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Human presynaptic receptors

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ABSTRACT

Presynaptic receptors are sites at which transmitters, locally formed mediators or hormones inhibit or facilitate the release of a given transmitter from its axon terminals. The interest in the identification of presynaptic receptors has faded in recent years and it may therefore be justified to give an overview of their occurrence in the autonomic and central nervous system; this review will focus on presynaptic receptors in human tissues.
Autoreceptors are presynaptic receptors at which a given transmitter restrains its further release, though in some instances may also increase its release. Inhibitory autoreceptors represent a typical example of a negative feedback; they are tonically activated by the respective endogenous transmitter and/or are constitutively active. Autoreceptors also play a role under pathophysiological conditions, e.g. by limiting the massive noradrenaline release occurring during congestive heart failure. They can be used for therapeutic purposes; e.g., the α_2-adrenoceptor antagonist mirtazapine is used as an antidepressant and the inverse histamine H_3 receptor agonist pitolisant has been marketed as a new drug for the treatment of narcolepsy in 2016.
Heteroreceptors are presynaptic receptors at which transmitters from adjacent neurons, locally formed mediators (e.g. endocannabinoids) or hormones (e.g. adrenaline) can inhibit or facilitate transmitter release; they may be subject to an endogenous tone. The constipating effect of the sympathetic nervous system or of the antihypertensive drug clonidine is related to the activation of inhibitory α_2-adrenoceptors on postganglionic parasympathetic neurons. Part of the stimulating effect of adrenaline on the sympathetic nervous system during stress is related to its facilitatory effect on noradrenaline release via β_2-adrenoceptors.

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Contents

1. Introduction 2
2. How to identify presynaptic receptors in human tissues? 2
3. Presynaptic receptors in the sympathetic nervous system 4
4. Presynaptic receptors in the parasympathetic nervous system 10
5. Presynaptic receptors in the central nervous system 10
6. Concluding remarks 17
Conflict of interest 17
Acknowledgments 17
References 18

Abbreviations: 5-HT, 5-Hydroxytryptamine, serotonin; ACh, Acetylcholine; AChE, Acetylcholine esterase; AMPA, (*RS*)-α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BAPTA, 1,2-Bis(o-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid; B_{max}, Maximum binding capacity; CC, Cerebral cortex; DA, Dopamine; DP, Receptor for prostaglandins of the D series; EC_{50}, Concentration causing 50% of the maximum effect; $EC_{30\%}$, $EC_{40\%}$, Concentration increasing an effect by 30 and 40%, respectively; Enk, Enkephalin; EP, Receptor for prostaglandins of the E series; GABA, γ-Aminobutyric acid; HFS, High-frequency stimulation; HPLC, High performance liquid chromatography; K_b or K_d, Dissociation constant; K_i, Inhibition constant; mGluR, Metabotropic glutamate receptor; NA, Noradrenaline; nAChR, Nicotinic acetylcholine receptor; NMDA, N-Methyl-D-aspartate; NPY, Neuropeptide Y; N-VSCC, N-type voltage-sensitive Ca^{2+} channel; pA_2, Negative decadic logarithm of the antagonist concentration that causes a twofold shift to the right of the concentration-response curve of a given agonist; PG, Prostaglandin; POP, Pseudo-one-pulse stimulation; PSS, Physiological salt solution; PTH, Parathyroid hormone; SD, Standard deviation; SEM, Standard error of the mean; SOM, Somatostatin; SP, Substance P; Tat, Human immunodeficiency virus-1 (HIV-1)-encoded transactivator of transcription; TP, Receptor for thromboxane A_2; VSNaC, Voltage-sensitive Na^+ channel.

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1. Introduction

Synapses represent the junction between the nerve endings of a neuron and the soma-dendritic part of a subsequent neuron or an end organ (e.g. smooth muscles, glands). After crossing the synaptic cleft, the transmitter either inhibits or activates the subsequent neuron or the end organ via postsynaptic receptors. In addition, the transmitter modulates its own further release via presynaptic autoreceptors; in most instances, an inhibitory influence occurs (negative feedback). Presynaptic heteroreceptors (which may be inhibitory or facilitatory) are activated by other transmitters released from neighbouring neurons or by mediators formed in the vicinity of the nerve endings (e.g., biogenic amines, kinins, eicosanoids) or borne by the blood stream (hormones).

Postsynaptic receptors have attracted much more attention than presynaptic ones. The latter ones have been identified most frequently in tissues from animals and only to a limited extent also in human tissues. Since reviews dedicated to human presynaptic receptors are limited to only certain aspects of the whole topic (e.g. presynaptic receptors in the brain in the review by Raiteri, 2006), it may be justified to provide a comprehensive overview of the human presynaptic receptors described so far.

2. How to identify presynaptic receptors in human tissues?

2.1. Identification of release-modulating receptors

Human presynaptic receptors have frequently been identified by superfusion experiments with human tissues, including strips or segments from smooth muscle and slices or synaptosomes from specific brain regions. Exocytotic transmitter release is most often induced by electrical stimulation. This type of stimulation closely mimics the physiological chain of events eventually leading to quasi-physiological exocytotic transmitter release. The authenticity of the release process is proven by two types of experiments. First, transmitter release is abolished by tetrodotoxin, which inhibits the voltage-dependent sodium channels carrying the action potential invading the axon terminals. Second, transmitter release is also abolished by omission of calcium from the superfusion medium since calcium, entering the nerve endings via voltage-dependent calcium channels, is crucial for the exocytotic release process (reviewed in Boehm & Kubista, 2002; Fuder & Muscholl, 1995; Starke, 1977; Starke, Göthert, & Kilbinger, 1989).

