergic agonists [114, 115].

5. *Tissue differences*

Noradrenergic neurones are similar in morphology and biochemistry. All the more puzzling is the finding that they greatly differ in their sensitivity to presynaptic modulators (Table 1). Only one presynaptic receptor system, the α-adrenoceptor, has been found on all neurones studied. Negative results may reflect unsuited experimental conditions such as excessive calcium or stimulation at too high a frequency. However, the negative results listed in Table 1 were obtained at low frequencies and moderate calcium concentrations. It cannot be ruled out that in some tissues the noradrenergic nerve endings lack certain receptor mechanisms. Unfortunately, more direct ways to establish the *absence* of a receptor are not available.

Curves relating the release of noradrenaline per pulse to frequency of stimulation differ between tissues. For instance, per pulse release increases with increasing frequency in rabbit portal vein, but remains constant in mouse vas deferens (at near normal calcium [18]). It has been suggested that presynaptic sensitivity to angiotensin and morphine is associated with particular shapes of the frequency–release curve [18]. Though the basis for such an association is unknown, the possibility merits investigation.

6. *Physiologic significance*

Three groups of potential physiological functions of presynaptic receptor systems can be distinguished.

(1) Presynaptic receptors may be sites of action of modulators originating from a remote part of the organism and transported by the blood stream. Angiotensin is one candidate. Presynaptically effective concentrations occur in plasma, at least when renin secretion is high. The facilitatory effect may assist in the circulatory compensation for acute hemorrhage [116]. Studies of the influence of angiotensin antagonists on noradrenaline release from blood-perfused organs might further clarify whether facilitation by blood-borne angiotensin plays a physiological role.

(2) Presynaptic receptors may be sites of action of modulators secreted from adjacent neurones or other cells. In peripheral tissues, postganglionic sympathetic and parasympathetic nerve endings often lie in close apposition. It seems very likely that acetylcholine, secreted from parasympathetic fibres, can act on muscarine receptors of neighbouring sympathetic terminals and inhibit the release of noradrenaline [117, 118]. Interestingly, released noradrenaline also inhibits the per pulse release of acetylcholine [119]. Thus, a mutual presynaptic antagonism between the two divisions of the autonomic nervous system appears to supplement the classical postsynaptic antagonism. It remains to be established whether presynaptic cholinergic modulation of catecholaminergic transmission also takes place in the central nervous system. In particular, the numerous cholinergic interneurones in the corpus striatum could partly modulate release of dopamine at the presynaptic level [99].

The presence of enkephalin in brain and its depressant effect on noradrenaline release open up the possibility that this endogenous morphine receptor ligand serves as a physiologic presynaptic inhibitor. If so, naloxone should enhance release. Until now, the evidence is inconclusive. Naloxone does not affect the electrically evoked release of noradrenaline in slices from several brain areas [53, 54, 120]; on the other hand, potassium-evoked release in occipital cortex slices is slightly increased [86].

(3) The most extensive evidence has been gathered for a third physiologic function, namely for presynaptic prostaglandin, α- and β-receptors (noradrenergic neurones) and dopamine receptors (dopaminergic neurones) being links of local synaptic feedback mechanisms. As first proposed by Hedqvist [26], prostaglandins are formed during noradrenergic transmission, probably mostly in postsynaptic cells, and depress further secretion of noradrenaline ("transsynaptic" feedback). Drugs like indometacin and meclofenamic acid which block prostaglandin biosynthesis interrupt the feedback circuit and enhance noradrenaline release [121, 122]. However, the increase is small, maximally by about 50 per cent. In cat spleen, meclofenamic acid and indometacin fail to cause any increase [28, 123].

