# Presynaptic Neuropeptide Receptors

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**Abstract** Presynaptic receptors for four families of neuropeptides will be discussed: opioids, neuropeptide Y, adrenocorticotropic hormone (ACTH), and orexins. Presynaptic receptors for the opioids (μ, δ, κ, and $ORL_1$) and neuropeptide Y ($Y_2$) inhibit transmitter release from a variety of neurones, both in the peripheral and central nervous systems. These receptors, which were also identified in human tissue, are coupled to $G_{i/o}$ proteins and block voltage-dependent $Ca^{2+}$ channels, activate voltage-dependent $K^+$ channels, and/or interfere with the vesicle release machinery. Presynaptic receptors for ACTH ($MC_2$ receptors) have so far been identified almost exclusively in cardiovascular tissues from rabbits, where they facilitate noradrenaline release; they are coupled to $G_s$ protein and act via stimulation of adenylyl cyclase. Presynaptic receptors for orexins (most probably $OX_2$ receptors) have so far almost exclusively been identified in the rat and mouse brain, where they facilitate the release of glutamate and γ-aminobutyric acid (GABA); they are most probably linked to $G_q$ and directly activate the vesicle release machinery or act via a transduction mechanism upstream of the release process. Agonists and antagonists at opioid receptors owe at least part of their therapeutic effects to actions on presynaptic receptors. Therapeutic drugs targeting neuropeptide Y and orexin receptors and presynaptic ACTH receptors so far are not available.

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# 1 Introduction

One reason to describe presynaptic neuropeptide receptors in a separate chapter is the chemistry of their endogenous ligands – peptides with up to about 50 amino acids. However, peptides have more properties that discriminate them from endogenous ligands at other types of presynaptic receptors. First, peptide transmitters, unlike transmitters of low molecular weight (e.g., noradrenaline, acetylcholine, GABA, or glutamate), are not formed in the axon terminals but are synthetized in the perikaryon of the neurone and are transported to the axon terminals; they are stored there in separate vesicles characterized by a large diameter and a dense core. Second, peptide transmitters frequently are cotransmitters, which are released in addition to one or even two low-molecular-weight transmitter(s). Third, endogenous peptides do not act via ionotropic receptors as opposed to many small transmitters, e.g., GABA (via $GABA_{A/C}$ receptors), glutamate (via NMDA or AMPA receptors), acetylcholine (via nicotinic receptors), or serotonin (via 5-$HT_3$ receptors). In other words, peptide transmitters are slower to act than some transmitters of low molecular weight.

There are dozens of presynaptic receptors for endogenous peptides. This review will focus on receptors for four peptides or peptide families: the opioid peptides, neuropeptide Y and related peptides, adrenocorticotropic hormone (corticotropin, ACTH), and the orexins. This choice is representative, since part of the receptors inhibit and part of them facilitate transmitter release; moreover, the receptors under consideration are coupled to the major G proteins, namely $G_{i/o}$, $G_s$ and $G_q$ (Table 1).

**Table 1** Synopsis of Receptors Activated by the Four Peptide Families

| Peptide Family | Endogenous Ligands | Receptors | | G Protein |
|---|---|---|---|---|
| | | Total | With Presynaptic Location | |
| Opioid | Endorphins, enkephalins, dynorphins, nociceptin | μ, δ, κ, $ORL_1$ | μ, δ, κ, $ORL_1$ | $G_{i/o}$ |
| Neuropeptide Y | Neuropeptide Y, peptide YY, pancreatic polypeptide | $Y_1$, $Y_2$, $Y_3$, $Y_5$, $Y_6$[1] | $Y_2$ | $G_{i/o}$ |
| Melanocortin | ACTH, α-, β-, γ-melanocyte-stimulating hormone | $MC_1$, $MC_2$, $MC_3$, $MC_4$, $MC_5$ | $MC_2$ | $G_s$ |
| Orexin | Orexin A and B | $OX_1$, $OX_2$ | $OX_2$? | $G_q$ |

[1] This subtype is functional in the mouse only.

This review is based mainly on four types of experiments in which exocytotic, vesicular, ATP-dependent transmitter release was determined directly or indirectly. Other types of transmitter release including "basal" release or carrier-mediated release will not be considered. (1) In superfusion studies transmitter release is determined directly (as "overflow"). (2) In other studies on isolated tissues transmitter release is not determined directly but via the endorgan response. (3) In electrophysiological studies, spontaneously occurring or electrically evoked currents or potentials elicited by the transmitter are studied at the postsynaptic membrane. (4) A small part of the experiments stem from pithed animals in which the noradrenaline spillover or the increase in blood pressure or heart rate elicited by electrical sympathetic nerve stimulation is studied. Apart from experiments on pithed animals, in vivo studies were usually not considered in this review since their interpretation bears difficulties. In the studies under (2), (3) and (4), control experiments were carried out in which direct effects of the drug under study at the postsynaptic receptor were excluded. In the electrophysiological studies a special type of experiment was performed to demonstrate presynaptic receptor location: spontaneously occurring currents or potentials were determined in the presence of tetrodotoxin in order to block impulse flow along the axon. If the drug affects the frequency of the remaining currents or potentials without affecting their amplitude, a presynaptic site of action can be assumed. Although transmitter release was not determined directly in numerous of the studies considered here, the term "transmitter release" will be used for this type of investigation as well.

For each of the four presynaptic receptors or receptor families, the occurrence in the autonomic and/or central nervous system will be described. Next, the signal transduction will be considered. Subsequently we will discuss their physiological role and their possible role in disease and therapy.

## 2 Presynaptic Opioid Receptors

Although an example of a presynaptic opioid receptor, activated by morphine, was discovered 90 years ago (Trendelenburg 1917), the endogenous peptides acting on opioid receptors have been described only since 1975 (Figure 1). There are four types of opioid receptors, termed μ, δ, and κ opioid and opioid receptor-like$_1$ (ORL$_1$). Although other nomenclatures have been proposed (e.g., OP$_3$, OP$_1$, OP$_2$ and OP$_4$, respectively; Alexander et al. 2006), the traditional designations will be used in the present review. The term "opioid receptors" will be used in a broad sense covering not only the opioid receptors *sensu stricto* (μ, δ, and κ) but also the ORL$_1$ receptor. There are at least four types of endogenous peptides acting on opioid receptors: endorphins, enkephalins, dynorphins, and nociceptin. These peptides are not synthetized as such but are cleaved from precursors (e.g., proopiomelanocortin), which in turn have been processed from pre-precursors (e.g., pre-proopiomelanocortin). ß-Endorphin activates μ, the enkephalins activate δ, and the dynorphins activate κ opioid receptors, whereas nociceptin activates

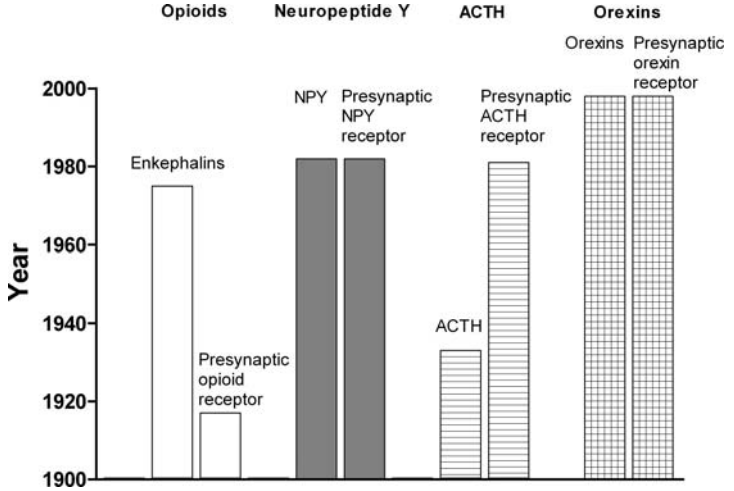


**Fig. 1** First description of the four peptides (or peptide families) and their respective presynaptic receptors. The papers are (from left to right): Trendelenburg (1917); Hughes et al. (1975); Tatemoto et al. (1982); Allen et al. (1982); Collip et al. (1933); Göthert (1981); de Lecea et al. (1998); van den Pol et al. (1998).

