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Presynaptic autoreceptors regulating transmitter release

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Abstract

The discovery that the cytoplasmic membrane of presynaptic nerve terminals possess receptors that modulates release of neurotransmitters was made 35 years ago. This new concept represents a clear departure from the traditional view that neuronal communication was unidirectional, i.e. from the nerve terminal to the postsynaptic receptor, because the transfer of information via presynaptic receptors occurs in the opposite direction: from the synaptic cleft to the nerve terminals which release the neurotransmitter. Presynaptic release-modulating autoreceptors and heteroreceptors represent suitable targets for pharmacological intervention by exogenous compounds acting as agonists, partial agonists or antagonists. Such compounds may be of therapeutic value by influencing transmitter release presynaptically, and having fewer side effects than the well-established approach of using agonists or antagonist drugs to stimulate or block postsynaptic receptors.

Keywords: Neurotransmitters; Presynaptic autoreceptors; Presynaptic heteroreceptors; Transmitter release; Antidepressants; Migraine; Schizophrenia; Hypertension

1. Historical perspective

Following the identification of noradrenaline (NA) as a chemical transmitter in the peripheral and in the central nervous system, it was generally accepted that the noradrenergic nerve terminals were associated with the functions of synthesis, storage, release and subsequent neuronal transport of the neurotransmitter through the sodium and chloride dependent NA transporter. The membranes of the noradrenergic varicosities and nerve endings were considered to have no receptors, which were only located at the postsynaptic level and associated with the postsynaptic actions of the released transmitter.

The classical view was that NA released from nerve endings acted on postsynaptic α- or β-adrenoceptors to elicit the specific responses of the effector organ in the periphery and on postsynapic neurons in the central nervous system (Fig. 1).

Brown and Gillespie (1957) reported, in the perfused cat spleen, that the adrenoceptor blocking agent phenoxybenzamine (PBZ) caused a frequency dependent increase in the release of NA, and attributed this effect to the blockade by PBZ of the postsynaptic α-adrenoceptors. They showed the amount of NA released into the blood perfusing the spleen was increased when the α-adrenoceptors of the spleen were blocked. These authors proposed a transsynaptic control of NA release whereby activation of the postsynaptic α-receptors had an inhibitory effect on the NA-releasing terminals.

Since PBZ possesses several important pharmacological actions we examined the effects of different concentrations of PBZ on the sympathetically isolated nerve muscle preparation of the cat nictitating membrane. This in vitro nerve–muscle preparation of the cat nictitating membrane has a dense noradrenergic innervation and contains as much as 10 μg NA per g wet tissue, associated with terminal varicosities, remote from the cell bodies in the superior cervical ganglion.

We studied different concentrations of PBZ on several effects of the drugs: (a) inhibition of the neuronal NA transporter; (b) inhibition of extraneuronal uptake; (c) blockade of responses to sympathetic nerve stimulation; (d) blockade of responses of the smooth muscle of the nictitating membrane to exogenous NA; (e) release and metabolism of ^{3}H-NA elicited by nerve stimulation (Enero et al., 1972).

In parallel experiments, designed to evaluate the possibility of transsynaptic regulation of NA release, we carried out similar experiments in guinea pig atria and in perfused cat hearts, where the postsynaptic effects produced by NA released during nerve stimulation are mediated by β-adrenoceptors. Both phentolamine and PBZ produced large increases in NA

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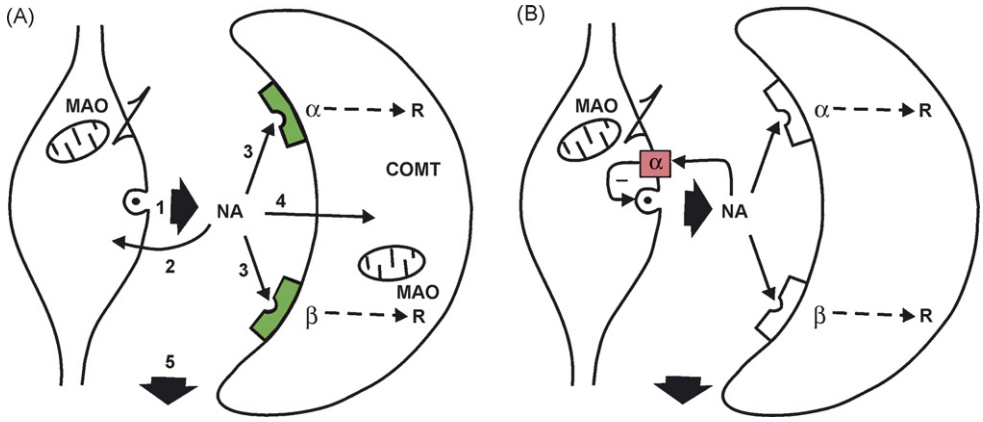