Released noradrenaline inhibits its own further release by a second mechanism which is independent of prostaglandins [121] and entirely presynaptic, namely by activation of presynaptic α-adrenoceptors. Studies with α-adrenolytic drugs underscore the general operation and great effectiveness of the presynaptic α-adrenergic feedback. In contrast to prostaglandin synthetase inhibitors, these drugs increase the release of noradrenaline in all tissues and maximally by about 400 per cent. It was this finding that gave the first clue to a role of α-receptors in the fate of noradrenaline [124]. Not only α-receptor agonists (see 1.4.), but also antagonists differ in their relative pre- and postsynaptic effects. In rabbit pulmonary artery, yohimbine preferentially blocks presynaptic α-receptors, whereas phenoxybenzamine and azapetine preferentially block postsynaptic α-receptors [125] (cf. [126]). By selective presynaptic blockade, yohimbine at low concentrations, in contrast to what one would expect from the classical postsynaptic antagonist effect, *increases* the contractile response to stimulation [127].—The α-adrenergic agonists clonidine [128] and oxymetazoline enhance noradrenaline release under certain conditions (oxymetazoline in rabbit pulmonary artery strips stimulated at more

than 5 Hz*). It seems likely that in these cases the agonists possess a lower intrinsic inhibitory activity than noradrenaline and by competition with the latter diminish overall presynaptic α-receptor activation.—In some tissues, the release of noradrenaline per pulse falls with successive pulses. Biochemical and electrophysiological studies indicate that part of this depression during trains of pulses is due to α-adrenergic inhibition with increasing perineuronal levels of noradrenaline [43, 129].

Langer and his colleagues [28, 35, 49] suggested that released noradrenaline, acting on presynaptic β-adrenoceptors, promotes its own release by a positive feedback. Presynaptic β-receptors may be selectively activated by low concentrations of noradrenaline, for instance during low rates of impulse flow, so that release per pulse increases. As frequency and noradrenaline concentration rise, the α-adrenergic negative feedback may be triggered, so that release per pulse falls [28, 49]. In agreement with this hypothesis, propranolol reduces release of noradrenaline in some tissues [49, 80]. On the other hand, it should be noted that presynaptic β-receptors have been found on some neurones only. Moreover, in cat spleen propranolol fails to reduce release even though isoprenaline causes significant facilitation [35]; the same may hold good for human blood vessels [50, 51]. Thus, even where presynaptic β-receptors exist they do not necessarily mediate a positive feedback.

α-Adrenergic feedback inhibition of noradrenaline release may have a counterpart in dopaminergic feedback inhibition of dopamine release. Neuroleptic drugs such as pimozide and fluphenazine enhance striatal release of dopamine evoked by electrical stimulation or high potassium, presumably by blocking presynaptic dopamine receptors and opening the feedback loop [6, 37, 91]. Unfortunately, there are diametrically opposed findings [130] which cast some doubt on this mechanism. Dopamine may also inhibit its own synthesis via presynaptic dopamine receptors. When impulse flow in the nigro-striatal dopaminergic fibres is interrupted, the rate of striatal tyrosine hydroxylation increases [87, 88, 94]. Cessation of impulse-evoked secretion probably leads to a decrease of perineuronal dopamine and, hence, diminished presynaptic receptor activation and disinhibition of tyrosine hydroxylase.

7. *Outlook*

Pharmacological research has led to the detection of a somewhat bewildering number of presynaptic receptor systems. It seems quite possible that some are of pharmacological interest only since they never encounter effective concentrations of their endogenous agonists *in vivo*. Others, however, appear to play a significant physiological role. Several major questions arise at the present state of knowledge. The chain of events between the agonist–presynaptic receptor interaction and the change in release or biosynthesis is not known for any receptor system. Furthermore, what is the reason for the surprising tissue differences in effects of presynaptic modulators? Much more work is needed for a better understanding of the physiological function; an effort should be made to compare the relative importance of soma-dendritic receptors (or variations in impulse frequency) and presynaptic receptors (or variations in release per impulse) under diverse *in vivo* conditions. Finally, presynaptic receptors may mediate therapeutic as well as side effects of drugs. An example for which this possibility has already been put to experimental trial is the antihypertensive agent clonidine. It exerts a variety of effects, including the decrease of blood pressure, by activation of central α-adrenoceptors. Are these receptors, or some of them, presynaptic receptors on noradrenergic neurones? Animal experiments argue against a major contribution of central presynaptic α-receptors to clonidine-induced hypotension [131, 132]. On the other hand, several behavioural effects can best be explained by α-adrenergic presynaptic inhibition [97, 133, 134].

* K. Starke and T. Endo, unpublished.

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