Role of Presynaptic receptors in health and disease

Anandabaskar Nishanthi, Mourouguessine Vimal
1. Department of Pharmacology, JIPMER, Puducherry, India.
2. Department of Pathology, Sri Manakula Vinayagar Medical College, Puducherry, India.
*Corresponding author: Anandabaskar Nishanthi, Department of Pharmacology, JIPMER, Puducherry, India.
E-Mail: nishanthi11189@gmail.com

ABSTRACT

Maintenance of homeostasis is the norm of nature. In order to maintain homeostasis in neuronal transmission, fine tuning of neurotransmitter release from the presynaptic nerve terminals is required. This role is played by the receptors present on the presynaptic nerve terminals, which sense the amount of neurotransmitter in the synaptic cleft and in turn regulate the neurotransmitter release. These receptors on activation, operate negative or positive feedback loops to inhibit or stimulate the neurotransmission respectively. Presynaptic receptors are present ubiquitously in all neuronal systems and mediate various physiological roles. They are also being used as pharmacological targets for certain diseases. They are utilized as potential targets for therapeutic agents in schizophrenia, narcolepsy, depression, Parkinson’s disease and Alzheimer’s disease. With advancing technologies for research, new presynaptic receptors are being discovered, their physiological roles demystified and are being manipulated as drug targets. This review focuses on various types of presynaptic receptors present in the different neuronal systems, their physiological role and how they are being employed as pharmacological targets.

1. INTRODUCTION

In 1957, Brown and Gillespie reported a causal relationship between blockade of α adrenoceptor with phenoxybenzamine and increase in noradrenaline overflow, which was elicited by nerve stimulation in perfused cat spleen. It was thus postulated that α adrenoceptors are present on the presynaptic nerve terminals, which on activation, inhibited the release of noradrenaline into the synaptic cleft. This led to the discovery of presynaptic receptors which play important physiological roles. Presynaptic receptors are those receptors present on, in or near the presynaptic axon nerve terminals, which on activation modulate neurotransmission. Presynaptic receptors act as sensors of the amount of neurotransmitters in the synaptic cleft. Low levels of neurotransmitter in synaptic cleft will activate the facilitatory presynaptic receptors, thus increasing the neurotransmitter release. On the contrary, high levels of neurotransmitter in the synaptic cleft will activate the inhibitory presynaptic receptors, thus inhibiting the neurotransmitter release. Thus, presynaptic receptors help in fine tuning of the neurotransmission to maintain homeostasis.

Types of presynaptic receptors: Presynaptic receptors can be classified into autoreceptors and heteroreceptors based on their location and the neurotransmitter that is modulated by these receptors. Autoreceptors are those receptors located on the presynaptic nerve terminals, which on activation inhibit or enhance the release of their own neurotransmitter. They mediate negative or positive feedback loops, modulating their own neurotransmission. For example activation of α2 autoreceptors present on the presynaptic nerve terminal of adrenergic neurons causes inhibition of noradrenaline release. This is called as homotropic interaction, in which the neurotransmitter released from the presynaptic terminals modulates its own neurotransmission by acting on the autoreceptors.

In contrast, heteroreceptors refer to those presynaptic receptors which are not activated by the neurotransmitters released from the nerve terminals on which they are situated. Heteroreceptors are activated by transmitters released from other neurons in the vicinity. For example activation of α2 heteroreceptors present on the presynaptic nerve terminals of cholinergic neurons inhibits the release of acetylcholine from these nerve terminals. Thus, the opposing actions of sympathetic and parasympathetic systems are not only brought about by the effector mechanisms but also stimulation of one neuronal family inhibits the activation of the other by acting on the heteroreceptors.
This type of intercommunication between different neuronal families is called as heterotopic interaction, where one neuronal family influences the neurotransmission of the other by acting on the heteroreceptors. Presynaptic receptors can also be classified as metabotropic or ionotropic receptors based on their signaling mechanisms. Metabotropic receptors are those that are coupled to G-proteins. Some examples are α₂, β₂, M₂, 5HT-1, 5 HT-2A, D₂ and H₃. Ionotropic receptors are ligand gated multisubunit ion channels. Some examples are GABA_A and nicotinic acetylcholine receptors.

