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Molecular mechanisms underlying the modulation of exocytotic noradrenaline release via presynaptic receptors

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This review is dedicated to Georg Hertting on the occasion of his 80th birthday

Abstract

The release of noradrenaline from nerve terminals is modulated by a variety of presynaptic receptors. These receptors belong to one of the following three receptor superfamilies: transmitter-gated ion channels, G protein-coupled receptors (GPCR), and membrane receptors with intracellular enzymatic activities. For representatives of each of these three superfamilies, receptor activation has been reported to cause either an enhancement or a reduction of noradrenaline release. As these receptor classes display greatly diverging structures and functions, a multitude of different molecular mechanisms are involved in the regulation of noradrenaline release via presynaptic receptors. This review gives a short overview of the presynaptic receptors on noradrenergic nerve terminals and summarizes the events involved in vesicle exocytosis in order to finally delineate the most important signaling cascades that mediate the modulation via presynaptic receptors. In addition, the interactions between the various presynaptic receptors are described and the underlying molecular mechanisms are elucidated. Together, these presynaptic signaling mechanisms form a sophisticated network that precisely adapts the amount of noradrenaline being released to a given situation.

Keywords: Presynaptic; Vesicle exocytosis; Ca^{2+} channels; G protein-coupled receptors; Transmitter-gated ion channels

Abbreviations: BoNT/A, botulinum neurotoxin type A; CAPS, Ca^{2+}-dependent activator protein for secretion; DAG, diacylglycerol; Gβγ, G protein βγ subunits; GAP-43, growth associated protein of 43 kDa; GEFII, guanine nucleotide exchange factor II; GPCR, G protein-coupled receptors; hrs-2, hepatocyte growth factor-regulated tyrosine kinase substrate 2; IP_3, inositol trisphosphate; K_M, M-type K^+; LDCV, large dense core vesicles; MARCKS, myristoylated alanine-rich C kinase substrate; nAChR, nicotinic acetylcholine receptors; NO, nitric oxide; NSF, *N*-ethylmaleimide-sensitive fusion protein; PACAP, pituitary adenylyl cyclase-activating peptides; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; SNAP, soluble *N*-ethylmaleimide sensitive factor attachment proteins; SNARE, soluble *N*-ethylmaleimide sensitive factor attachment protein receptors; VAMP, vesicle associated membrane protein; VIP, vasoactive intestinal peptide.

Contents

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1. Introduction

Changing the strength of synaptic transmission is a powerful means to modify the communication in a neuronal network: minor modifications at single synapses may lead to fundamental alterations in the entire network, and such changes are believed to be the basis of memory formation (Kandel, 2001). Two types of modifications in the strengths of single synapses have been observed: one depends on the prior activity in the synapse (Zucker & Regehr, 2002), and the other one is caused by mediators released from neurons or even glial cells. Such endogenous mediators exert their effects either via ionotropic receptors within a time scale of milliseconds or via metabotropic receptors with actions occurring rather within seconds or even minutes. The first group can be categorized as fast neurotransmitters, whereas the second group is rather appreciated as slow neuromodulators (Kaczmarek & Levitan, 1987). To change the strength of synaptic transmission, neurotransmitters as well as neuromodulators may either affect the release of the synaptic transmitter or the resulting response. Since synaptic transmitters are released from specialized nerve endings, also known as presynapses, the former phenomenon is designated presynaptic modulation. Accordingly, receptors mediating such a presynaptic modulation are categorized as 'presynaptic receptors', and Riker et al. (1957), who detected stimulatory effects of quaternary ammonium compounds at the neuromuscular junction, appear to be the first to use this specific term. At the same time, Frank and Fuortes (1957) showed that γ-aminobutyric acid (GABA) reduced excitatory transmitter release from primary afferent nerve endings in the spinal cord. In the same year, first evidence for the modulation of noradrenaline release via presynaptic receptors was presented: (i) Brown and Gillespie (1957) reported that phenoxybenzamine raised noradrenaline release, but the authors did not realize that this phenomenon might have been caused by the blockade of presynaptic α-adrenoceptors which mediated an autoinhibitory feedback modulation; (ii) Trendelenburg (1957) showed that morphine reduced contractions of the nictitating membrane through a presynaptic site of action.

Hence, it is five decades that the modulation of transmitter release via presynaptic receptors has been investigated. Meanwhile, effects of either neurotransmitters or receptor agonists and antagonists on transmitter release have been described for a huge number of different synapses, and the results have been summarized in several reviews (Langer, 1977; Westfall, 1977; Starke, 1981; Starke et al., 1989; Vizi et al., 1991; Langer, 1997; Wu & Saggau, 1997; Miller, 1998; Boehm & Kubista, 2002). A group of neurotransmitters for which presynaptic modulation has been described in great detail are the monoamines, and various reviews have dealt with the receptor-dependent modulation of catecholamine release in general (Langer, 1974, 1981) and of noradrenaline release in particular (Starke, 1977, 1987; Fuder & Muscholl, 1995). In this review, we concentrate on the mechanisms underlying the modulation of noradrenaline release via presynaptic receptors.

Neurotransmitters that activate presynaptic receptors may be released from either the very same nerve terminal or from a different axon ending. In the first case, the presynaptic receptor is designated autoreceptor, whereas in the latter case, the receptor is named presynaptic heteroreceptor. Although presynaptic heteroreceptors have been discovered first (see above), the description of presynaptic autoreceptors was particularly important for the identification of receptor subtypes. For instance, α_2-adrenoceptors and H_3 histamine receptors were detected as presynaptic autoreceptors mediating the feedback regulation of transmitter release (Langer, 1974; Arrang et al., 1983). The functions of presynaptic autoreceptors were the focus of specialized reviews (Starke, 1987; Starke et al., 1989).

As stated above, receptors located at the presynapse are designated presynaptic receptors and thus appear to be categorized by morphological means. The presynapse is an axonal structure filled with vesicles which are exocytosed to release the neurotransmitter. Exocytosis occurs at 'active zones' which, however, cover only a small part of the entire nerve ending (Matthews, 1996; Zhai & Bellen, 2004). Accordingly, one has to pose the question whether a presynaptic receptor is only a binding site located at the active zone, or whether binding sites located somewhere else at the nerve terminal are also presynaptic receptors. In the latter case, one would have to precisely set the boundaries of the presynapse to know whether a receptor is a presynaptic one. Hence, it appears impossible to characterize a presynaptic receptor by mere morphological means. Accordingly, presynaptic receptors are rather characterized by their functions, that is, the modulation of one or more of the physiological tasks of the presynapse. Apart from vesicle exocytosis and concomitant transmitter release, nerve terminals