Pharmacology of Endogenous Opioids, Opiates and Their Receptors

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Abstract

The search for analgesia is the main drive for the discovery of opioid receptors and their endogenous ligand peptides. Although opioid peptides are very similar in their *N*-terminal sequence, they are classified into different types according to their precursor proteins. The peptides activate opioid receptors by binding to orthosteric-binding sites to mediate intracellular second messengers. Biased signaling and allosteric modulation is a new approach to obtain receptor subtype selectivity and separates the desirable from a myriad of unwanted pharmacological effects. This chapter describes endogenous opioids and opiates with an emphasis on structure, origin and processing, receptors, physiological roles, and potential involvement in therapeutic interventions. Further, it also provides a brief discussion on the effect of opioids on various ion channels and recent developments of established and investigational opioid molecules.

Keywords

Opioids receptors · Endorphin · Enkephalin · Dynorphin · GPCR · Neurological disorders · Ion channels

Abbreviations

ACTH Adrenocorticotropin
BACE1 Beta-site APP cleaving enzyme 1

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CLIP	Corticotropin-like intermediate peptide
DOR	Delta opioid receptor
GPCR	G protein-coupled receptor
KOR	Kappa opioid receptor
MOR	Mu opioid receptor
MSH	Melanotropins or melanocyte-stimulating hormone
N/OFQ	Nociceptin/orphanin FQ
OP	Opioid peptide
OR	Opioid receptor
ORL-1	Opioid receptor-like-1
POMC	Proopiomelanocortin

12.1 Introduction

The inscription of the ancient Sumerian clay tablet insinuates the use of the natural extract of poppy plant (*Papaver somniferum)* as analgesia and post-surgical pain (Norn et al. 2005; Brownstein 1993). The active ingredient of the extract is morphine, which necessitates the presence of receptors for binding inside the human body. The search for endogenous ligands acting on those opioid receptors (ORs) started in the 1960s and succeeded in a few years by using radiolabeled ligands (Pert and Snyder 1973). On the search for ligands for those ORs, several peptides were isolated. The early peptides were enkephalins (Hughes et al. 1975) which showed higher potency than morphine on opioid receptors (Kosterlitz and Hughes 1975). Soon the untriakontapeptide (endorphin) was discovered (Li and Chung 1976), then dynorphins (Cox et al. 1975) and endomorphins (Zadina et al. 1997).

Although opioid peptides (OPs) share almost similar *N*-terminal amino acid sequence, their precursor proteins are different. The processing of precursor proteins differs from one tissue to another as well as variation of the half-life of opioid peptides. Some endogenous opioid peptides like endomorphins act as a selective agonist for μ-opioid receptor (MOR) and thus have a good potential for clinical use. However, the low oral bioavailability of endomorphins restricts its use unless given as glycosylated derivatives (Varamini et al. 2012). Currently, three types of opioid receptors are known, namely Mu, Delta, and Kappa opioid receptors (MORs, DORs and KORs, respectively). The receptors can be activated by orthosteric ligands and cooperated with allosteric ligands to produce modulation of orthosteric affinity/efficacy as well as biasing the intracellular signaling.

12.2 Opioid Peptides

12.2.1 Classification, Synthesis, Storage, Release, and Removal

Endogenous opioid peptides are classified into three categories, namely endorphins, enkephalins, and dynorphins. The peptides are endogenously produced by peptidases digestion of larger precursor proteins, namely proopiomelanocortin,

proenkephalin and prodynorphin, respectively (Pleuvry 1991). Endomorphins is regarded as the fourth category of OPs; however, the precursor for endomorphins is not precisely known from the human genome (Terskiy et al. 2007) and may involve an oxidative transformation of guanine nucleotide from suspected gene leading to G → T transversion in the produced mRNA (messenger ribonucleic acid) (Matsushima et al. 2019). The proopiomelanocortin (POMC) precursor is processed to give rise to adrenocorticotropin (ACTH), melanotropins (MSH) and β-endorphin (Castro and Morrison 1997). The processing of precursor protein depends on a particular cell type. At anterior pituitary, POMC is processed in corticotrophs to generate mainly ACTH and β-lipotropin. When processed in melanotrophs, it produces MSH primarily (De Wied 1999). Both ACTH and β-lipotropin (1–91 aa) have no analgesic activity. The further processing of β-lipotropin gives rise to β-endorphin (61–91 aa), which in turn may yield [Met]-enkephalin (61–65) (Cox et al. 1976; Takeuchi 2001). In melanotrophs of pars intermediate of the pituitary, POMC is processed further to produce α-MSH (from *N*-terminal of POMC) which is attributed to different levels of specific peptidases in different regions of the pituitary (Day 2009). In addition to the pituitary, POMC is also detected in the arcuate nucleus of the hypothalamus, solitary tract of the medulla and several peripheral tissues (Papadimitriou and Priftis 2009).