Fig. 1. (A) Classical view. Classical concept of neurotransmission in the 1960s. Varicosities of noradrenergic terminals are involved in the synthesis, storage and calcium-dependent release in response to the occurrence of an action potential. Postsynaptic receptors on effector cells. The generally held opinion was that nerve endings had no receptors. (1)—exocytotic release of NA; (2)—noradrenaline transporter mediating neuronal uptake; (3)—effects on α-or β-adrenoceptors on effector cells; (4)—extraneuronal uptake; R—response; MAO—monoamine oxidase; COMT—catechol-O-methyltransferase. (B) View in 2007. In addition to the well-established postsynaptic receptors of the effector organ, terminal varicosities possess α_2-presynaptic receptors which modulate NA release through a negative-feedback mechanism which plays a physiological role in neurotransmission.

overflow during nerve stimulation at concentrations which did not inhibit the neuronal or extraneuronal uptake of NA (Langer et al., 1971).

These surprising results led to the hypothesis that in the noradrenergic varicosities there were presynaptic α-adrenoceptors regulating the release of NA. From 1971 and 1972 several detailed abstracts and extensive, full publications provided convincing evidence for the existence of presynaptic inhibitory α-autoreceptors in the cat nictitating membrane, in isolated guinea-pig atria, in the perfused rabbit and cat heart, and in rat irides (Langer et al., 1971; Enero et al., 1972; Farnebo and Hamberger, 1971).

The evidence can be summarized as follows: (1) the calcium-dependent release of NA evoked by electrical stimulation, was inhibited by α-adrenoceptor agonists; (2) α-adrenoceptor antagonists, on their own, enhanced neurotransmitter release; (3) the interaction between agonists and antagonists that modify transmitter release was of a competitive nature (Langer, 1997).

However, not all the experimental evidence was rigorous enough as proof for the hypothesis of presynaptic autoreceptors. For instance, Kirpekar and Puig (1971) employed the flow-stop protocol in the perfused cat spleen, which was later shown to increase metabolism of released NA during ''flow-stop'', as demonstrated by Dubocovich and Langer (1973). This experimental condition (flow-stop) increases the proportion of released NA which is metabolised, an effect blocked by PBZ. Therefore, these results did not constitute sufficient experimental evidence, even if the hypothesis proposed by Kirpekar and Puig (1971) turned out to be correct.

The presynaptic hypothesis proposed that NA release was regulated through a negative-feedback mechanism by presynaptic inhibitory α-adrenoceptors, whereby the synaptic concentration of the released neurotransmitter regulates its own release through a negative-feedback mechanism. This mechanism is highly dependent on the frequency of stimulation. Evidence for this autoregulation of neuronal chemical signalling by presynaptic inhibitory autoreceptors was obtained in vitro and in vivo conditions both in the peripheral as well as the central nervous system (Langer et al., 1971; Enero et al., 1972; Farnebo and Hamberger, 1971; Langer, 1981; Langer, 1997).

A second discovery came from the analysis of the effects of PBZ on presynaptic α-adrenoceptors that regulate transmitter release, and postsynaptic smooth muscle α-adrenoceptors that mediate vasoconstriction in the cat spleen. To our surprise, we found in the perfused cat spleen that PBZ was 100 times more potent in blocking the postsynaptic α-adrenoceptors than in blocking presynaptic α-adrenoceptors regulating NA release (Dubocovich and Langer, 1974; Cubeddu et al., 1974).

Such results on different α-receptor subtypes were subsequently confirmed by establishing differences in relative order of potencies of a variety of agonists and antagonists on pre and postsynaptic α-adrenoceptors. The proposal to divide the α-adrenoceptors in α_1 and α_2 subtypes was made in 1974 (Langer, 1974) and the following years confirmed and extended these findings. Cloning and expression succeeded in identifying α_1-adrenoceptors (with three varieties, A, B and D) and α_2-adrenoceptors (A, B and C) as reviewed by Bylund et al. (1994). Most of the presynaptic receptors belong to the α_{2A} subtype (Starke, 2001).

Following Ahlquist (1948) classification of adrenopceptors into α and β categories, it was generally accepted for the following 26 years that α-receptors represented a homogenous population. Establishing pharmacological differences between α_1-and α_2-receptors in 1974 was a landmark for the discovery of other receptor subtypes and stimulated the search for innovative drugs with high affinity, selectivity and the potential for useful therapeutic indications. The further subdivision of α_1-and α_2-adrenoceptors each into three further subtypes (Bylund et al., 1994) opens more possibilities for the discovery of new therapeutic agents.

Following the discovery of presynaptic autoreceptors and the two classes of α-adrenoceptors in the early 1970s, many