$ORL_1$ receptors. Although nociceptin is selective for $ORL_1$ receptors, the other three peptides show a marked degree of promiscuity with regard to the classical opioid receptors (μ, δ, and κ). Endorphins occur in the brain (almost exclusively in neurones which have their somata in the infundibular nucleus) and in the adenohypophysis. Enkephalins are found on many sites in the CNS but also occur in the adrenal medulla and in the gut wall. Dynorphins are also found in the CNS and in the gut (for review, see Gutstein and Akil 2006).

Figure 2 gives an example how presynaptic opioid receptors can be identified in a superfusion model. We examined the effect of subtype-selective agonists on noradrenaline release in mouse brain cortex slices. Figure 2a shows that noradrenaline release was inhibited by a μ and an $ORL_1$ receptor agonist but was not affected by high concentrations of a δ and κ opioid receptor agonist. In further experiments we showed that the effects of the μ agonist (Figure 2b) and of the $ORL_1$ agonist (Figure 2c) indeed involve μ and $ORL_1$ receptors since the concentration-response curves were shifted to the right by antagonists with apparent $pA_2$ values close to their potency values in other functional studies for each receptor subtype (Guerrini et al. 1998; Berger et al. 2006).

Using superfusion experiments, electrophysiological techniques, pithed animal preparations, and experiments in which transmitter release was determined indirectly via the end-organ response (e.g., twitch response of vas deferens preparations), numerous presynaptic opioid receptors have been identified (Table 2). For the identification of the receptors, classical drug tools were used; for future studies, knockout mice (now available for each of the four opioid receptor subtypes) and special nucleotides (e.g., antisense oligodeoxynucleotides or short interfering

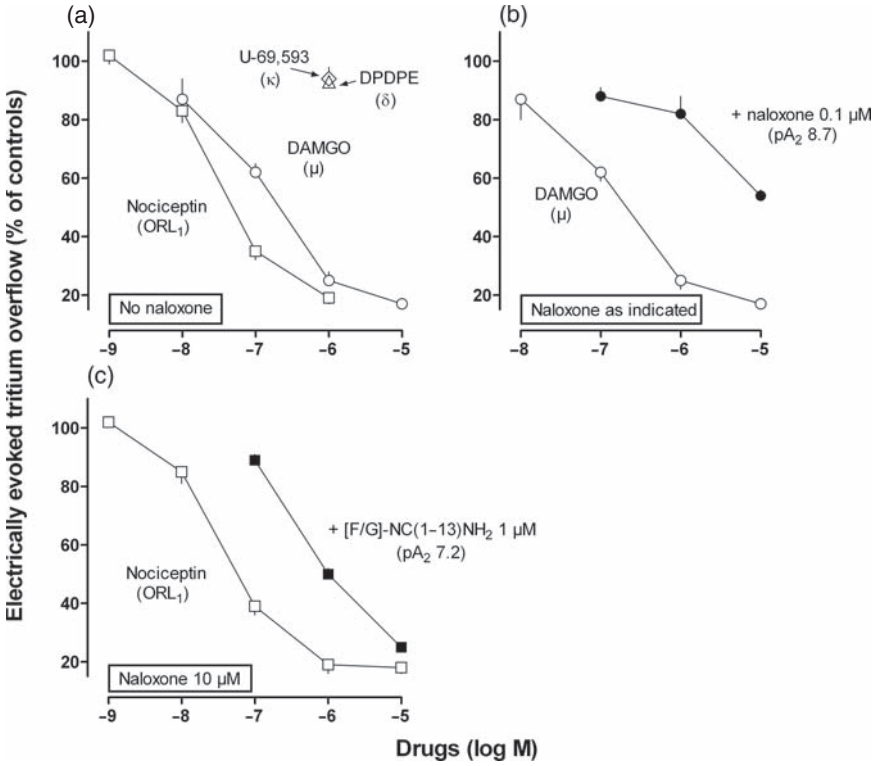


**Fig. 2** Effect of opioid receptor agonists on the electrically (0.3 Hz) evoked tritium overflow from superfused mouse brain cortex slices preincubated with $^{3}$H-noradrenaline. The evoked overflow represents quasi-physiological exocytotic noradrenaline release. (**a**) shows that noradrenaline release was inhibited by agonists at the μ and the $ORL_1$ receptor but not affected by high concentrations of a δ and κ receptor agonist. The effect of DAMGO in fact involved μ receptors since it was antagonized by a low concentration of naloxone, which possesses some preference for μ over δ, κ and $ORL_1$ receptors (**b**). On the other hand, the effect of nociceptin was indeed related to the activation of $ORL_1$ receptors since it was antagonized by the $ORL_1$ antagonist [$Phe^1\Psi(CH_2\text{-}NH)Gly^2$]-nociceptin(1–13)$NH_2$ ([F/G]-NC(1–13)$NH_2$) ([F/G]-NC(1–13)$NH_2$) (**c**). Data with nociceptin and its antagonist from Schlicker et al. (1998; redrawn); other data published in abstract form only (Schlicker and Kathmann 2000). Similar data were published by Trendelenburg et al. (2000).

RNA) are promising new approaches. In all examples listed in Table 2 transmitter release was inhibited. Each of the four opioid receptor subtypes can serve as an inhibitory presynaptic receptor (Table 1), and each has been identified also in human tissue (Table 2). In a few papers (not further considered here) a facilitatory rather than inhibitory effect of opioids on transmitter release was reported. In such cases, the possibility has to be considered that the opioid receptor was located presynaptically at an inhibitory interneurone projecting to the neurone under study (and not at the latter itself).