Mechanisms of action of presynaptic receptors:
Presynaptic receptors modulate neurotransmitter release by various mechanisms. These mechanisms depend on the inhibitory or facilitatory nature of the presynaptic receptors. They also depend on whether they are G-protein-coupled receptors or ligand gated ion channels. They inhibit the neurotransmitter release by the following mechanisms:

Inhibition of voltage gated calcium channels in the presynaptic terminals: This type of signaling is mostly seen with metabotropic receptors, which are usually inhibitory autoreceptors or heteroreceptors. Activation of the metabotropic presynaptic receptors leads to activation of the G-proteins, which inhibits the enzyme adenyl cyclase. This causes a reduction in the levels of cAMP, leading to inhibition of voltage gated calcium channels which are involved in neurotransmitter release. For example α₂ presynaptic receptors are metabotropic receptors which inhibit neurotransmission by decreasing intracellular calcium.

Activation of presynaptic ion channels: Activation of inhibitory presynaptic receptors, open potassium or chloride ion channels, which leads to membrane hyperpolarization and inhibition of neurotransmitter release. Alternatively, activation of facilitatory presynaptic receptors leading to opening of sodium or calcium channels, leading to depolarization and exocytosis of the neurotransmitter. For example presynaptic nicotinic acetylcholine receptors are calcium permeable channels, thus calcium influx caused by their activation can lead to facilitation of neurotransmitter release.

Regulation of vesicle release complex: Activation of presynaptic receptors can influence the proteins involved in fusion of vesicles containing neurotransmitter to the plasma membrane of the presynaptic nerve terminals. It has been found that these receptors interact with syntaxin 1A and synaptotagmin.

Adrenergic presynaptic receptors: Adrenergic receptors are classified into two types: α and β receptors. Both are G-protein coupled receptors. The α adrenoceptors are further classified into α₁ and α₂ receptors. The β receptors are further classified into β₁, β₂ and β₃ receptors. The α₁A, α₁B and α₁D are the subtypes of α₁ receptors, and α₂A, α₂B and α₂C are the subtypes of α₂ receptors.

Both α₂ and β₂ receptors are present presynaptically as autoreceptors and heteroreceptors, thus modulating the neurotransmitter release. The α₂ receptors are inhibitory autoreceptors, which by negative feedback mechanism decrease the release of noradrenaline from the presynaptic nerve terminals. The α₂A and α₂C are the principal inhibitory presynaptic receptors with α₂B inhibiting the transmitter release only at selected sites. The β₂ receptors are stimulatory presynaptic receptors which enhance neurotransmission in adrenergic and other neuronal systems. For postsynaptic receptors, the concentration of noradrenaline required to stimulate α receptors is 100 times compared to that needed to stimulate β receptors. The same holds true for presynaptic receptors too. Low concentration of noradrenaline in the synapse stimulates presynaptic β receptors, whereas higher concentration stimulates presynaptic α receptors.

Apart from α₂ and β₂ receptors, other presynaptic receptors are also present in the adrenergic nerve terminals. They are classified into inhibitory and stimulatory presynaptic receptors. The various inhibitory presynaptic receptors in adrenergic nerve terminals are:
- Muscarinic receptors
- Dopaminergic receptors
- Serotonergic receptors
- Prostaglandin receptors
- Adenosine receptors
- Opiate receptors

The stimulatory presynaptic receptors in the adrenergic nerve terminals are angiotensin II and nicotinic receptors. Unlike α₂ and β₂ receptors, the other presynaptic receptors are not present in all adrenergic nerves.

Physiological role: Feedback inhibition of noradrenaline release from the sympathetic nerve terminals by α₂A autoreceptors protects the heart from excess sympathetic stimulation under normal resting conditions. However this protective role of α₂A adrenoceptors gets lost in chronic heart failure due to the desensitization of these receptors occurring due to high concentration of noradrenaline in the synaptic cleft. Thus, desensitization of these autoreceptors can lead to progression of cardiovascular diseases. It is also found that activation of α₂A autoreceptors in the locus coeruleus mediates sedation and is involved in sleep promoting pathway.

