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PRESYNAPTIC RECEPTORS

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This is the first article on presynaptic receptors in the *Annual Review of Pharmacology and Toxicology.* Because other reviews are likely to follow, it seems appropriate to set the stage by a discussion of more general aspects, namely terminology, development, location of receptors, mode of action, and physiological function. The emphasis on general aspects also distinguishes this essay from review articles that have been published elsewhere (see Table 1).

DEFINITION

A neuron can receive chemical messages at the dendrites, the perikaryon, the axon, and the axon terminals. In other words, it possesses receptors along its entire length. However, since neuronal activity normally is not regulated at the axons, only two groups of receptors have potential physiological importance. The first group consists of soma-dendritic receptors. They are located on, in, or near the cell body and dendrites and when activated *primarily modify the function of the soma-dendritic region* (for example, protein synthesis and the generation of action potentials). The second group consists of presynaptic receptors. They are located on, in, or near the axon terminals and when activated *primarily modify the function of the terminal region* (for example, transmitter synthesis and release). These definitions are strict in their functional parts, but vague in their topographic parts. The reason is that, as a rule, we do not know the precise location of the receptors that affect soma-dendritic or terminal activity (1).

Processes in axon terminals are modified by substances that occur natu-

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rally in the body, but also by chemicals apparently unrelated to endogenous compounds, such as local anesthetics, tetrodotoxin, tetraethylammonium, scorpion venoms, botulinus toxin, veratridine, and reserpine. Calcium plays a decisive role in nerve terminals, and other metal cations mimic or block its effect. All these agents act through what by definition are presynaptic receptors. However, the term is commonly applied only to receptors for endogenous compounds and their exogenous congeners. Only such receptors are discussed.

Axon terminals take up transmitter precursors, synthesize the transmitter, secrete it, inactivate it, retrieve the vesicles, maintain ionic gradients, and so forth. All this can be affected by receptors. By definition, we may call the GABA uptake mechanism of GABAergic axon terminals the presynaptic receptor for uptake inhibitors, or the monoamine oxidase in catecholaminergic terminal axons the presynaptic receptor for MAO inhibitors. However, at present we know only two functions of nerve terminals that are modified by endogenous organic compounds, namely, transmitter synthesis and release.

DEVELOPMENT

The concept of a receptor-mediated modulation of the activity of nerve terminals has enjoyed wide attention for the past decade. Yet, its origins can be traced to much earlier electrophysiological and biochemical observations. A brief look back will illustrate the variety of neuronal systems (and methods) in which (and by which) presynaptic receptors have been found.

That cholinergic axon terminals carry receptors was early suspected when effects of catecholamines on neuromuscular transmission were analyzed. Adrenaline and noradrenaline increase end-plate potentials produced by motor nerve stimulation, but not potentials elicited by iontophoretically applied acetylcholine. This suggested that catecholamines caused more transmitter to be liberated (2) by an action on presynaptic receptors that were later identified as α-adrenoceptors (see 3). Electrophysiological studies also revealed effects of cholinergic agonists and antagonists at motor nerve endings. The findings were complex, and both inhibition and facilitation by agonists have been reported (see 4–6).

Another root of the presynaptic receptor concept is the electrophysiology of inhibition in the central nervous system. Inhibitory transmitters can act on postsynaptic cell bodies or dendrites, making them less excitable (postsynaptic inhibition). Work on spinal monosynaptic reflexes in motoneurons has indicated, however, that there is another type in which the inhibitory transmitter acts on primary afferent nerve endings, reducing the release of the excitatory transmitter (presynaptic inhibition; 7). GABA is assumed to

be the inhibitory transmitter, and we may call its receptors presynaptic GABA receptors of the primary afferents. Inhibition by GABA of neurotransmitter release has now been demonstrated biochemically as well (see Table 1).

Biochemical evidence for receptors on or near axon terminals was first provided by numerous reports, since 1945, that nicotine-like drugs release noradrenaline from postganglionic sympathetic neurons in preparations devoid of sympathetic ganglion cells (8; see 9–11). The presynaptic nicotine receptors probably are insignificant physiologically. A more consequential discovery was made in 1968 when Lindmar et al (12) found that postganglionic sympathetic neurons possess in addition presynaptic muscarine receptors that mediate depression of action potential-evoked noradrenaline release. These receptors do come into play physiologically (see 10, 13). At about the same time, biochemical evidence for a presynaptic facilitatory effect of angiotensin II on postganglionic sympathetic fibers, and for a presynaptic inhibitory effect of prostaglandins, began to accrue (see 9, 14).