**Table 2** Synopsis of presynaptic inhibitory opioid receptors

| | $\mu$ opioid receptors | | | |
|---|---|---|---|---|
| | Transmitter | Tissue | Species | References |
| Sympathetic nervous system | *preganglionic* Acetylcholine | Superior cervical ganglion | Cat, rabbit | 2 |
| | | Hypogastric ganglion | Mouse | Rogers and Henderson 1990 |
| | | Superior and inferior mesenteric ganglion | Guinea-pig | 2 |
| | *postganglionic* Noradrenaline | Tail artery | Rat | 1 |
| | | Nictitating membrane | Cat | 1 |
| | | Colon | Guinea-pig | 1 |
| | | Vas deferens | Rat, mouse | 1 |
| Parasympathetic/ enteric nervous system | Acetylcholine | Heart | Rabbit | 2 |
| | | Lung | Rat | Yu et al. 2006 |
| | | Ciliary ganglion | Chick | Endo and Yawo 2000 |
| | | Small intestine myenteric plexus | Guinea pig | Cherubini and North 1985 |
| | | Ileum | Guinea-pig, rat | 2, Storr et al. 2002 |
| | | Colon | Cat | 2 |
| | | Gall bladder | Guinea-pig | Guarraci et al. 2002 |
| Central nervous system | Noradrenaline | Cerebral cortex, hippocampus, cerebellum | Guinea-pig | 3 |
| | | Cerebral cortex, hippocampus, amygdala, nucleus tractus solitarii, periaqueductal grey, cerebellum | Rat | 3 |
| | | Cerebral cortex | Mouse | see Fig. 2 |
| | Dopamine | Striatum | Rat | Schlosser et al. 1995 |
| | Serotonin | Cerebral cortex | Human | Berger et al. 2006 |
| | | Cerebral cortex, hippocampus | Rat | 3, Berger et al. 2006 |
| | Acetylcholine | Nucleus accumbens, olfactory tubercle, hippocampus, amygdala | Rat | 3 |
| | Glutamate | Cerebral cortex | Rat | Ostermeier et al. 2000 |
| | | Amygdala | Rat | *Zhu and Pan 2005** |
| | | Arcuate nucleus, ventromedial hypothalamus | Rat | Emmerson and Miller 1999 |
| | | Subthalamic nucleus | Rat | Shen and Johnson 2002 |
| | | Hypothalamus (supraoptic nucleus) | Rat, mouse | *Liu et al. 1999*; *Honda et al. 2004* |
| | | Periaqueductal grey | Rat | Vaughan and Christie 1997 |
| | | Raphe pallidus | Rat | Bouryi and Lewis 2004 |
| | | Dorsal motor nucleus | Rat | Browning et al. 2002 |
| | | Nucleus tractus solitarii | Rat | Glatzer and Smith 2005 |
| | | Rostral ventrolateral medulla | Rat | *Hayar and Guyenet 1998* |
| | | Spinal cord | Rat | Glaum et al. 1994 |

(*Continued*)

**Table 2** Continued

| | $\mu$ opioid receptors | | | |
|---|---|---|---|---|
| | Transmitter | Tissue | Species | References |
| | GABA | Hippocampus | Rat | Capogna et al. 1993 |
| | | Amygdala | Rat | *Finnegan et al. 2005; 2006* |
| | | Globus pallidus | Rat | Stanford and Cooper 1999 |
| | | Hypothalamus (supraoptic nucleus) | Mouse | *Honda et al. 2004* |
| | | Subthalamic nucleus | Rat | Shen and Johnson 2002 |
| | | Ventral tegmental area | Rat | Bergevin et al. 2002 |
| | | Locus coeruleus | Rat | *Pan et al. 2004* |
| | | Periaqueductal gray | Rat | Kishimoto et al. 2001 |
| | | Rostral ventrolateral medulla | Rat | Hayar and Guyenet 1998 |
| | | Spinal cord (substantia gelatinosa) | Rat | Grudt and Henderson 1998 |
| | | Spinal cord (dorsal horn) | Rat | *Kerchner and Zhuo 2002* |
| | Glycine | Spinal cord (substantia gelatinosa) | Rat | *Grudt and Henderson 1998* |
| | Substance P | Hypothalamus, spinal cord | Cat | 3, 4 |
| | | Spinal cord | Rat | Aimone and Yaksh 1989 |
| | ß-Endorphin, dynorphin | Hypothalamus | Rat | Nikolarakis et al. 1989 |
| | Cholecystokinin | Hypothalamus | Cat | 3, 4 |
| | $\delta$ opioid receptors | | | |
| | Transmitter | Tissue | Species | References |
| Sympathetic nervous system | *preganglionic* Acetylcholine | Hypogastric ganglion | Mouse | Rogers and Henderson 1990 |
| | *postganglionic* Noradrenaline | Atrium | Guinea-pig, mouse | 1 |
| | | Arteries and veins | Rabbit | 1 |
| | | Colon | Guinea-pig | 1 |
| | | Spleen | Cat | 1 |
| | | Vas deferens | Hamster, rat, mouse | 1 |
| | | Cultured sympathetic neurones | Chicken | 1 |
| Parasympathetic nervous system | Acetylcholine | Heart | Rabbit | 2 |
| | | Ciliary ganglion | Chick | Endo and Yawo 2000 |
| | | Ileum | Mouse | 2 |
| | | Colon | Cat | 2 |
| | | Gall bladder | Guinea-pig | Guarraci et al. 2002 |
| | | Sacral colonic ganglia | Cat | 2 |

(*Continued*)

**Table 2** Continued

| | $\delta$ opioid receptors | | | |
|---|---|---|---|---|
| | Transmitter | Tissue | Species | References |
| Central nervous system | Noradrenaline | Cerebral cortex | Human | Berger et al. 2006 |
| | Dopamine | Striatum | Rat | Schlosser et al. 1995 |
| | Serotonin | Hippocampus | Rat | 3 |
| | Acetylcholine | Striatum, nucleus accumbens, olfactory tubercle | Rat | 3 |
| | Glutamate | Cerebral cortex | Rat | Ostermeier et al. 2000 |
| | | Raphe pallidus | Rat | Bouryi and Lewis 2004 |
| | | Spinal cord | Rat | *Glaum et al. 1994* |
| | GABA | Globus pallidus | Rat | *Stanford and Cooper 1999* |
| | | Subthalamic nucleus | Rat | Shen and Johnson 2002 |
| | | Locus coeruleus | Rat | Pan et al. 2002 |
| | Substance P | Hypothalamus, spinal cord | Cat | 3, 4 |
| | | Spinal cord | Rat | 3, 4, Aimone and Yaksh 1989 |
| | Metenkephalin, ß-endorphin, dynorphin | Hypothalamus | Rat | Nikolarakis et al. 1989 |
| | $\kappa$ opioid receptors | | | |
| | Transmitter | Tissue | Species | References |
| Sympathetic nervous system | Noradrenaline | Heart | Rabbit, guinea-pig | 1 |
| | | Vasculature | Rabbit | 1 |
| | | Colon | Guinea-pig | 1 |
| | | Vas deferens | Rabbit, mouse | 1 |
| | | Cultured sympathetic neurones | Chicken | 1 |
| Parasympathetic nervous system | Acetylcholine | Small intestine (myenteric plexus) | Guinea-pig | Cherubini and North 1985 |
| | | Ileum | Guinea-pig, mouse | 2 |
| | | Colon | Cat | 2 |
| | | Gall bladder | Guinea-pig | Guarraci et al. 2002 |
| Sensory neurones | Calcitonin gene-related peptide | Skin | Rat | Averbeck et al. 2001 |
| Central nervous system | Noradrenaline | Cerebral cortex, hippocampus, cerebellum | Guinea-pig | 3 |

(*Continued*)