While most presynaptic receptors have been identified functionally by analysis of exocytotic release, modulation of release also occurs when this release is transporter-mediated, for instance, amino acid neurotransmitters (see Attwell, Barbour, & Szatkowski, 1993; Levi & Raiteri, 1993). The release-enhancing effect of activated $GABA_A$ autoreceptors seems to occur via a cooperation of exocytosis and a reversal of the GABA carrier (Mantovani, Moser, Haas, Zentner, & Feuerstein, 2009; see also Section 5.2.1). However, the modulation of transporter-mediated release by human presynaptic receptors has only been investigated rarely (Hatta, Yasuda, & Levi, 1997; Hatta, Maruyama, Marshall, Imamura, & Levi, 1999; Maruyama, Hatta, Yasuda, Smith, & Levi, 2000).

The superfusion technique for functional analysis of presynaptic receptors offers some advantages regarding receptor theory: The known concentration of an exogenous receptor ligand in the quasi-exhaustless superfusion fluid is not diminished by the binding to a receptor within the superfused tissue (Zone A phenomenon according to Straus & Goldstein, 1943). An incubation approach with a finite incubation volume, however, may not guarantee that only a negligible fraction of total drug is combined with receptor sites. The quasi-exhaustless superfusion fluid allows one to equate the known concentration of an exogenous ligand with the uncombined ligand (Feuerstein & Limberger, 1999; see also Feuerstein, Sauermann, Allgaier, Agneter, & Singer, 1994).

The transmitter released upon electrical stimulation may be determined by methods like HPLC, but mostly radioisotope experiments were carried out. For this purpose, isolated tissues are first preincubated with a physiological salt solution containing the radioactively labelled neurotransmitter (e.g., ^{3}H-noradrenaline, ^{3}H-dopamine, ^{3}H-serotonin, ^{3}H-GABA) which is taken up into the nerve endings via the respective neuronal transporter and accumulated within the vesicles or, as in the case of ^{3}H-GABA and ^{3}H-glutamate, in both vesicles and the cytoplasm of terminals (for review, see Nicholls, 1989; Starke et al., 1989). To study acetylcholine and histamine release ^{3}H-choline and ^{3}H-histidine are used which, in turn, are transformed to ^{3}H-acetylcholine and ^{3}H-histamine, respectively (reviewed in Starke et al., 1989). In the case of the latter, care must be taken to separate ^{3}H-histamine from ^{3}H-histidine (Arrang, Garbarg, & Schwartz, 1983).

It has already been mentioned that electrical stimulation is the most appropriate way to induce exocytotic transmitter release. However, the choice of stimulation parameters varies extremely depending on the type of transmitter or tissue. For measurement of noradrenaline release from brain slices weak stimulation conditions are sufficient whereas stronger conditions (in particular, an increase in stimulation frequency and/or current strength) are necessary to release appropriate amounts of acetylcholine, GABA or glutamate. Although noradrenaline release in brain slices can be elicited easily, more drastic stimulation conditions are required to induce noradrenaline release in peripheral tissues. Although an increase in the stimulation frequency increases the amount of transmitter release, it decreases the extent of the presynaptic effect (which may even escape detection). Selecting the most appropriate stimulation conditions is frequently not trivial (for stimulation protocols, see Starke et al., 1989).

The electrical stimulation parameters, especially their thresholds to elicit a sufficient amount of transmitter release, are dependent on the superfusion chambers used, most importantly on their relation between dead volume and surface of electrodes. In this context sufficient means that release should be evaluable without too high of coefficients of variation (SD/mean) and - correspondingly - without too large of sample sizes to obtain, for instance, reliable estimates of the average release per stimulation period. To identify presynaptic receptors appropriate agonists at a given receptor are studied in the absence or presence of antagonists. It proved favourable in many studies to administer two periods of electrical stimulation and to add the agonist under study to the medium during the second period of stimulation (Fig. 1A) and the antagonist during both periods. Auxiliary drugs may be present in the medium as well and this will be explained here for noradrenergic neurons (although it is true also for other types of neurons; Fig. 1). A blocker of the neuronal noradrenaline transporter (e.g. desipramine) may be added to the medium to avoid auto- or heteroexchange (i.e. an increase of ^{3}H-noradrenaline release via the noradrenaline transporter) elicited by unlabelled noradrenaline itself (which may be used as agonist) or another drug, respectively. Such an uptake blocker may also be used to avoid the interaction of a test drug with the uptake mechanism or to increase the amount of measured tritium. A blocker of the presynaptic α_2-autoreceptor (e.g. rauwolscine) may be used to avoid the interference of test drugs with the α_2-autoreceptor, to increase the amount of noradrenaline release and/or to increase the extent of the effect elicited via a presynaptic heteroreceptor (for composition of superfusion media, see Starke et al., 1989).

2.2. How to prove the presynaptic site

Even if a release-modulating receptor has been identified, its exact location is still not clear. The situation is simplest for postganglionic sympathetic neurons for which only a presynaptic site of action is possible since the ganglion with the synapse between the pre- and postganglionic neuron is far from the end organ studied in the superfusion experiment. If parasympathetic neurons are studied instead, the release-modulating receptor might also be located on the preganglionic

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