Proenkephalin peptide contains six copies of [Met]-enkephalin and one copy of [Leu]-enkephalin, which are separated from each other by dibasic peptides as digestive site (Takahashi 2016). Although proenkephalin is produced by both the brain and adrenal gland, however, it is processed differently in each tissue (Geracioti et al. 2009). Proenkephalin-producing neurons are more widespread in the brain than POMC neurons (Geracioti et al. 2009). Prodynorphin is also called proenkephalin-B since it contains three copies of [Leu]-enkephalins in addition to dynorphin A, dynorphin B and α-neoendorphin (Fig. 12.1 and Table 12.1).

In neuron soma, precursor neuropeptides are synthesized in the endoplasmic reticulum, and through Golgi apparatus, the peptides are processed by proteases and undergo functional group modification and then transported to axons as vesicles. At the nerve terminal, the vesicles may contain both precursor and opioid peptides (Hökfelt et al. 2000). The processing of precursor peptide is activated by potassium-induced depolarization of the neuron (Yakovleva et al. 2006). Moreover, the acidic pH of secretory vacuoles promotes digestion of precursor peptides such as POMC (Cawley et al. 2016). The opioid peptides vesicles appeared distinct from amino acid neurotransmitter vesicles, and the former appear denser under a microscope. The dense vesicles are distributed over neuronal cells but especially abundant in dendrites, cell body and axon varicosities and can be released from either site with machinery different from neurotransmitters (Russo 2017; Gu et al. 2017).

Post-translational modifications may take place on opioid peptides such as glycosylation, acetylation, methylation and phosphorylation which alter their biological activities (Froehlich 1997). While glycosylation improves the blood-brain barrier (BBB) penetration (Egleton et al. 2000), acetylation attenuates the activity of the peptide. Glycosylation may occur even on precursor proteins and thus controls the degree of digestion to active opioid peptides and protects against non-specific digestion (Hughes et al. 1980; Loh and Gainer 1978).

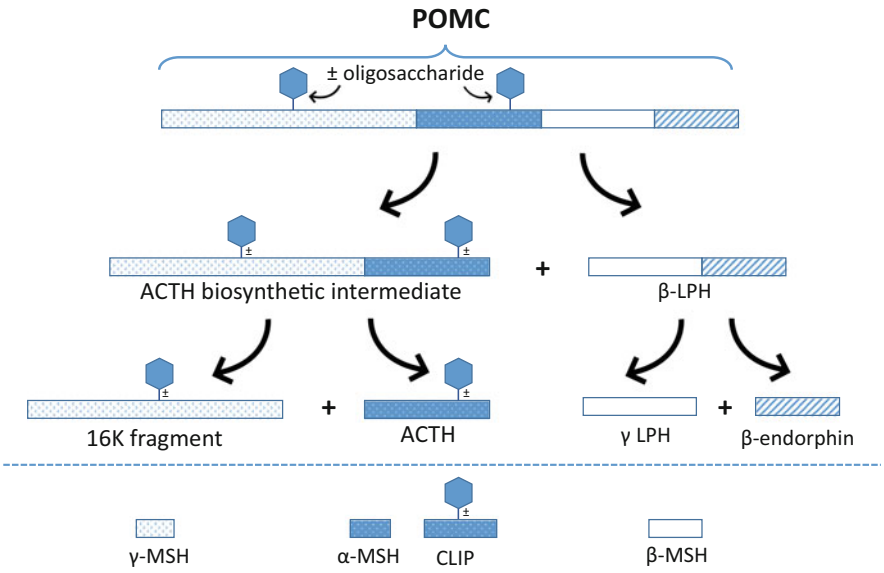


Fig. 12.1 The processing of POMC (Retrieved from Mains and Eipper 1981)

The neuropeptides (including opioids) may diffuse to distal sites (up to millimeters), unlike other neurotransmitters, which remain within the synaptic space. They exert their effect by interacting with opioid and other receptors and may have longer extracellular half-lives (van den Pol 2012; Russo 2017). Long-distance signaling within the brain through no synapses is called volume transmission (Agnati et al. 1995; Veening et al. 2012). Volume transmission is common with G protein-coupled receptors (GPCRs) that are more sensitive to neuropeptides where the nanomolar concentration of opioid peptides is sufficient to activate the receptors. This is unlike the ionotropic receptors like γ-aminobutyric acid (GABA), where micromolar concentration is needed (Ludwig and Leng 2006).