An adrenergic inhibition of the release of acetylcholine from preganglionic sympathetic neurons was shown biochemically in 1953 (15); it is now known to be mediated by presynaptic α-adrenoceptors (see 16). Catecholamines also reduce acetylcholine release in the intestine (17) via an α-adrenoceptor (see 16); however, the possibility that this is a soma-dendritic α-receptor of the cholinergic neurons of the enteric plexuses has not been ruled out. Knowledge of the inhibition of intestinal acetylcholine release by morphine also stems from the 1950s; again, however, the mode of action (soma-dendritic or presynaptic inhibition?) is uncertain (see 9).

A final incentive for research on presynaptic receptors was the biochemical demonstration that neurons may have such receptors for their own transmitter. Following a proposal by Carlsson (18), we may call these sites presynaptic autoreceptors. They may be links in feedback mechanisms by which the transmitter controls its own release or biosynthesis. Biochemical experiments that retrospectively can be explained by presynaptic autoreceptors date back at least to 1957 (19). The idea was first explicitly proposed in 1971, simultaneously for noradrenergic (see 9), central cholinergic (20), and GABA neurons (21).

Table 1 summarizes the presynaptic receptors known or discussed today. Presynaptic receptors have become a large family. They occur at neurons containing biogenic amines, amino acids, and peptides. Their activation leads to facilitation or inhibition of transmitter release or synthesis. The table contains some key references, mostly to review articles and recent biochemical in vitro work. The reason for the emphasis on biochemistry is that biochemical methods offer the most direct approach to changes in transmitter economics (9). In vitro experiments are stressed because in vivo

Table 1 A summary of presynaptic receptors

Neuron	Presynaptic receptor	Effect[a]	References
Noradrenaline	α-Adrenoceptor	Inhibition of release	9b, 16b, 22–26b, 27–35
	β-Adrenoceptor	Facilitation of release	9b, 22b, 23b, 25b, 30, 32, 36b, 37–39
	Dopamine	Inhibition of release	9b, 16b, 25b, 40–42
	Serotonin	Facilitation of release	43
	Serotonin	Inhibition of release	44–46
	Histamine	Inhibition of release	25b, 47, 48
	Nicotine	Facilitation of release	9–11b, 24b, 25b, 49–51
	Muscarine	Inhibition of release	9b, 10b, 13b, 16b, 24b, 25b, 27, 52
	GABA	Facilitation of release	24b, 53–57
	GABA	Inhibition of release	57–59
	Opiates	Inhibition of release	9b, 16b, 24b, 25b, 28, 60b, 61, 62
	Angiotensin II	Facilitation of release	9b, 16b, 25b, 27, 63–65
	Angiotensin II	Enhancement of synthesis	9b
	Prostaglandins	Inhibition of release	9b, 14b, 16b, 24b, 25b, 32, 66b, 67
	Adenosine	Inhibition of release	16b, 25b, 68b, 69–73
Adrenaline	α-Adrenoceptor	Inhibition of release	74
Dopamine	Dopamine	Inhibition of release	24b, 75–78b
	Dopamine	Inhibition of synthesis	75, 77, 79b
	Nicotine	Facilitation of release	24b, 80, 81
	Muscarine	Facilitation of release	24b, 80, 82b
	Muscarine	Inhibition of release	24b, 83
	GABA	Facilitation of release	24b, 55, 56, 84–86
	GABA	Inhibition of release	24b, 57, 82b
	Glycine	Facilitation of release	85–88