Pharmacological role: Clonidine and α-methyl noradrenaline are more potent stimulators of presynaptic α₂ adrenoceptors in the central nervous system.
system, thus inhibiting noradrenaline release during nerve stimulation. They are called as central sympatholytic drugs and are used in treatment of hypertension. Instead of α-methyl noradrenaline, its precursor α-methylldopa is used as it can cross the blood brain barrier.

Apaclonidine and brimonidine are presynaptic α2 adrenoceptor agonists, which decrease the aqueous humour secretion and are used in the treatment of glaucoma.

Dexmedetomidine is used as a sedative and analgesic in intubated and critically ill patients, especially those admitted in intensive care units. It is an agonist of α2 presynaptic receptors, thus inhibiting the release of noradrenaline in the locus coeruleus and mediating sedation.

Mirtazapine is an antidepressant that acts by antagonizing α2 autoreceptors and α2 heteroreceptors in the adrenergic and serotonergic nerve terminals respectively. Blockade of α2 autoreceptors and α2 heteroreceptors enhances the release of noradrenaline and serotonin respectively in the synaptic cleft, thus mediating its antidepressant effects. They also have 5HT-2 and 5HT-3 receptor blocking property.

Cholinergic presynaptic receptors: There are two types of acetylcholine receptors, namely muscarinic and nicotinic receptors. The muscarinic receptors are of 5 types: M1, M2, M3, M4 and M5. The M2 and M4 receptors are located in the presynaptic nerve terminals of cholinergic and other neuronal families, functioning as inhibitory autoreceptors and heteroreceptors respectively. The M2 receptors are the predominant presynaptic receptors present in the central and peripheral nervous system. They are G-protein coupled receptors, which on activation inhibit the release of acetylcholine or other neurotransmitters from the presynaptic terminals.

Nicotinic acetylcholine receptors are classified into two types: muscle type or neuronal type. The neuronal type of nicotinic receptors are present predominantly as autoreceptors and heteroreceptors in the central nervous system. They are excitatory presynaptic receptors mediating a positive feedback, which on activation enhances the release of neurotransmitters from the presynaptic terminals. They modulate the release of various neurotransmitters like acetylcholine, noradrenaline, dopamine, serotonin and glutamate. They are ligand gated cation channels composed of α and β subunits. There are 9 types of α subunit (α2 – α9) and 3 types of β subunit (β2 – β4). The association of different types of α and β subunits confers distinct structural and functional properties to the resultant nicotinic receptor.

Physiological role: The neuronal type of nicotinic acetylcholine (nACh) receptors are involved in mediating reward, attention, memory and learning. The areas of the brain concerned with memory formation are rich in neuronal nACh receptors. It is postulated that the majority of the cognitive functions controlled by nACh receptors are mediated by presynaptic nACh receptors, rather than those found postsynaptically.

Pharmacological role: Alzheimer’s disease is a neurodegenerative disorder associated with deposition of beta amyloid proteins. The beta amyloid proteins are toxic to the nicotinic acetylcholine receptors, especially to α2 nACh receptors. This leads to a depletion of nACh receptors and produces defects in the cholinergic synaptic transmission especially those mediated by the nACh receptors. Presynaptic nACh receptors are involved in maintaining cognition and its depletion leads to Alzheimer’s disease. Drugs that target nACh receptors could provide new treatment strategies for this disease.

Varenicline is a partial agonist at nACh receptors and is used for smoking cessation. It is partial agonist at the α4β2 nACh receptors and full agonist at the α2 nACh receptors. The α4β2 nACh receptors are present as stimulatory heteroreceptors on the dopaminergic neurons in the mesolimbic system, which on activation enhance dopaminergic neurotransmission. During smoking, when sufficient levels of nicotine are attained in blood, they stimulate the neuronal α4 β2 nACh receptors present presynaptically to induce the release of dopamine in the mesolimbic system, thus activating the reward circuitry. Varenicline being a partial agonist at α4β2 nACh receptors, enhance dopaminergic neurotransmission in the mesolimbic areas to some extent compared to the full agonist nicotine and thus help to alleviate the nicotine withdrawal symptoms.