**Table 2** Continued

| | $\kappa$ opioid receptors | | | |
|---|---|---|---|---|
| | Transmitter | Tissue | Species | References |
| | Dopamine | Striatum, frontal cortex, olfactory tubercle, nucleus accumbens, mediobasal hypothalamus, amygdala | Rat | 3 |
| | | Striatum | Cat, guinea-pig | 3 |
| | Serotonin | Cerebral cortex | Human, rat | Berger et al. 2006 |
| | | Superior colliculus | Rabbit | 3 |
| | Histamine | Cerebral cortex | Rat | 3 |
| | Acetylcholine | Cerebral cortex | Human | Feuerstein et al. 1996 |
| | Glutamate | Hippocampus | Guinea-pig | Gannon and Terrian 1991; Simmons et al. 1994 |
| | | Hypothalamus (arcuate nucleus) | Rat | *Emmerson and Miller 1999* |
| | | Nucleus accumbens (shell) | Rat | *Hjelmstadt and Fields 2001* |
| | | Rostral ventromedial medulla | Rat | Ackley et al. 2001 |
| | GABA | Globus pallidus | Rat | Ogura and Kita 2000 |
| | Glycine | Nucleus ambiguus | Rat | *Wang et al. 2004* |
| | Metenkephalin | Brainstem | Rat | Ueda et al. 1987 |
| | Dynorphin | Hippocampus | Guinea-pig | Gannon and Terrian 1991 |
| | | Hypothalamus | Rat | Nikolarakis et al. 1989 |
| | $ORL_1$ receptors | | | |
| | Transmitter | Tissue | Species | References |
| Sympathetic nervous system | Noradrenaline | Heart | Rat | 1 |
| | | Atrium | Mouse | 1 |
| | | Tail artery | Rat | 1 |
| | | Resistance vessels | Rat | 1 |
| | | Anococcygeus muscle | Rat | 1 |
| | | Vas deferens | Rabbit, rat mouse | 1 |
| Parasympathetic/enteric nervous system | Acetylcholine | Small intestine (myenteric plexus) | Guinea-pig | Nicholson et al. 1998; Liu et al. 2001 |
| | Non-adrenergic-non-cholinergic transmitter | Small intestine (myenteric plexus) | Guinea-pig | Nicholson et al. 1998 |

(*Continued*)

**Table 2** Continued

| | $ORL_1$ receptors | | | |
|---|---|---|---|---|
| | Transmitter | Tissue | Species | References |
| Central nervous system | Noradrenaline | Cerebral cortex, cerebellum, hippocampus, hypothalamus | Mouse | 5 |
| | | Cerebral cortex | Human | Rominger et al. 2002 |
| | Serotonin | Cerebral cortex | Human, rat, mouse | 5; Berger et al. 2006 |
| | Glutamate | Hippocampus | Rat | Yu et al. 1997 |
| | | Hypothalamus (arcuate nucleus) | Rat | Emmerson and Miller 1999 |
| | | Periaqueductal grey | Rat | *Vaughan et al. 1997* |
| | GABA | Periaqueductal grey | Rat | *Vaughan et al. 1997* |

1 Reviewed by Boehm and Kubista (2002)
2 Reviewed by Illes (1989)
3 Reviewed by Mulder and Schoffelmeer (1993)
4 Reviewed by Jackisch (1991)
5 Reviewed by Schlicker and Morari (2000)
* In the studies given in *italics* opioids decreased postsynaptic currents or potentials also in the presence of tetrodotoxin.

Presynaptic opioid receptors were found in all parts of the autonomic nervous system (sympathetic, parasympathetic, and enteric) and on many sites of the central nervous system. The release of more than 10 transmitters can be inhibited via opioid receptors. The latter serve as presynaptic heteroreceptors in most instances, i.e., the opioid modulating release differs from the transmitter subject to modulation. However, there are also examples of presynaptic opioid autoreceptors. For example, in the study of Nikolarakis et al. (1989) on rat hypothalamus slices, antagonists of the μ, δ, and κ opioid receptor increased the release of endogenous opioids, suggesting that the latter decreased their own release. Another example of an autoreceptor has been shown in the guinea pig hippocampus, where the release of dynorphin (which mainly activates κ opioid receptors) was inhibited by the κ opioid receptor agonist U-69,593 (Gannon and Terrian 1991). With respect to the distribution of presynaptic opioid receptors, marked species differences exist. For example, noradrenaline release in the cerebral cortex is inhibited via δ and $ORL_1$ receptors in humans, via κ and $ORL_1$ receptors in the guinea pig, and via μ and $ORL_1$ receptors in the rat and mouse (Table 2, Figure 2). These examples show that there are nerve terminals in which more than one opioid receptor can be identified. Transmitter release from the postganglionic sympathetic neurone in the mouse vas deferens is even subject to inhibition via each of the four opioid subtypes (Table 2).

Which mechanisms are involved in the opioid receptor-mediated inhibition of transmitter release? In general, the four types of opioid receptor are $G_{i/o}$ protein-coupled receptors (Alexander et al. 2006), but theoretically another transduction pathway might exist for presynaptic opioid receptors. However, the coupling of presynaptic opioid receptors to $G_{i/o}$ (labelled with **1** in Figure 3) has been

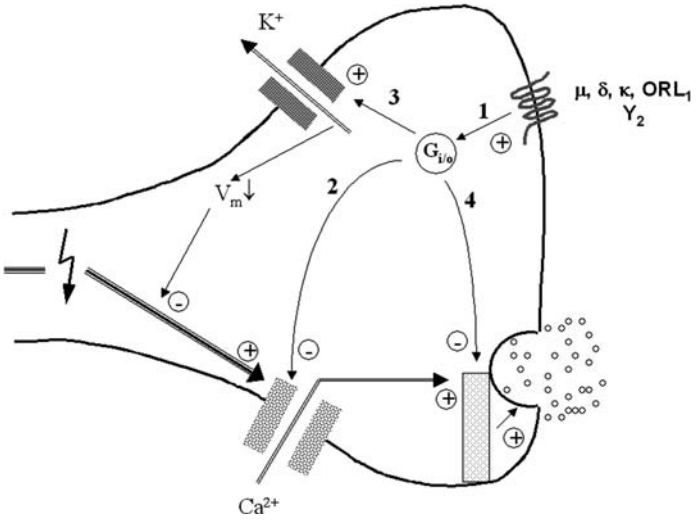


**Fig. 3** Mechanisms involved in the opioid (μ, δ, κ, $ORL_1$) and neuropeptide Y ($Y_2$) receptor-mediated inhibition of exocytotic transmitter release. Following activation of the respective receptor and $G_{i/o}$ (**1**), three signal transduction pathways are possible, namely inhibition of voltage-dependent $Ca^{2+}$ channels (**2**), opening of $K^+$ channels (**3**), and a direct inhibitory effect on the vesicle release machinery (**4**). *Glossary*: $->$ - leading to; $=>$ - ion flux; $\equiv>$ - action potential; $V_m$ - membrane potential; "(+)" and "(−)" mean stimulatory and inhibitory effect, respectively.

demonstrated in several studies, using pertussis toxin or the somewhat less selective agent N-ethylmaleimide. In this manner, coupling to $G_{i/o}$ has been shown (1) for presynaptic μ opioid receptors inhibiting the release of noradrenaline in rat and guinea pig hippocampus (Werling et al. 1989) and of GABA in rat hippocampus (Capogna et al. 1993) and periaqueductal grey (Kishimoto et al. 2001; Hahm et al. 2004) and (2) for presynaptic κ opioid receptors inhibiting noradrenaline release in rabbit hippocampus (Allgaier et al. 1989).