Table 1 *(Continued)*

Neuron	Presynaptic receptor	Effect[a]	References
	Glutamate	Facilitation of release	86, 89
	Opiates	Inhibition of release	24[b], 61, 90, 91
	Angiotensin II	Facilitation of release	92
	Substance P	Facilitation of release	91
	Prolactin	Facilitation of release	93
	Prostaglandins	Inhibition of release	24[b]
	Adenosine	Inhibition of release	94, 95
	Benzodiazepines	Facilitation of release	96
Serotonin	Serotonin	Inhibition of release	97, 98
	α-Adrenoceptor	Inhibition of release	99, 100
	Dopamine	Facilitation of release	101, 102
	Nicotine	Facilitation of release	103
	Muscarine	Inhibition of release	103
	GABA	Facilitation of release	55
	GABA	Inhibition of release	57
	Angiotensins	Modulation of synthesis	104
	Substance P	Facilitation of release	91, 101
	Adenosine	Inhibition of release	94
Acetylcholine	Muscarine[c]	Inhibition of release	16[b], 105–108
	Nicotine and muscarine[d]	Modulation of release	4, 5[b], 6
	α-Adrenoceptor[e]	Inhibition of release	9[b], 16[b], 109
	α-Adrenoceptor[f]	Facilitation of release	110
	Dopamine[g]	Inhibition of release	16[b], 78b, 82[b], 111–115
	GABA[h]	Inhibition of release	116

Table 1 *(Continued)*

Neurons	Presynaptic receptor	Effect[a]	References
	Opiates[e]	Inhibition of release	9[b], 16[b], 106, 111, 117–119
	Angiotensin II[e]	Facilitation of release	9[b]
	Substance P[f]	Modulation of release	120
	Prostaglandins[i]	Modulation of release	9[b], 14[b], 121, 122
	Adenosine[e,f]	Inhibition of release	16[b], 94, 123–125
GABA	GABA	Inhibition of release	126–129
	Dopamine	Modulation of release	78a, 130, 131
	Adenosine	Inhibition of release	94, 132
	Benzodiazepines	Modulation of release	133, 134
Glutamate	Dopamine	Inhibition of release	135, 135a
Enkephalin	GABA	Inhibition of release	136
Substance P	GABA	Inhibition of release	137
	Opiates	Inhibition of release	138
Oxytocin	Opiates	Inhibition of release	139
Vasopressin	Opiates	Inhibition of release	140

[a] "Facilitation of release" indicates either that action potential-evoked release is enhanced or that a de novo release is elicited from previously quiescent nerve terminals. "Modulation of release" (or synthesis) indicates that both enhancement and inhibition have been observed.
[b] Review article.
[c] Postganglionic parasympathetic and central neurons.
[d] Preganglionic and motoneurons.
[e] Autonomic and central neurons.
[f] Motoneurons.
[g] Corpus striatum.
[h] Preganglionic neurons.
[i] Autonomic and motoneurons.

distinction between presynaptic and soma-dendritic effects is difficult (see 24). Note that not all neurons with a certain transmitter are endowed with the same receptors; on the contrary, there are marked tissue and species differences (see 9). Note also that Table 1 lists only the positive findings;

space does not allow inclusion of the equally important negative findings indicating the absence of a certain receptor.

LOCATION

When presynaptic receptors are going to be examined, it must be ruled out that the drugs affect the axon terminals by interacting primarily with the neuron's soma-dendritic receptors, changing, for instance, the rate of firing. This is easy for postganglionic sympathetic fibers, whose cell bodies are in general far from the innervated organ. It may be more difficult for postganglionic parasympathetic or central neurons (see 24). For instance, Hadházy & Szerb (141) studied the release of acetylcholine from slices of the rat corpus striatum, which contains cholinergic neurons with cell bodies and endings, and from slices of the rat hippocampus, which contains only cholinergic axon terminals. The muscarinic agonist oxotremorine reduced, and atropine increased, release of acetylcholine from either area. The effect in the hippocampus was obviously presynaptic. On the other hand, in the corpus striatum a modulation via soma-dendritic receptors of the cholinergic neurons cannot be ruled out.

Even after a presynaptic mechanism has been ascertained, the question remains as to whether the drugs affect the axon terminals directly, or whether they act primarily on nearby cells which then emit a second signal to the axon terminals. This is again particularly difficult to decide in tissues with neuronal networks where the drugs may act on interneurons that impinge upon the axon terminals under study, forming axo-axonic synapses. Sometimes, reasoning by analogy suggests an answer. Muscarinic agonists reduce the release of acetylcholine from central neurons (see above; 105, 106, 141), intestinal neurons (107, 108), and some skeletal muscle motoneurons (6). The analogy suggests that the drugs act on the one element common to these tissues, namely the cholinergic axon terminals themselves. The following experiments may provide more direct evidence.

