The role of α- and β-presynaptic receptors in the regulation of noradrenaline release elicited by nerve stimulation

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Summary
1. Two presynaptic mechanisms appear to be involved in the regulation of noradrenaline release during nerve stimulation. The first one, mediated by β-adrenoceptors, operates at low frequencies of nerve stimulation, leading to an increase in transmitter release. The second one, mediated through α-adrenoceptors, is triggered when higher concentrations of the transmitter are reached in the synaptic cleft, leading to inhibition of transmitter release, probably through a restriction in the availability of calcium for the secretory process.

2. It is postulated that part of the anti-hypertensive effects of drugs like clonidine, α-methyldopa and β-receptor-blocking agents may be related to their long-term effects on presynaptic adrenoceptors.

Key words: clonidine, α-methyldopa, phenoxybenzamine, presynaptic receptors, propranolol.

The release of noradrenaline elicited by nerve stimulation in the peripheral sympathetic system is regulated through a negative feedback mechanism mediated by presynaptic α-adrenoceptors (Langer, Adler, Enero & Stefano, 1971; Farnebo & Hamberger, 1971; Enero, Langer, Rothlin & Stefano, 1972; Starke, 1972; Langer, 1973; Rand, Story, Allen, Glover & McCulloch, 1973; Langer, 1974; Langer, Dubocovich & Celuch, 1975a; Langer, Enero, Adler-Graschinsky, Dubocovich & Celuch, 1975b). According to this hypothesis the neurotransmitter released by nerve stimulation, once it reaches a threshold concentration in the synaptic gap, would activate presynaptic α-adrenoceptors, triggering a negative feedback mechanism that inhibits further release of the transmitter.

In support of this hypothesis it has been found that stimulation of presynaptic α-adrenoceptors reduces noradrenaline release during nerve stimulation (Farnebo & Hamberger, 1971; Langer, Enero, Adler-Graschinsky & Stefano, 1972; Starke, 1972). On the other hand, block of presynaptic α-adrenoceptors by phentolamine or phenoxybenzamine increases the release of noradrenaline during nerve stimulation, regardless of whether the adrenergic receptor that mediates the responses of the effector organ is α or β in type (Langer, 1970; Starke, Montel & Schumann, 1971; Enero et al., 1972; Cubeddu, Barnes, Langer & Weiner, 1974; Farah & Langer, 1974).

The negative feedback mechanism for noradrenaline release should be expected to operate most effectively when the transmitter released by nerve impulses reaches a threshold concentration in the synaptic gap. In agreement with this view, it has been shown that when the endogenous noradrenaline stores are depleted, the effectiveness of phenoxybenzamine in increasing the release of [3H]noradrenaline and dopamine-β-hydroxylase during nerve stimulation is almost completely lost (Enero & Langer, 1973; Cubeddu & Weiner, 1975).

Although both the pre- and the post-synaptic α-receptors are stimulated by α-receptor agonists and blocked by α-receptor antagonists, it appears that the postsynaptic α-receptors that mediate the responses of the effector organ are not identical with the presynaptic α-adrenoceptors which regulate the release of noradrenaline during nerve stimulation. Phenoxybenzamine is about 30 times more potent in blocking the postsynaptic α-receptors when compared with the presynaptic α-receptors in the perfused cat spleen (Dubocovich & Langer, 1974;
Cubeddu et al., 1974). In support of the view that the pre- and the post-synaptic α-receptors are not identical, it has been recently shown that clonidine, α-methylnoradrenaline and oxymetazoline are more potent in reducing noradrenaline release during nerve stimulation than in simulating the post-synaptic α-adrenoceptors (Starke, Montel, Gaykner nerve stimulation than in simulating the post-

Additional evidence in favour of the presynaptic location of the α-adrenoceptor involved in the regulation of noradrenaline release was obtained recently in the rat submaxillary gland. These experiments were carried out after atrophy of the secretory cells elicited by duct ligation 15 days before the experiment (Standish & Shafer, 1957). In these atrophied salivary glands the secretory responses to adrenergic or cholinergic agonists are abolished but there are no changes in either the cholinergic or the noradrenergic innervation. Exposure to phentolamine (3·1 μmol/l) increased the release of [3H]noradrenaline from slices of the normal submaxillary gland elicited by 60 mmol/l potassium, by 2·97 (±0·59)-fold (n = 8); under these experimental conditions the increase in release obtained by phentolamine in atrophied salivary glands was 3·65 (±0·78)-fold (n = 7).

It appears that the negative feedback mechanism which regulates the release of noradrenaline during nerve stimulation operates by restricting the calcium available for the excitation-secretion coupling. In support of this view, it has been found that the inhibition of transmitter release obtained by exposure to exogenous noradrenaline is more pronounced when the calcium concentration in the medium is reduced from 2·6 to 0·26 mmol/l (Langer et al., 1975a). The potentiation of the inhibitory effects of α-receptor agonists on neurotransmission by decrease of calcium concentration indicates that activation of presynaptic α-receptors may reduce the availability of calcium for the secretory process.

It is noteworthy that the sensitivity of the presynaptic α-adrenoceptors can be modified after exposure to a large concentration of an α-receptor agonist. In the cat spleen perfused with cocaine, there was a nearly twofold increase in transmitter release by nerve stimulation after 60 min of exposure to 0·59 μmol/l of (−)noradrenaline. This effect is probably due to a short-lasting subsensitivity of the presynaptic α-adrenoceptors resulting from the exposure to noradrenaline. These results are compatible with the view that chronic stimulation or blockade of presynaptic receptors may lead to changes in their sensitivity to the neurotransmitter, as it has been already demonstrated for the postsynaptic receptor. Consequently, attention should be drawn to the fact that chronic stimulation or blockade of the presynaptic receptors may lead to changes in their sensitivity which may affect the regulation of neurotransmission. The latter may be of interest in connection with prolonged anti-hypertensive therapy with agents which act on presynaptic receptors.