Dopaminergic presynaptic receptors: There are 5 types of dopaminergic receptors, namely D1, D2, D3, D4 and D5. They are G-protein coupled receptors and divided into two major groups: the D1 and D2 classes of dopamine receptors. This classification is based on their structural, pharmacological and biochemical properties. The D1 class includes D1 and D5 receptors. They are present exclusively on the postsynaptic nerve terminals. The D2 class includes D2, D3 and D4 receptors. In contrast to the D1 class of dopamine receptors, D2 class receptors are present both presynaptically and postsynaptically in the dopaminergic neurons. The D2 receptors are the predominant type of autoreceptors involved in presynaptic regulation of dopamine release. There are two isoforms or splice variants of D2 dopamine receptors, D2L (D2-Long) and D2S (D2-Short). D2S is predominantly presynaptic whereas D2L is predominantly postsynaptically.

Physiological role: There are three main dopaminergic systems in the human brain: nigrostriatal,
mesocorticolimbic and tuberoinfundibular systems. Nigrostriatal pathway is involved in locomotor activity, mesocorticolimbic pathway is involved in governing the behavior of an individual, and tuberoinfundibular pathway is involved in regulating prolactin release from the pituitary gland.

It is found that D_{1}, D_{2} and D_{3} receptors are primarily involved in regulation of locomotor activity of an individual. Activation of the D_{2} class of autoreceptors cause decrease in the release of dopamine, which results in decreased locomotor activity. On the contrary, activation of postsynaptic dopamine receptors stimulate locomotion. D_{1}, D_{2} and some extent D_{3} receptors are also involved in reward and reinforcement mechanisms\textsuperscript{13}.

**Pharmacological targets:** Parkinson’s disease is a neurodegenerative disorder associated with bradykinesia, rigidity, resting tremors and postural instability. Dopamine agonists like bromocriptine and cabergoline can be used in the treatment of this disorder. It is found that dopamine agonists act on both presynaptic and postsynaptic D_{2} dopamine receptors to exert their action. By acting on the presynaptic D_{2} receptors, they inhibit the release of dopamine from the dopaminergic nerve terminals and thus reduce the dopamine turnover. Dopamine and its metabolites are neurotoxic to the dopaminergic neurons. Thus reduction in the dopamine turnover is associated with reduced oxidative stress, contributing to the neuroprotective action of the dopamine agonists\textsuperscript{14}.

Schizophrenia is a chronic and disabling mental disorder associated with positive symptoms (delusions, hallucinations and disorganized thoughts), negative symptoms (anhedonia and poverty of speech) and cognitive symptoms (deficit in attention and memory). Aripiprazole is an atypical antipsychotic used for treatment of schizophrenia. It has a unique mechanism of action, acting on both presynaptic and postsynaptic D_{2} dopamine receptors. The dopamine hypothesis for schizophrenia was based on presence of dopaminergic neurons only in the mesolimbic regions, which on overstimulation lead to excessive dopamine transmission, producing symptoms of schizophrenia. However, later it was found that in schizophrenia patients, there was dopaminergic overactivity in the mesolimbic areas (associated with positive symptoms) and hypofunctioning in the mesocortical areas (associated with negative and cognitive symptoms). Dysregulation of dopamine release by the D_{2} autoreceptors is postulated as a reason for the imbalance in the cortical and subcortical dopaminergic transmission in Schizophrenia. Aripiprazole, being a partial agonist at D_{2} receptors lowers dopaminergic transmission in the mesolimbic areas where there is excess of dopaminergic transmission as it competes with dopamine for D_{2} receptors and produces only partial stimulation of these receptors. In the mesocortical areas, where dopamine levels are low, aripiprazole enhances dopaminergic transmission by its partial agonistic action on D_{2} receptors. The stabilizing effect of this drug on the dopamine system is attributed to its action on D_{2} autoreceptors and postsynaptic receptors\textsuperscript{15}.