1. Release by high potassium concentrations in the presence of tetrodotoxin. High potassium releases neurotransmitters by depolarizing the axon terminals directly; tetrodotoxin blocks the traffic of action potentials. Hence, when a drug modifies this release, it does not act by way of action potentials in interneurons. It must act either on the terminals under study or on neighboring cells. This model has been used to exclude interneuronal pathways in the muscarinic inhibition of acetylcholine release (142), the α-adrenergic inhibition of noradrenaline release (143), and the dopaminergic inhibition of dopamine (78) and glutamate (135) release [for related approaches, see (80, 84, 98)].

2. Biosynthesis in, or release from, synaptosomes. Drug effects on synaptosomes, i.e. resealed torn-off axon terminals, suggest a direct action on the terminals. For instance, dopaminergic agonists inhibit the synthesis of dopamine in synaptosomes (144), α-adrenergic agonists diminish the release of noradrenaline from synaptosomes (31), and GABAergic agonists depress release of GABA from synaptosomes (127). It should be kept in mind, however, that synaptosomes often have the postsynaptic membrane still attached, so that the receptors may be located there. Furthermore, presently available synaptosome preparations are heterogeneous, and a primary action on "wrong" synaptosomes cannot be entirely ruled out.

3. Release from neurons in tissue culture. Isoprenaline increases the release of noradrenaline from axonal sprouts of sympathetic ganglia grown in organ culture. Since there are no postsynaptic cells, the site of action—the β-autoreceptor—must be neuronal and, in all likelihood, on the axon terminals (38). Similar experiments for other systems would be desirable.

4. Radioligand binding studies. If axon terminals carry receptors, destruction of the terminals should lead to a loss of receptors. Receptor concentrations can be measured by radioligand binding. Indeed, destruction of catecholamine terminal axons by 6-hydroxydopamine decreases the concentration of GABA and dopamine receptors in the corpus striatum (145–147), muscarine receptors in the heart (148), and opiate receptors in several brain regions (149). Moreover, degeneration of primary afferent (including probably substance P) fibers results in a loss of opiate receptors in spinal cord and brain (150), and degeneration of cortico-striatal (including probably glutamate) fibers results in a loss of dopamine receptors in the corpus striatum (151). These findings suggest location of some presynaptic receptors, known from functional studies (Table 1), on catecholamine, substance P, and glutamate axon terminals. Yet, there are also negative results. Except in one case (152), disappearance of noradrenergic axons did not decrease the number of α-adrenoceptors in the innervated tissues (153, 154). Although presynaptic muscarine receptors exist at cholinergic neurons in rat hippocampus (see above; 141), lesion of these neurons failed to reduce the number of muscarine receptor binding sites (155). These findings appear to contradict a presynaptic location of α- and muscarine autoreceptors.

However, all the binding data must be viewed with caution. Positive results may be misleading, because lesion of an axon A may be followed by trans-synaptic degeneration of the innervated neuron B, so that not only (topographically presynaptic) receptors on A terminals but also receptors on B may disappear. Negative results may be misleading, because receptors on terminals may be a functionally important and yet quantitatively minor group which may be overlooked in binding experiments. Moreover, lesions

of axon A may cause proliferation of postsynaptic receptors for the transmitter of A, and this may compensate for any loss of (auto)receptors on the degenerated A terminals.

In conclusion, none of these approaches is proof against criticism. Taken together, however, the available evidence leaves little doubt that at least some receptors listed in Table 1 are presynaptic also in a topographic sense.

MECHANISM

We know little about the mode of operation of presynaptic agonists. The main problem is that nerve terminals are small and are only a minor fraction of the tissue in which they are imbedded. Only some aspects can be touched upon here. For details, see the articles cited in Table 1.