Exposure to (−)-isoprenaline (12 nmol/l) enhances the release of noradrenaline during nerve stimulation at low frequencies in several noradrenergically innervated organs: guinea-pig atria, perfused cat spleen, cat thoracic aorta and cat nictitating membrane. These effects of (−)-isoprenaline on transmitter release are concentration-dependent and readily reversed by washing. The enhancement in transmitter release obtained with (−)-isoprenaline is stereospecific, since it was not observed with (+)-isoprenaline (Celuch, Dubocovich & Langer, 1976).

The effects of (−)-isoprenaline on transmitter release can be prevented by preincubation with 0·1 μmol/l (±)-propranolol. These results are compatible with the presence of β-adrenoceptors in noradrenergic nerve endings (Langer, Adler-Graschinsky & Enero, 1974; Adler-Graschinsky & Langer, 1975). These receptors would mediate a positive feedback mechanism for noradrenaline released at low frequencies of nerve stimulation. Dahlöf, Åblad, Borg, Ek & Waldeck (1975) suggested that these presynaptic receptors are of the β₁ type, because they are blocked by metoprolol, a selective β₁-receptor blocking agent.

The facilitation of transmitter release triggered by the activation of presynaptic β-receptors may be mediated through an increase in the levels of cyclic AMP in noradrenergic nerve endings. Papaverine, a phosphodiesterase inhibitor, enhances noradrenaline release during nerve stimulation and in addition it shifts to the left the dose-response curve to (−)-isoprenaline on transmitter release (Dubocovich & Langer, 1976). On the other hand, the effect of papaverine on noradrenaline release is significantly reduced by exposure to 0·1 μmol/l propranolol.

It is noteworthy that Stjärne & Brundin (1975) have shown that isoprenaline increases [3H]noradrenaline release elicited by field stimulation from strips of human omental arteries and veins. A similar effect was obtained with low concentrations
of adrenaline (Stjärne & Brundin, 1975) although a further increase in the concentration of adrenaline led to inhibition of transmitter release due to stimulation of α-presynaptic recept.

Although propranolol administered acutely prevented the increase in transmitter release obtained in the presence of isoprenaline (Celuch et al., 1976), the β-receptor-blocking agent on its own did not always reduce significantly noradrenaline release. Propranolol reduced transmitter release elicited by nerve stimulation in isolated guinea-pig atria (Adler-Graschinsky & Langer, 1975) and in the calf muscle of the cat pretreated with phenoxybenzamine (Dahlöf et al., 1975). However, exposure to propranolol (0.1 μmol/l) did not reduce transmitter release in the perfused cat spleen (Celuch et al., 1976) or in human omental arteries and veins (Stjärne & Brundin, 1975).

It is possible that long-term β-receptor blockade may be more effective in reducing the amount of transmitter released per impulse from noradrenergic nerves. In support of this view it has been reported that in the pithed rat preparation, chronic, but not acute, administration of practolol reduced the pressor responses to preganglionic sympathetic stimulation (Lewis, 1974).

Consequently, it appears that two presynaptic mechanisms are involved in the regulation of noradrenaline release during nerve stimulation. The first one, mediated by β-adrenoceptors, would be activated by low concentrations of noradrenaline leading to an increase in transmitter release. The second one, mediated through α-adrenoceptors, is triggered when higher concentrations of the transmitter are reached in the synaptic cleft, leading to inhibition of transmitter release. Compatible with this hypothesis is the fact that, in most tissues, the concentrations of noradrenaline required for stimulation of postsynaptic α-adrenoceptors are about 100-fold those necessary to stimulate β-adrenoceptors (Adler-Graschinsky & Langer, 1975).

In view of the fact that the most pronounced increases in transmitter release are obtained when the α-adrenoceptors are blocked by drugs, it appears that the major regulatory mechanism for noradrenaline release under physiological conditions is mediated by the presynaptic α-adrenoceptors.

Although the anti-hypertensive effects of clonidine and α-methyldopa appear to be predominantly of central origin, it is likely that stimulation of presynaptic α-adrenoceptors in the periphery may contribute to the hypotensive effects of these drugs. It is of interest that both clonidine and α-methylnoradrenaline are more potent agonists on the presynaptic α-adrenoceptors than on the postsynaptic receptors (Starke et al., 1974, 1975).

It is possible that the anti-hypertensive effect of β-receptor-blocking agents is at least partly due to a decrease in noradrenaline release as a consequence of the prolonged block of the presynaptic β-adrenoceptors that mediate the positive feedback mechanism which regulates noradrenaline release by nerve stimulation. Ljung, Åblad, Dahlöf, Henning & Huttberg (1975) reported that prolonged administration of propranolol or metoprolol to spontaneously hypertensive rats resulted in a reduction of the responses to postganglionic nerve stimulation in the portal vein preparation without concomitant changes in sensitivity to exogenous noradrenaline. These authors concluded that the reduced transmitter release which occurs after prolonged blockade of receptors of the β1 type contributes to the anti-hypertensive effects of β-receptor-blocking drugs.

References