**Serotonergic Presynaptic receptors:** Serotonergic receptors constitute the largest family of receptors with 7 subtypes, namely 5-HT_{1A}, 5-HT_{2A}, 5-HT_{3}, 5-HT_{4}, 5-HT_{5}, 5-HT_{6} and 5-HT_{7}. The 5-HT_{1A} receptor is further subdivided into 5-HT_{1A1}, 5-HT_{1B} and 5-HT_{1D}. The 5HT_{2A} receptors are further subdivided into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. All serotonin receptors are G protein coupled receptors except 5-HT_{3}, which is a ligand gated ion channel permeable to sodium and potassium ions.

The 5-HT receptors located presynaptically are 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A} and 5-HT_{6}. They are present on both serotonergic neurons (autoreceptors) and other neuronal families (heteroreceptors), modulating neurotransmitter release in the central and peripheral nervous system\textsuperscript{16}.

**Physiological role:** Serotonergic presynaptic receptors in the central nervous system are involved in controlling the mood of an individual. They also play important roles in pathogenesis of migraine. These presynaptic receptors in the enteric nervous system mediate heterotropic interaction between serotonergic and cholinergic neurons and promote gastrointestinal motility.

**Pharmacological role:** Buspirone is a 5-HT_{1A} agonist used for treatment of generalized anxiety disorder. It acts on both presynaptic and postsynaptic 5-HT_{1A} receptors. It acts as a full agonist at postsynaptic 5-HT_{1A} receptors which are inhibitory autoreceptors. These autoreceptors on activation, inhibit the release of serotonin from the serotonergic neurons in the central nervous system. Buspirone acts like a partial agonist on the postsynaptic 5-HT_{1A} receptors, thus functioning like an antagonist in the presence of high serotonin concentrations. According to the serotonergic hypothesis of anxiety, blockade of serotonergic transmission in the central nervous system is associated with anxiolytic effects. Thus, 5-HT_{1A} agonists like buspirone, gepirone and ipsapirone exert anxiolytic activity and are used in generalized anxiety disorder\textsuperscript{16}.

Vilazodone is a combined selective serotonin reuptake inhibitor (SSRI) and 5-HT_{1A} receptor partial agonist approved by FDA for the treatment of major depression in 2011. Its antidepressant action is due to enhancement of serotonergic activity in the central nervous system by inhibiting the reuptake of serotonin in the serotonergic neurons and also by its partial agonistic action on the 5-HT_{1A} autoreceptors, which on continuous use leads to their desensitization. Thus the
autoreceptor mediated negative feedback trying to reduce the serotonin release into the synapse will be reduced by the partial agonistic action of vilazodone at the 5-HT_{1A} autoreceptors. This further enhances serotonergic transmission, thus producing antidepressant action. It is postulated that this negative feedback mechanism plays a major role in the delayed action of SSRI as it takes time to overcome the autoreceptor mediated inhibition of serotonin release and for the occurrence of desensitization of these autoreceptors with SSRIs^{17}.

Triptans are 5-HT_{1B/D} receptor agonists used for the treatment of migraine. The 5-HT_{1B} and 5-HT_{1D} receptors are present presynaptically as inhibitory autoreceptors, and postsynaptically in the central nervous system. The 5HT_{1B} receptors are also present on the endothelium of the meningeal blood vessels. The 5-HT_{1B/D} agonistic action of triptans prevent vasoactive peptide release from the activated trigeminal nerves in migraine patients. They also inhibit the transmission of pain signal from the meningeal blood vessels to the sensory neurons located in the brainstem. The 5HT_{1B} agonistic action mediates contraction of the vascular smooth muscles of the meningeal blood vessels. All these mechanisms have been postulated for pain relief from migraine headaches on treatment with triptans^{18}.

Cisapride and mosapride are prokinetic drugs that act on the presynaptic 5-HT_{3} receptors present on the cholinergic nerves of the myenteric plexus. The presynaptic 5HT_{3} receptors are excitatory heteroreceptors and on activation, enhance the release of acetylcholine from the myenteric plexus. The released acetylcholine promotes gastrointestinal motility and contributes to the prokinetic action of cisapride and mosapride. Prokinetic activity of these drugs is also contributed by its antagonistic action on 5-HT_{3} receptors in the myenteric plexus^{19}.