In order to better understand how the events downstream of G protein activation are influenced by opioid receptors, one should briefly recall the major steps of the electrosecretory coupling. When an action potential invades the axon terminal, voltage-dependent $Ca^{2+}$ channels open. The $Ca^{2+}$ ions entering the axoplasma finally lead to fusion of vesicles with the plasma membrane and release of the transmitter into the synaptic cleft. $Ca^{2+}$ influx is crucially dependent on the membrane potential; e.g., hyperpolarization will impair $Ca^{2+}$ influx. Hyperpolarization can be elicited by the efflux of $K^+$ ions. In general, $G_{i/o}$-coupled receptors can decrease $Ca^{2+}$ influx via voltage-dependent $Ca^{2+}$ channels (labelled with **2** in Figure 3), increase $K^+$ efflux via voltage-dependent $K^+$ channels (**3** in Figure 3), and/or directly interfere with the release process (**4** in Figure 3) (Miller 1998). Each of the three mechanisms, alone or in combination, has been reported to play a role in opioid receptor-mediated inhibition of transmitter release. To show the involvement of ion channels, (more or less) selective drug tools have been used. The direct influence on the release machinery has been shown in electrophysiological studies in

which impulse flow was abolished by tetrodotoxin or $Ca^{2+}$ influx through voltage-dependent $Ca^{2+}$ channels was blocked by appropriate agents. If a drug inhibits the frequency of postsynaptic currents or potentials under this scenario, a direct interference with the release process can be assumed (Miller 1998).

Voltage-dependent *$Ca^{2+}$ channels* play a role in the μ receptor-mediated inhibition of noradrenaline release in the rat cerebral cortex (Mulder and Schoffelmeer 1993), of glutamate release in the chick ciliary ganglion (Endo and Yawo 2000), and of GABA release in the rat striatum (Barral et al. 2003). Voltage-dependent *$K^+$ channels* are involved in the μ receptor-mediated inhibition of the release of glutamate in the rat subthalamic nucleus (Shen and Johnson 2002) and periaqueductal grey (Vaughan and Christie 1997) and of GABA in the rat striatum (Barral et al. 2003), amygdala (Finnegan et al. 2006), subthalamic nucleus (Shen and Johnson 2002), ventral tegmental area (Bergevin et al. 2002), and periaqueductal grey (Vaughan and Christie 1997). They are also involved in the κ receptor-mediated inhibition of glutamate release in the guinea pig dentate gyrus (Simmons et al. 1994). A *direct effect on the release machinery* has been shown for each of the four opioid receptors in at least one region of the central nervous system, and both for fast excitatory (glutamate) and inhibitory transmission (GABA, glycine) (references given in italics in Table 2).

Are the presynaptic opioid receptors described here activated by endogenous opioids? If so, one would expect that an opioid receptor antagonist like naloxone would alter transmitter release in the direction opposite to that elicited by opioid receptor agonists, i.e., would increase transmitter release. In most experimental models, an effect of naloxone per se has not been found, suggesting that the corresponding opioid receptors are not subject to an endogenous tone (listed in the reviews by Starke 1977; Jackisch 1991; Boehm and Kubista 2002). In a series of models, however, naloxone did increase transmitter release. This has been shown for the opioid receptors (most probably μ, see Table 2) modulating noradrenaline release in the rat cerebral cortex (Taube et al. 1976) and for the opioid receptors modulating acetylcholine release in the guinea pig thalamus (Beani et al. 1982). It has also been shown for the μ and δ opioid receptors inhibiting substance P release in the cat spinal cord (Go and Yaksh 1987) and the δ opioid receptors inhibiting acetylcholine release in the cat parasympathetic colonic ganglia (Kennedy and Krier 1987) and the rat striatum (Sándor et al. 1991). Using subtype-selective opioid receptor antagonists, an endogenous tone has furthermore been shown for the μ, δ, and κ opioid autoreceptors causing inhibition of ß-endorphin, metenkephalin, and dynorphin release in the rat hypothalamus (Nikolarakis et al. 1989), for the μ and κ opioid receptors inhibiting noradrenaline and acetylcholine release in the guinea pig myenteric plexus (Cosentino et al. 1995), for the κ opioid autoreceptors inhibiting metenkephalin in the rat brainstem (Ueda et al. 1987), and for the $ORL_1$ receptors inhibiting noradrenaline release in the rat anococcygeus muscle (Ho et al. 2000) and serotonin release in the human cerebral cortex (Berger et al. 2006). In a final study on human cerebral cortex (Feuerstein et al. 1996), an endogenous tone at δ opioid receptors was shown to be likely. This is suggested by the fact that the selective δ opioid receptor antagonist naltrindole facilitated acetylcholine release in the presence (but

not absence) of a cocktail of peptidase inhibitors and that the cocktail per se inhibited acetylcholine release. The simplest explanation is that the concentration of endogenous opioids in the synaptic cleft normally is relatively low but can reach a critical level if degradation is blocked. (The situation in the study is complicated since the δ opioid receptor is not located at the cholinergic axon terminals but on an unidentified interneurone; Feuerstein et al. 1996.)

The observation that an endogenous tone at presynaptic opioid receptors is rarely detectable fits well to the fact that an endogenous tone is rare in opioid receptor models in general (see Table 21-2 in the review by Gutstein and Akil 2006). Endogenous opioid systems come into play under stressful situations. For example, the slight euphoria occurring after physical exercise or the suppression of pain that sometimes occurs in severely injured persons is believed to be caused by a marked increase in the release of endogenous opioids (Gutstein and Akil 2006).

Drugs acting at opioid receptors are among the oldest and continue to be among the most important medicines. There is no doubt that at least some targets for their desired, as well as undesired, effects are presynaptic receptors. This holds true for analgesia. Presynaptic μ receptors involved in the analgesic effect of, e.g., morphine are located both spinally and supraspinally. Spinal presynaptic μ opioid receptors inhibit the release of transmitters like glutamate, substance P, and calcitonin gene-related peptide from the terminals of the primary afferent neurones conveying pain from the periphery to the central nervous system (Zöllner and Stein 2007). One supraspinal site is in the periaqueductal grey, from where the descending pain-suppressing tract originates. This tract is under the control of tonically active GABAergic neurones, the axon terminals of which are equipped with presynaptic μ receptors. Activation of these receptors increases the pain-suppressing effect of the descending pathway (Vaughan and Christie 1997). Finally, presynaptic μ opioid receptors on tonically active GABAergic interneurones in the ventral tegmental area are associated with the rewarding properties of opioids. These GABAergic interneurones synapse with dopaminergic neurones projecting to the nucleus accumbens; activation of the presynaptic μ receptors leads to an increase in dopamine release and, hence, euphoria (Bergevin et al. 2002).

## 3 Presynaptic Neuropeptide Y Receptors

Neuropeptide Y and its presynaptic receptors were discovered 25 years ago (Figure 1). There are four subtypes of neuropeptideY receptors, $Y_1$, $Y_2$, $Y_4$ and $Y_5$ (Table 1, Alexander et al. 2006); a fifth subtype, $Y_6$, is functional in the mouse, whereas in primates the related gene is nonfunctional due to a frame-shift mutation (Alexander et al. 2006). Neuropeptide Y receptors are also activated by another two peptides, peptide YY (PYY) and pancreatic polypeptide (PP). The three peptides are not synthetized as such but are processed from larger precursors via two steps, i.e., an initial cleavage of the N-terminal signal peptide and the subsequent cleavage of the C-terminal part (Tatemoto 2004). The affinity of PYY is very similar to that

of neuropeptide Y at each of the five receptor subtypes; PP has about the same affinity as neuropeptide Y (or PYY) at $Y_5$ receptors, a lower affinity at $Y_1$, $Y_2$ and $Y_6$ receptors and a higher affinity at $Y_4$ receptors (Alexander et al. 2006). Neuropeptide Y is a neurotransmitter in sympathetic, parasympathetic, enteric, and sensory neurones and in neurones of the CNS. PYY and PP are hormones; the former is stored in the pancreas and the latter in the terminal intestine (Brain and Cox 2006).