The release of neurotransmitters decreases when either the impulses invade fewer axon terminals (varicosities in the case of varicose terminal axons), or the secretion per impulse from each single axon terminal (varicosity) declines. Stjärne (26) has proposed that endogenous, released noradrenaline produces α-adrenergic feedback inhibition of further release mainly by hyperpolarization of the axons and, hence, depression of impulse propagation and of the recruitment of varicosities. One argument is that α-adrenolytic drugs, which interrupt the feedback loop, greatly facilitate the release of noradrenaline evoked by electrical stimulation (for which propagation of action potentials is necessary), but facilitate very little release evoked by high potassium concentrations (for which propagation of action potentials is not necessary). Similarly, morphine may presynaptically inhibit the release of acetylcholine from enteric neurons by inhibition of impulse propagation and a decrease in the number of varicosities excited (106, 118).

Stjärne (26) did not exclude the possibility that presynaptic α-adrenoceptors, when activated, also inhibit electrosecretory coupling and, hence, the release of noradrenaline from each individual varicosity. α-Receptor agonists reduce, and antagonists enhance, the release of noradrenaline elicited by reintroduction of calcium after perfusion of tissues with calcium-free medium (provided high potassium keeps the neurons depolarized; 27, 28). This is rather direct support for an α-adrenergic inhibition of electrosecretory coupling, specifically, of the influx of calcium through voltage-dependent channels. With the same model Göthert and co-workers (27, 28, 98, 100) have shown that muscarinic agonists and opiates (cf 62) decrease the calcium-evoked release of noradrenaline, that angiotensin II facilitates calcium-evoked noradrenaline release, and that serotonin and α-adrenergic agonists inhibit the calcium-evoked release of serotonin. Moreover, musca-

rinic agonists seem to depress the release of acetylcholine by reducing the depolarization-evoked influx of calcium ions (106). It appears as if many presynaptic receptors were coupled with calcium channels as one effector system.

Hyperpolarization impedes impulse propagation and hence may depress transmitter release. Yet *de*polarization of axon terminals may, by a decrease in action potential amplitude, result in diminished release as well. Depolarization by GABA of primary afferent terminals was the original explanation for the electrophysiological presynaptic inhibition (see above). In fact, when inhibition by GABA of the release of acetylcholine was demonstrated biochemically, a parallel concentration dependence of presynaptic depolarization and decrease in release was found (116).

Links in more biochemical terms between receptors and release have also been postulated. The Na^+,K^+-activated ATPase of the neuronal membrane may play a role in transmitter release, and several drugs have been proposed to inhibit transmitter release by activation of the enzyme (see 16, 156). β-Adrenoceptor agonists and angiotensin II may facilitate the release of noradrenaline by activating a presynaptic adenylate cyclase (see 9, 22). Conversely, α-adrenergic agonists may inhibit noradrenaline release by activating a presynaptic guanylate cyclase (29).

For the time being, we are left with a number of interesting possibilities. There is an obvious need for further work in order to elucidate, for each presynaptic receptor, the steps linking receptor activation and transmitter release or synthesis.

FUNCTION

Presynaptic receptors may serve at least three physiological purposes (see 9). They allow modulation of the activity of nerve terminals by compounds originating from a remote part of the body and transported by the blood stream. They allow modulation by substances secreted from neighboring cells, in particular from neighboring neurons. And they allow modulation by the neuron's own transmitter or other agents entering into the synapse upon transmitter release.

Modulation by Blood-Borne Agents

A look at Table 1 shows that mainly catecholamines and angiotensins are potential physiological blood-borne modulators. Presynaptic facilitation of neuromuscular (see 3) and postganglionic sympathetic transmission (see 22) by adrenal medullary hormones has been proposed; however, the one example for which some experimental support can be adduced is enhancement of postganglionic sympathetic transmission by angiotensin II. Low concen-

trations of the peptide, close to the normal blood levels, are required (see 9). Zimmerman and co-workers (64, 157) have identified two conditions under which facilitation by endogenous angiotensin II occurs, namely hemorrhage and suprarenal aortic constriction. Both conditions increased plasma renin levels and, simultaneously, vasoconstrictor responses to sympathetic nerve stimulation but not, or not regularly, to injected noradrenaline. The increase in vasoconstrictor responses was prevented by nephrectomy (157) and by the angiotensin antagonist saralasin (64). Since postsynaptic responses reflect presynaptic events rather indirectly, it would be highly desirable to study in vivo release of noradrenaline at different plasma renin concentrations, or after giving angiotensin antagonists, with more direct biochemical techniques.