**Histaminergic presynaptic receptors:** It is almost 100 years since the extraction of histamine from mould ergot by Sir Henry Dale^{20}. Since then, biological roles of histamine and its action on various histamine receptors have been elucidated. There are four types of histamine receptors namely, H_{1}, H_{2}, H_{3} and H_{4}.

The third histamine receptor was discovered in 1980s, a decade after histamine was added to the list of neurotransmitters^{21}. Histamine H_{3} receptors are presynaptic receptors. They are present in the presynaptic nerve terminals of the histaminergic neurons and operate a negative feedback loop to inhibit the release of histamine from them. They are termed as inhibitory autoreceptors. Histamine H_{3} receptors are also present as heteroreceptors in non histaminergic neurons, modulating the release of other neurotransmitters like serotonin, dopamine, acetylcholine, noradrenaline and GABA in the CNS and periphery^{20}.

The histamine H_{3} receptors are G protein coupled receptors and they exhibit constitutive activity. Their mechanism of inhibition of neurotransmitter release involves activation of G proteins which inhibit adenyl cyclase and thus reduce cAMP levels in the presynaptic nerve terminals. This leads to blockade of calcium channels in the presynaptic nerve terminals that are essential for triggering the neurotransmitter release by exocytosis^{22}.

**Physiological role:** H_{3} receptors are present in hypothalamus, cerebral cortex, hippocampus, amygdala, nucleus accumbens, striatum, olfactory tubercles, cerebellum, substantia nigra and brainstem^{22}.

H_{3} receptors are involved in sleep wake regulation. Histamine maintains the waking state of an individual by acting mainly on the H_{1} receptors. The H_{3} receptors constitutively inhibit the release of histamine from the histaminergic neurons and thus prevent desensitization of postsynaptic H_{1} receptors under constant histamine release^{22}.

H_{3} receptors are also involved in appetite signaling pathways. H_{3} receptor antagonists induce satiety by causing disinhibition of histamine release from the histaminergic nerve terminals^{23}.

H_{3} receptors are also involved in cognitive processes including learning and memory. An increased histaminergic tone can enhance attention, learning and memory and improve cognition^{24}.

**Pharmacological role:** H_{3} receptor agonists promote sleep and have anxiolytic properties. Alfa-methylhistamine and imetit are the H_{3} receptor agonists.

H_{3} receptor antagonist produces wakefulness, increases vigilance and enhances cognition. The dose of H_{3} receptor antagonist required to produce wakefulness is higher than that required to improve cognition. H_{3} receptor antagonists show great potentials in the treatment of narcolepsy, attention deficit hyperactivity disorder, Alzheimer’s disease, Parkinson’s disease and obesity.

Thioperamide was the first developed H_{3} antagonist. Its hepatotoxic potential precluded its use in human studies. Ciprolisant is an H_{3} antagonist which reached phase II clinical trials for treatment of attention deficit hyperactivity disorders^{20}.

Ciproxifan is an H_{3} receptor antagonist or inverse agonists which promotes wakefulness and produces sustained cortical activation in cats, suggesting its use in the treatment of narcolepsy.

Pitolisant (previously called BF2.649) is an H_{3} receptor antagonist in phase III clinical trials in narcolepsy. A randomized controlled trial comparing
pitolisant with modafinil and placebo in narcolepsy patients revealed that pitolisant was superior to placebo and not non-inferior to modafinil in terms of its efficacy\(^{25}\). H\(_3\) receptor antagonist cause disinhibition of histamine H\(_3\) receptor and increase the histamine release from the histaminergic neurons and activates postsynaptic H\(_1\) receptor and promotes waking. Their precognitive action involves not only histaminergic but also other neurotransmitter systems modulated by H\(_3\) heteroreceptors and involved in cognition like the cholinergic system.