Figure 4 shows how a presynaptic neuropeptide Y receptor was identified in a superfusion model. In mouse brain cortex slices, serotonin release was concentration-dependently inhibited by neuropeptide Y and this effect was potently mimicked by neuropeptide Y-(13-36). Since the latter is selective for $Y_2$ over $Y_1$ and $Y_5$ receptors (Alexander et al. 2006) one may conclude that neuropeptide Y acts via $Y_2$ receptors.

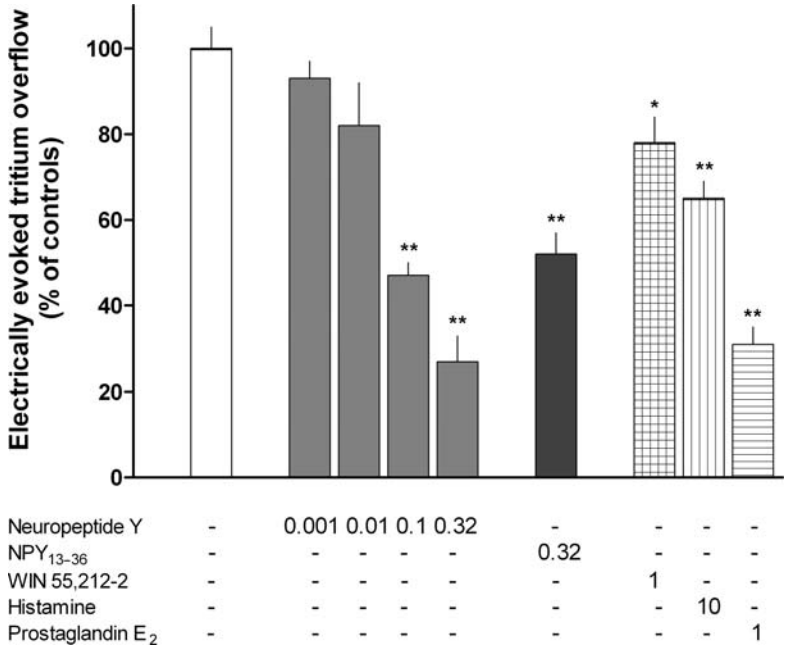


**Fig. 4** Effect of various peptides and nonpeptides on the electrically (3 Hz) evoked tritium overflow from superfused mouse brain cortex slices preincubated with $^3$H-serotonin. The evoked overflow represents quasi-physiological exocytotic serotonin release. In all experiments, serotonin autoreceptors were blocked by metitepine. The figure shows that human neuropeptide Y concentration-dependently inhibited serotonin release and that this effect was mimicked by human neuropeptide Y (13–36) ($NPY_{13–36}$), which has a high affinity for $Y_2$ but a very low affinity for $Y_1$ receptors. These results are compatible with the view that neuropeptide Y acts via $Y_2$ receptors in the present model. For the sake of comparison, the figure also shows the inhibitory effects of another three agonists, acting via cannabinoid $CB_1$, histamine $H_3$ and prostaglandin $EP_3$ receptors and used at concentrations causing the maximum or near-maximum effect at their respective receptors. Drug concentrations in μM. $^*P < 0.05$, $^{**}P < 0.003$, compared to the control (from Nakazi et al. 2000 and Nakazi 2001; redrawn).

Figure 4 also shows that the extent of inhibition obtained with neuropeptide Y was very marked and comparable to that obtained with prostaglandin $E_2$ (acting via $EP_3$ receptors), which was examined for the sake of comparison. The maximum inhibition obtained with WIN 55,212-2 (acting via cannabinoid $CB_1$ receptors) and histamine (acting via $H_3$ receptors ) was far lower.

Many examples of inhibitory presynaptic neuropeptide Y receptors have been found in tissues from experimental animals and humans (Table 3), based on experiments with each of the four techniques described in the Introduction (overflow experiments, electrophysiological techniques, pithed animals, electrically induced twitches in isolated tissues). For the identification of the receptors, the three peptides and modified (e.g., truncated) congeners (Figure 4) were the only tools for many years. More recently, selective antagonists (e.g., in the study by Schwertfeger et al. [2004] on the human heart) and knockout mice (e.g., in the study by Smith-White et al. [2002] on the mouse heart) have been used. According to most studies, only $Y_2$ receptors serve as presynaptic neuropeptide Y receptors.

Presynaptic neuropeptide Y receptors have been identified in the sympathetic, parasympathetic and enteric nervous system, on sensory neurones, and on many sites in the CNS; they inhibit the release of 11 different transmitters (Table 3). Most presynaptic neuropeptide Y receptors are heteroreceptors, but some serve as autoreceptors, both in the sympathetic nervous system (pig spleen and kidney) and the brain (rat hypothalamus) (Table 3). Marked species differences occur. For example, $Y_2$ receptors inhibit the sympathetically mediated tachycardia, the vagally mediated bradycardia, and the vagally mediated bronchoconstriction in the guinea pig but not in the rabbit (Serone et al. 1999; Abrahamsson 2000). Moreover, $Y_2$ receptors inhibit noradrenaline release in the guinea pig carotid but not femoral artery, and conversely inhibit noradrenaline release in the rat femoral but not carotid artery (Potter and Tripovic 2006).

Like opioid receptors, neuropeptide Y receptors are $G_{i/o}$ protein-coupled, and for this reason the marked similarities in signal transduction are not surprising. The coupling to $G_{i/o}$ was proven for the presynaptic $Y_2$ receptors inhibiting the substance P-mediated plasma extravasation in the rat dura mater (Yu and Moskowitz 1996) and the release of noradrenaline in the rat pineal gland (Simmoneaux et al. 1994) (step **1** in Figure 3). With respect to the downstream pathways, a coupling to voltage-dependent $Ca^{2+}$ channels (**2** in Figure 3) has been shown for the presynaptic neuropeptide Y receptors inhibiting noradrenaline release in the dog splenic artery (Yang and Chiba 2002), glutamate release in the rat hippocampus (Klapstein and Colmers 1992; Qian et al. 1997), and GABA release in the rat thalamus (Sun et al. 2001). Relatively little information is available on whether presynaptic neuropeptide Y receptors can couple to voltage-dependent $K^+$ channels (step **3** in Figure 3). This may hold true for the neuropeptide Y receptor involved in inhibition of ATP release in the mouse vas deferens (Stjärne et al. 1989). For three presynaptic neuropeptide Y receptors in the rat spinal cord a direct effect on the vesicle release machinery (step **4** in Figure 3) can be assumed, since agonists inhibited the frequency of the miniature inhibitory or excitatory postsynaptic currents (Moran et al. 2004; italics in Table 3).