Modulation by Neighboring Neurons

The most obvious function of presynaptic receptors is mediation of the effect of transmitters secreted from adjacent axon terminals. This has been shown most clearly in the peripheral autonomic nervous system. In many tissues, postganglionic sympathetic and parasympathetic fibers lie in close proximity. Although morphologically differentiated axo-axonic contacts are rare, the arrangement leaves little doubt that an interaction can occur. Indeed, vagal stimulation inhibits the release of noradrenaline elicited by simultaneous stimulation of sympathetic nerves, and the inhibition is abolished by atropine (see 9, 10, 13, 25). Conversely, stimulation of sympathetic nerves appears to inhibit the release of acetylcholine elicited by parasympathetic nerve stimulation, and the inhibition is abolished by phentolamine (see 16, 109). The mode of the α-adrenergic inhibition of acetylcholine release is uncertain (soma-dendritic or presynaptic inhibition?). On the other hand, the muscarinic inhibition of noradrenaline release clearly reflects presynaptic inhibition of postganglionic sympathetic neurons by neighboring cholinergic fibers. A mutual presynaptic antagonism may supplement the classical postsynaptic antagonism between the two divisions of the autonomic nervous system. Where and when the presynaptic antagonism operates remains to be determined.

In the central nervous system, specialized axo-axonic synapses may be the morphological substrate of presynaptic modulation by adjacent terminals. Yet, axon terminals lacking synaptic differentiation can also be engaged in this kind of interaction; presynaptic inhibition of cerebrocortical serotonin neurons by noradrenaline neurons is an example (99, 100). In the development of the presynaptic receptor concept, inhibition by GABA holds a prominent place (see above). Potential targets of GABA are listed in Table 1. Yet, to which of these targets endogenous GABA normally has access is unknown. It has been shown, for instance, that the GABA antago-

nists picrotoxin and bicuculline, given in vivo directly into the corpus striatum, enhance the release of dopamine, possibly by removing a presynaptic GABAergic inhibition (82, 158). However, in such in vivo experiments the site of drug action is notoriously difficult to pinpoint (see 24). Moreover, in vitro the GABA receptors mediating inhibition of dopamine release are bicuculline-resistant (57). Hence, the interpretation of the in vivo results remains doubtful, and the question of a physiological presynaptic GABAergic inhibition of dopamine release unanswered. Endorphins may also be physiological central presynaptic inhibitors. Exogenous opiates at low concentrations reduce the release of noradrenaline from brain slices (see Table 1), and binding studies indicate location of opiate receptors on noradrenergic varicosities (149). If endorphins normally act on these receptors, naloxone, given alone, should increase noradrenaline release. However, this has not been found except in one series of experiments (159).

Neurotransmitters can be released from dendrites. For instance, dopamine is liberated from dendrites in the substantia nigra onto GABAergic axon terminals (160). Exogenous dopamine releases GABA from these terminals (130). The analogous effect of endogenous dopamine would be a paradigm of presynaptic receptors mediating dendro-axonic transmission.

Modulation by Synaptic Feedback Mechanisms

The release of transmitters is accompanied or followed by the entry of other substances such as electrolytes and proteins into the synaptic cleft. At least four of these substances may influence the function of the axon terminals, namely potassium ions, prostaglandins, adenosine and its derivatives, and the transmitter itself. The slight depolarization produced by potassium may depress subsequent transmitter release because of a decrease in action potential amplitude, but may also increase release by promoting impulse propagation. Prostaglandins and adenosine may originate from the axon terminals and from postsynaptic sites; their potential roles are discussed in the articles cited in Table 1. The present discussion is limited to effects of the transmitter itself, in other words, to presynaptic autoreceptors and their contribution to synaptic feedback loops.

Presynaptic autoreceptors have been postulated for noradrenaline, adrenaline, dopamine, serotonin, acetylcholine, and GABA neurons. The basic evidence is as follows. The respective agonists inhibit (in the case of presynaptic β-receptors of noradrenergic neurons facilitate) transmitter release (and, in the case of dopamine, transmitter synthesis). Antagonists specifically counteract the effects of the agonists. Given alone, the antagonists often produce effects opposite to those of the agonists, thus revealing a normal endogenous modulation. All effects are presynaptic, since they can

be obtained in the absence of the cell bodies. In some cases, experiments with synaptosomes, neurons grown in organ culture, or radioligands suggest that the autoreceptors are located on the respective axon terminals.