**GABAergic presynaptic receptors:** GABA (\(\gamma\)-aminobutyric acid) is the primary inhibitory neurotransmitter in mammalian brain. There are three types of GABA receptors, namely GABA\(_A\), GABA\(_B\) and GABA\(_C\). GABA\(_C\) receptor was recently found to be a subtype of GABA\(_A\) receptor and renamed as GABA\(_A\)-\(\rho\). Both GABA\(_A\) and GABA\(_B\) receptors are present presynaptically and postsynaptically in the GABAergic neurons. GABA\(_A\) receptor is a ligand gated chloride ion channel, whereas GABA\(_B\) receptor is a G-protein coupled receptor. GABA\(_A\) is an excitatory autoreceptor, which on stimulation enhances the release of GABA from the presynaptic nerve terminals. GABA\(_A\) heteroreceptors are also stimulatory and present in other neuronal systems, modulating their neurotransmitter release. GABA\(_B\) receptors are inhibitory autoreceptors which mediate the negative feedback loop and inhibit the release of GABA from the presynaptic nerve terminals\(^{26}\).

**Physiological role:** GABAergic presynaptic receptors are predominant in the central nervous system and mediate monosynaptic and polysynaptic reflexes in the spinal cord, thus regulating the skeletal muscle tone.

**Pharmacological targets:** Baclofen is a centrally acting skeletal muscle relaxant used to treat spastic conditions. It depresses monosynaptic and polysynaptic reflex transmission in the spinal cord. It is a GABA\(_B\) agonist and it acts on the presynaptic GABA\(_B\) Receptors to reduce the excitatory neurotransmission by either reducing calcium conductance or increasing potassium conductance in the presynaptic nerve terminals\(^{27}\).

**2. CONCLUSION**

Presynaptic receptors are present ubiquitously in all neuronal systems. They mediate important physiological roles and are employed as targets for drug discovery. Each neuronal system is endowed with both inhibitory and facilitatory presynaptic receptors, thus modulating neurotransmission and maintaining physiological homeostasis. The various inhibitory and facilitatory presynaptic receptors are enumerated in table 1.

### Table 1: Inhibitory and facilitatory presynaptic receptors in different neuronal systems

<table>
<thead>
<tr>
<th>Neuronal family</th>
<th>Inhibitory</th>
<th>Facilitatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic neurons</td>
<td>(\alpha_2A), (\alpha_2B), (\alpha_2C)</td>
<td>(\beta_2)</td>
</tr>
<tr>
<td>Cholinergic neurons</td>
<td>M(_2)</td>
<td>NACH</td>
</tr>
<tr>
<td>Dopaminergic neurons</td>
<td>D(_{2S}), D(_3)</td>
<td>D(_1)</td>
</tr>
<tr>
<td>Serotonergic neurons</td>
<td>5HT(<em>{1A}), 5HT(</em>{1B}), 5HT(_{1D})</td>
<td>5HT(_{4})</td>
</tr>
<tr>
<td>Histaminergic neurons</td>
<td>H(_3)</td>
<td>H(_1)</td>
</tr>
<tr>
<td>GABAergic neurons</td>
<td>GABA(_B)</td>
<td>GABA(_A)</td>
</tr>
</tbody>
</table>

The presynaptic receptors in adrenergic neurons are involved in blood pressure regulation and sleep promotion. Drugs like clonidine, \(\alpha\)-methyl dopa, apraclonidine, brimonidine, dexmedetomidine, mirtazapine act on presynaptic receptors of the adrenergic neurons to mediate their actions. The presynaptic nicotinic acetylcholine receptors are concerned with reward, learning, memory and attention, hence are utilized as therapeutic targets for smoking cessation and Alzheimer’s disease. The dopaminergic presynaptic receptors play important roles in controlling locomotor activity and mediating reward. They are utilized as targets for treatment of Parkinson’s disease and schizophrenia. Serotonergic system is also bestowed with presynaptic receptors in the central and peripheral nervous system, which are involved in regulating mood and gastrointestinal motility respectively. Buspiron, vilazodone, triptans, cisapride and mosapride are some drugs that target these receptors. Histaminergic H\(_3\) presynaptic receptors play crucial roles in regulating sleep wake cycle, appetite, attention, memory and cognition. Pitolisant is a H\(_3\) receptor antagonist used for treatment of narcolepsy. Presynaptic GABA receptors are involved in maintenance of spinal reflexes regulating skeletal muscle tone and baclofen is a skeletal muscle relaxant that utilizes these receptors for its action.

It is postulated that there are many more presynaptic receptors yet to be uncovered, their physiological roles to be identified and utilized as targets for drug discovery.

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