**Table 3** Synopsis of presynaptic neuropeptide Y receptors

| | Transmitter | Tissue | Species | References |
|---|---|---|---|---|
| Sympathetic nervous system | Noradrenaline | Heart | Human, guinea-pig | 1 |
| | | Submandibular artery | Human | 1 |
| | | Splenic artery | Dog | Yang and Chiba 2002 |
| | | Gracilis muscle vasculature | Dog | 1 |
| | | Ear artery | Rabbit | 1 |
| | | Carotid artery | Guinea-pig | Potter and Tripovic 2006 |
| | | Mesenteric, renal, femoral, basilar artery, resistance vessels | Rat | 1; Potter and Tripovic 2006 |
| | | Saphenous vein | Dog | 1 |
| | | Portal vein | Rat | 1 |
| | | Kidney | Human, pig, rabbit | 1 |
| | | Spleen | Pig | 1 |
| | | Urinary bladder | Guinea-pig | 1 |
| | | Vas deferens | Rat, mouse | 1 |
| | | Uterus | Rat | 1 |
| | | Oviduct | Rabbit | 1 |
| | ATP | Vas deferens | Guinea-pig, mouse | 1 |
| | Neuropeptide Y | Spleen | Pig | Modin et al. 1994 |
| | | Kidney | Pig | 1 |
| Para-sympathetic nervous system | Acetylcholine | Heart | Human | Schwertfeger et al. 2004 |
| | | Heart | Dog, guinea-pig, rat, mouse | 1; Abrahamsson 2000 |
| | | Bronchial arterioles | Dog | Mahns et al. 1998 |
| | | Nasal vessels | Dog, cat | 1 |
| | | Trachea, bronchial muscle | Guinea-pig | Abrahamsson 2000; 1 |
| | | Uterus | Rat | 1 |
| Sensory nerves | Substance P | Dura mater vasculature | Rat | Yu and Moskowitz 1996 |
| | Calcitonin-gene-related peptide | Mesenteric artery | Rat | 1 |
| | | Small intestine | Guinea-pig | 1 |
| CNS | Noradrenaline | Cerebral cortex, hippo-campus, hypothalamus, pineal gland, medulla oblongata | Rat | 1 |
| | Dopamine | Striatum | Rat | 1 |
| | Serotonin | Cerebral cortex | Rat, mouse | 1; Nakazi et al. 2000; Nakazi 2001 |
| | Glutamate | Cerebral cortex | Rat | Wang 2005 |
| | | Olfactory bulb | Rat | Blakemore et al. 2006 |
| | | Hippocampus | Rat | 1 |
| | | Striatum | Rat | 1 |

(*Continued*)

**Table 3** Continued

| | Transmitter | Tissue | Species | References |
|---|---|---|---|---|
| | | Hypothalamus | Rat, mouse | Rhim et al. 1997; Fu et al. 2004 |
| | | Spinal cord | Rat | *Moran et al. 2004*[*] |
| | GABA | Thalamus | Rat | 1 |
| | | Hypothalamus | Rat | 1 |
| | | Spinal cord | Rat | *Moran et al. 2004* |
| | Glycine | Spinal cord | Rat | *Moran et al. 2004* |
| | Neuropeptide Y | Hypothalamus | Rat | 1 |

1 Reviewed by Westfall (2004)
[*]In this study neuropeptide Y decreased the frequency of postsynaptic currents also in the presence of tetrodotoxin.

To address the question of whether presynaptic neuropeptide Y receptors are also activated by endogenous neuropeptide Y or related peptides, the selective $Y_2$ receptor antagonist BIIE 0246 was used. Based on these experiments, an endogenous tone can be assumed for the presynaptic $Y_2$ receptors inhibiting noradrenaline release in the perfused mesenteric arterial bed of the rat (Westfall 2004), noradrenaline and ATP release in the dog splenic artery (Yang and Chiba 2002), and the release of neuropeptide Y itself in the rat hypothalamus (King et al. 2000). The number of tonically activated presynaptic $Y_2$ receptors may be much higher since many sites were examined earlier than 1999 when BIIE 0246 became available.

There is now good evidence for a role of presynaptic neuropeptide Y receptors in disease states. As to the cardiovascular system, plasma neuropeptide Y levels are slightly increased in hypertensive patients and to a greater extent in cardiac failure (Morris 2004). An increase in neuropeptide Y levels is even an important prognostic marker for cardiovascular death in hemodialysis patients (Odar-Cederlof et al. 2003). The exact role played by the presynaptic neuropeptide Y receptor, however, cannot easily be pinpointed for at least two reasons. First, presynaptic inhibitory $Y_2$ receptors occur both on sympathetic and parasympathetic nerve endings of the human heart (Table 3); i.e., they inhibit two opposing systems. Second, within the sympathetic nervous system postsynaptic neuropeptide Y receptors ($Y_1$) lead to vasoconstriction and increase the effect elicited by other vasoconstrictors (Morris 2004), whereas presynaptic $Y_2$ receptors inhibit the release of noradrenaline, ATP, and neuropeptide and thereby impair vasoconstriction.

The pathophysiological role played by another presynaptic $Y_2$ receptor is better understood. In humans suffering from temporal lobe epilepsy (with Ammon's horn sclerosis) and in rats with chemically induced epilepsy, the density of $Y_2$ receptors on hippocampal glutamatergic mossy fibers is greatly increased. The increase is believed to be a protective mechanism against epileptic seizures since the $Y_2$ receptor-mediated inhibition of the release of the excitatory transmitter glutamate is also enhanced (Vezzani and Sperk 2004). In an electrophysiological study glutamate release from the mossy fibers was inhibited by exogenous neuropeptide Y in epileptic but not in control rats. In the epileptic animals there was even a tonic inhibition by

endogenous neuropeptide Y since the $Y_2$ antagonist BIIE 0246 increased glutamate release (Tu et al. 2005).

Clinical trials with neuropeptide Y receptor ligands have so far not been successful (Brain and Cox 2006).

## 4 Presynaptic ACTH Receptors

Although ACTH has been known since the 1930s, presynaptic ACTH receptors were identified much later (Figure 1) and have attracted the attention of investigators for only a few years. ACTH consists of 39 amino acid residues and is processed from proopiomelanocortin, i.e., the same precursor molecule giving rise to ß-endorphin (see section 2). Besides ACTH and endogenous opioids, a series of melanocyte-stimulating hormones are formed from proopiomelanocortin (Table 1). The latter activate $MC_1$, $MC_3$, $MC_4$ and $MC_5$ receptors. ACTH activates the $MC_2$ receptor (i.e., the receptor involved in its corticotropic effect) but also has a high affinity for some of the other melanocortin receptors (Gantz and Fong 2003; Alexander et al. 2006). ACTH is not only one of the hormones of the adenohypophysis but serves also as a neurotransmitter in hypothalamic neurones (Bloch et al. 1979; Bugnon et al. 1979).

Unlike the opioids and neuropeptide Y, ACTH increases transmitter release. As shown in superfusion studies and in pithed and anesthetized animal preparations, ACTH increases noradrenaline release in cardiovascular tissues from the rabbit; in an electrophysiological study it increased acetylcholine release in frog skeletal muscle (Table 4). Thus, according to our present knowledge, presynaptic ACTH receptors occur as heteroreceptors only. No effect of ACTH on noradrenaline release was found in rat atrium and rat and guinea pig pulmonary artery (Costa and Majewski 1988). Human tissues have not been examined. The studies summarized in Table 4 are based on experiments with the full-length ACTH molecule and its active sequence $ACTH_{1–24}$. The effect of ACTH was not mimicked by $ACTH_{4–10}$, a

**Table 4** Synopsis of presynaptic facilitatory ACTH receptors

| | Transmitter | Tissue | Species | References |
|---|---|---|---|---|
| Sympathetic nervous system | Noradrenaline | Heart | Rabbit | Costa and Majewski 1988; Szabo et al. 1988 |
| | | Aorta | Rabbit | Göthert 1984 |
| | | Pulmonary artery | Rabbit | Göthert 1981; 1984; Göthert and Hentrich 1984; Costa and Majewski 1988 |
| | | Various sympathetically innervated tissues | Rabbit | Szabo et al. 1987; 1989 |
| Motor nerves | Acetylcholine | Cutaneous pectoris and sartorius muscle | Frog | Johnston et al. 1983 |

behaviorally active peptide devoid of a corticotropic effect, and was antagonized by an appropriate concentration of the ACTH receptor antagonist $ACTH_{7–38}$ (Göthert 1981). The data suggest that the facilitatory effect is mediated via the $MC_2$ receptor.