A twofold conclusion has been drawn from these data. First, presynaptic autoreceptors do exist. Second, they are activated not only by exogenous agonists but also by the endogenous transmitter and thus mediate feedback mechanisms: As the perineuronal concentration of transmitter increases, release (or synthesis) is progressively depressed (in the case of β-receptors release is enhanced).

There can be little doubt in the first conclusion. The second one, however, is less firm. Sometimes the expected effects of antagonists, given alone, were not obtained. For instance, some postganglionic sympathetic neurons that respond to isoprenaline with an increase in noradrenaline release failed to respond to β-adrenolytic drugs with a decrease (9, 36). Apparently, the β-adrenoceptors are not activated by released transmitter, and there is no positive feedback. The reason may be that the receptors are β_2 and, hence, not very sensitive to noradrenaline. Similarly, GABA antagonists do not always promote release of GABA from superfused brain slices although agonists cause a decrease (126, 128). It has been argued that released GABA is rapidly washed out from the slices so that it remains subthreshold at the presynaptic receptors. While this may be true, the question of a physiological role of GABA autoreceptors still remains open.

It should also be noted that most experiments that support the concept of autoreceptor-mediated feedback mechanisms were carried out in vitro. In vitro conditions may impede (as has been argued for GABA) but may also enhance access of released transmitter to autoreceptors; such conditions may thus create artifactual feedbacks that never operate in vivo. We know very little about the in vivo function of presynaptic feedback mechanisms. An exception is the autoinhibition of noradrenaline release. For instance, α-adrenolytic drugs in vivo increase both the release of noradrenaline and the positive chronotropic effect elicited by cardiac sympathetic nerve stimulation (161–163), thus revealing an endogenous α-adrenergic inhibition.

However, it is precisely the autoinhibition of noradrenaline release that has recently been questioned by Kalsner and his colleagues (35, 164–169; it is not clear whether only the operation of the feedback is denied or the very existence of the receptors as well). This work can only briefly be considered here. A shortcoming seems to be the authors' failure to offer an alternative explanation for the observations on which the α-autoreceptor concept is based. Another general shortcoming is the disregard of some of the evidence for the concept. Inhibition of noradrenaline release by agonists,

and enhancement by antagonists, is not the only basis. For instance, the feedback hypothesis predicts that the inhibitory effect of exogenous agonists should be smaller, the higher the biophase concentration of endogenous noradrenaline and, hence, the stronger the endogenous inhibition. That this is so was shown early after the feedback hypothesis had been advanced (170–172). A more rigidly quantitative recent study yielded essentially similar results (34). And there is further, independent support that can be found in the reviews cited in Table 1.

A more specific objection concerns the choice of phenoxybenzamine (33 μM) as the only α-adrenoceptor antagonist, used in order to put the hypothesis to trial, in four papers (164, 166, 167, 169). In tissues preincubated with ^{3}H-noradrenaline, phenoxybenzamine increased the stimulation-evoked overflow of tritium, and presumably the release of noradrenaline. This would fit in with the presynaptic α-receptor hypothesis; however, some features of the increase, for instance lack of frequency dependence, were thought to be incompatible with the concept. Yet, phenoxybenzamine is a poor antagonist at presynaptic α-receptors (see 9, 22). What is more important, at the high concentration used it accelerated the basal outflow of tritium (164, 166, 167, 169). This effect is well known, unrelated to α-receptor blockade, and presumably is due to interference with the vesicular storage of noradrenaline in a manner akin to what reserpine does (see 173). Ability to increase the stimulation-evoked, exocytotic release of noradrenaline, however, is an inherent property of reserpine-like drugs which results either from the primary alteration of the vesicle membrane or from the ensuing increase in axoplasmic levels of noradrenaline or noradrenaline metabolites (174). Hence, a reserpine-like action is one mechanism by which phenoxybenzamine (33 μM) increases action potential-evoked release of noradrenaline. This component, of course, will not obey predictions made for an α-adrenolytic component and makes phenoxybenzamine (33 μM) a priori unsuited for testing the presynaptic α-receptor hypothesis. (An analogous objection can be raised against the administration of high concentrations of unlabeled noradrenaline for activation of the incriminated α-adrenoceptors; these concentrations also exert intraneuronal actions leading to an increase in the basal outflow of tritium; see 165.) Phenoxybenzamine (33 μM) has further non-α-adrenolytic effects. It blocks muscarine receptors (175). In at least one tissue used by Kalsner and his colleagues, namely the guinea pig vas deferens, presynaptic muscarine receptors mediate an endogenous inhibition of noradrenaline release (176), and their blockade may contribute to the release-facilitating effect of phenoxybenzamine. Again, this atropine-like component will not behave as predicted for α-receptor blockade and invalidates the use of phenoxybenzamine as a tool for assessing the hypothesis. Phenoxybenzamine has played

a trigger role in the development of the presynaptic α-receptor concept. However, our present state of knowledge cautions against reliance upon observations with this drug, especially at high concentrations, as arguments for or against the concept.

Although open to some criticism, the work of Kalsner and colleagues may lead to reevaluation and qualification of the hypothesis. Maybe α-adrenoceptors do not occur at all noradrenergic axons, which would not be surprising since tissue differences are so common for presynaptic receptors. Even existing receptors may be physiologically active in some tissues, but silent in others. Perhaps in some organs the main task of the receptors is not "pulse-to-pulse modulation" of release (177) but, as proposed by von Euler (178), to quench "stray or nonintended stimuli" during quiescent periods.

No evidence was found for presynaptic autoreceptors at enkephalin neurons (136, 179, 180).

Synaptic feedback mechanisms can be artificially established when false transmitters are incorporated into neurons. For instance, noradrenergic neurons take up adrenaline. When adrenaline is subsequently released, it may activate the presynaptic β-receptors that are only slightly sensitive to noradrenaline (see above). A β-adrenergic positive feedback then begins to work, and β-adrenolytic drugs, which do not normally change release, become presynaptic inhibitors (36, 37). Noradrenergic neurons normally contain too little dopamine for presynaptic dopamine receptors to become activated. However, dopamine may accumulate during treatment with DOPA, and presynaptic dopamine receptors may then become links of a new negative feedback loop (181).

Many aminergic neurons appear to contain in addition peptides such as substance P and somatostatin. Mesolimbic dopamine neurons contain cholecystokinin-like immunoreactivity, and cholecystokinin fragments inhibit the release of dopamine (182). Thus it is possible that neurons have autoreceptors not only for their classical transmitter but also for peptide cotransmitters, and that the peptide autoreceptors also mediate synaptic feedback mechanisms.

CONCLUSION

The activity of neurons can be influenced mainly at two sites: the cell body with the dendrites and the axon terminals. When activated, presynaptic receptors primarily modify the function of the axon terminals, for instance, transmitter biosynthesis and release.

In the last few years a large number of presynaptic receptor systems have been detected. Virtually all neurons seem to respond to various endo-

genous organic compounds with changes in the activity of the axon terminals. With each newly detected presynaptic receptor, questions are raised. Is the receptor located directly on the axon terminals, that is, is the receptor presynaptic not only functionally but also topographically? Which chemical and electrical steps link receptor activation with the cellular response? Does the receptor ever encounter relevant concentrations of the endogenous agonist in vivo; in other words, does it play a physiological role? The very multiplicity of the receptors makes it likely that some are physiologically silent. Axon terminals may be endowed with a certain receptor because this receptor is needed for the soma-dendritic region, and because the neuron finds it convenient to construct a membrane with the same receptors both for its cell body and dendrites and for its axon terminals. Many cells like muscle and gland cells probably possess receptors without normal input, which may be vestiges of evolution that continue to exist because they do us no harm.

Whether physiologically silent or not, presynaptic receptors may be sites of action of drugs. Imidazoline α-adrenoceptor agonists may cause sedation by presynaptic (and soma-dendritic) inhibition of central noradrenaline pathways. GABA antagonists may produce convulsions by interrupting GABAergic presynaptic inhibition. Opiates possibly relieve pain because they activate receptors on substance P terminals. Methylxanthines may stimulate the central nervous system because they antagonize presynaptic inhibitory effects of adenosine. Presynaptic receptors are an amazingly diversified mechanism for the physiological regulation of neurons. They are an even more diversified mechanism for pharmacological manipulation—a challenge to pharmacological analysis.

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