In general, the $MC_2$ receptor is $G_s$ protein-coupled (Table 1), and two studies in the rabbit pulmonary artery indicate that this is also true for the presynaptic receptor. The evidence is, indirect, however, in that it suggests activation of adenylyl cyclase, the typical transduction step downstream from $G_s$. In the study by Göthert and Hentrich (1984), the facilitatory effect of ACTH was increased by simultaneous administration of forskolin, an activator of the catalytic subunit of adenylyl cyclase, and AH 21–132, a phosphodiesterase inhibitor. In the study by Costa and Majewski (1988), the facilitatory effect of ACTH was occluded when the vessel was superfused with a lipid-soluble cAMP analogue.

The presynaptic $MC_2$ receptor plays no physiological role, since the concentration of ACTH found in the blood is far too low for its activation. This view is supported by the finding that the antagonist $ACTH_{7–38}$, when given alone, did not affect noradrenaline release in the rabbit heart (Szabo et al. 1989) or pulmonary artery (Göthert 1981). The situation may change under pathophysiological conditions when ACTH concentrations are increased. ACTH may then increase noradrenaline release in cardiovascular tissues and help to maintain cardiovascular function (Szabo et al. 1989). However, at presynaptically effective concentrations ACTH has additional postsynaptic cardiovascular effects: vasodilation and an increase in heart rate (Szabo et al. 1987; 1989).

Although $ACTH_{1–24}$ is used for diagnostic purposes and for the treatment of epilepsies in babies and infants, drugs specifically targeting *presynaptic* $MC_2$ receptors are not available.

## 5 Presynaptic Orexin Receptors

Orexins (also known as hypocretins) and presynaptic receptors activated by orexins were first described in 1998 (Figure 1). Orexin-A (hypocretin-1) and orexin-B (hypocretin-2) consist of 33 and 28 amino acid residues, respectively, and are derived from a common precursor molecule (prepro-orexin). They act on two receptors, $OX_1$ and $OX_2$. Orexinergic neurones have their perikarya in the lateral and posterior part of the hypothalamus and project to many parts of the brain, including the cerebral cortex, thalamus, limbic system, locus coeruleus and raphe nuclei, and to the spinal cord. Orexin-like immunoreactive neurones also occur in the small intestine (for review, see Smart and Jerman 2002).

Orexins increase transmitter release. This has been shown in electrophysiological studies for acetylcholine release in the myenteric plexus of the ileum and for GABA and glutamate release in a series of locations of the central nervous system (Table 5); in other words, presynaptic orexin receptors serve as heteroreceptors. Experiments on human tissue are so far lacking. In some of the experimental models listed in Table 5 orexin-A and orexin-B were studied and orexin-B was at least as

**Table 5** Synopsis of presynaptic facilitatory orexin receptors

| | Transmitter | Tissue | Species | References |
|---|---|---|---|---|
| Parasympathetic nervous system | Acetylcholine | Ileum | Guinea-pig | Katayama et al. 2003; 2005 |
| Central nervous system | GABA | Medial hypothalamus | Rat | *van den Pol et al. 1998** |
| | | Dorsal vagal complex | Rat | *Davis et al. 2003* |
| | Glutamate | Prefrontal cortex | Rat | Lambe and Aghajanian 2003 |
| | | Medial hypothalamus | Rat | *van den Pol et al. 1998* |
| | | Lateral hypothalamus | Mouse | *Li et al. 2002* |
| | | Laterodorsal tegmentum | Mouse | Burlet et al. 2002 |
| | | Caudal nucleus tractus solitarii | Rat | *Smith et al. 2002* |

*In the studies given in *italics* orexins facilitated postsynaptic currents or potentials also in the presence of tetrodotoxin.

potent as orexin-A (Burlet et al. 2002; Li et al. 2002; Davis et al. 2003; Lambe and Aghajanian 2003; Katayama et al. 2005). Since both orexins are equally potent at $OX_2$ receptors, whereas orexin-A is 10 times more potent than orexin-B at $OX_1$ receptors (Alexander et al. 2006), the presynaptic effects of orexins may involve $OX_2$ receptors or perhaps a mixture of $OX_1$ and $OX_2$. For final proof, selective antagonists would be necessary, but $OX_2$ receptor antagonists are so far not available and the $OX_1$ receptor antagonists have a relatively weak potency; the agonist peptide [$Ala^{11}$, D-$Leu^{15}$] orexin-B, which possesses a high preference for $OX_2$ receptors, may be helpful (Alexander et al. 2006). Experiments with knockout mice would be valuable as well.

Since the orexin receptors are $G_q$ protein-coupled (Alexander et al. 2006), one may assume that this also holds true for the presynaptic orexin receptor(s), but so far no data are available. Nonetheless, the six studies carried out in central nervous preparations permit some conclusions on the post-G protein mechanisms. In all instances, the orexins increased the frequency of spontaneous inhibitory or excitatory postsynaptic potentials or currents. The results differed, however, with respect to the influence of tetrodotoxin. In the medial and lateral hypothalamus (van den Pol et al. 1998; Li et al. 2002), dorsal vagal complex (Davis et al. 2003), and caudal nucleus tractus solitarii (Smith et al. 2002), orexins increased the frequency of the miniature potentials or currents also in the presence of tetrodotoxin, suggesting that they directly influenced the vesicle release machinery (references in italics in Table 5). On the other hand, in the prefrontal cortex (Lambe and Aghajanian 2003) and laterodorsal tegmentum (Burlet et al. 2002), the orexins did not retain their facilitatory effect in the presence of tetrodotoxin, suggesting an effect further upstream e.g., on $Ca^{2+}$ and/or $K^+$ channels.

The physiological and pathophysiological role of presynaptic orexin receptors is incompletely understood, and drugs targeting orexin receptors so far have not been developed. Orexins play an important role in the control of sleep and wakefulness, as highlighted by the findings that the knockout of preproorexin in mice (Chemelli

et al. 1999) or a mutation of the $OX_2$ gene in dogs (Lin et al. 1999) produces a disturbance resembling narcolepsy in humans. Indeed a decreased number of orexin neurones was found in humans suffering from that disease (Thannickal et al. 2000). There are two presynaptic facilitatory sites that may be involved in the control of sleep and wakefulness by the orexins. The first one is on glutamatergic neurones in the laterodorsal tegmentum, and the second one is on glutamatergic neurones in the prefrontal cortex (i.e., at the final synapse in the ascending arousal pathway). One may assume that the increase in glutamate release excites ascending cholinergic neurones involved in the arousal reaction in the first instance (Burlet et al. 2002; Table 5) and glutamatergic output neurones in the second model (Lambe and Aghajanian 2003; Table 5).

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