Another difference between opioid peptides and neurotransmitters is that opioid peptides lack reuptake mechanism by releasing neurons. Therefore, the inactivation mechanism is limited to digestion by peptidases extracellularly or after cellular internalization. Many peptidases degrade opioid peptides. The major peptidases involved in the degradation of opioid peptides are endopeptidases (those acting on *N*-terminal of peptides, the pharmacophoric domain). However, other peptidases also contribute such as an insulin-degrading enzyme, angiotensin-converting enzyme, neprilysin, serine peptidases and other dipeptidyl peptidases (Asvadi et al. 2014a; Malfroy et al. 1978; Turner 2004; Hersh and Rodgers 2008). Since the activity of these peptidases is affected by the pH of the tissue, the half-life of these peptidases increases in inflamed tissues that have acidic pH; therefore, opioid peptides are degraded more rapidly and differently (Asvadi et al. 2014b; Herath et al. 2012). The inhibition of the degrading enzymes by specific and non-specific inhibitors is effective in producing analgesia.

Table 12.1 Opioid peptides and their precursor proteins and receptor selectivity (Luca et al. 2007; Coward et al. 1998)

Endogenous peptide	Amino acid sequence	Receptor affinity	Precursor
β-Endorphin	YGGFMTSEKSQTPLVTLFKNAIIKNAYKKGE	$\delta = \mu$	Proopiomelanocortin
[Met]-enkephalin [Leu]-enkephalin Metorphinamide	YGGFM (YGGFMRF, YGGFMRGL) YGGFL YGGFMRRV-NH_2	$\delta >> \mu$	Proenkephalin
Dynorphin A Dynorphin A(1-8) Dynorphin B α-neoendorphin β-neoendorphin	YGGFLRRIRPKLKWDNQ YGGFLRRI YGGFLRRQFKVVT YGGFLRKYPK YGGFLRKYP	$\kappa >> \delta = \mu$	Prodynorphin
Nociceptin	FGGFTGARKSARKLANQ	*ORL	Pronociceptin
Endomorphin-1 Endomorphin-2	YPWF-NH_2 YPFF-NH_2	μ	Unknown

*ORL means orphan opioid-receptor-like

12.2.2 Physiological Role of Opioid Peptides

12.2.2.1 Sites of Action of Opioid Peptides

Opioids act at two sites on the neurons, *viz.* the presynaptic nerve terminal and the postsynaptic neuron. The postsynaptic actions of opioids are usually inhibitory, while presynaptically they inhibit the release of neurotransmitters. Thus, the central nervous system (CNS) effect of the opioids is an overall result of their actions at the multiple presynaptic sites of both inhibitory and excitatory neurons and also includes their actions at postsynaptic sites. As a consequence, the overall effect of opioids depends upon the location and density of opioid receptors on the neurons. For instance, presynaptic inhibition of neurotransmitter release leads to the excitatory effects in target neuron if the neurotransmitter produces an inhibitory effect. On the other hand, if the opioid also has a postsynaptic inhibitory effect on the target neuron, then excitatory effects may not occur (Winters et al. 2017; Fields and Margolis 2015). Morphine acts on μ-receptors and inhibits the discharge of numerous diverse neurotransmitters including acetylcholine, noradrenaline and the neuropeptide substance P (Kerage et al. 2019; Commons 2010; Dickenson 1994).

12.2.2.2 Opioid Peptides and Their Effect on Analgesic/Pain Pathways

Pain is usually considered to be associated with augmented activity in primary sensory neurons provoked either by strong thermal or mechanical stimuli or by the chemicals released by inflammation or tissue damage (Yam et al. 2018). The primary sensory neurons implicated in the pain sensation releases glutamate and substance P in the dorsal horn of the spinal cord principally (Zieglgänsberger 2018; Lembeck 2008). The nociceptive signal is then communicated *via* the spinothalamic tracts to the brain, thereby activating the descending pathways from the periaqueductal gray area in the midbrain which then exerts inhibitory control over the dorsal horn (Venkatraman et al. 2017; Mendell 2011).

Opioid receptors are located at various regions of the nervous system that are involved in pain transmission and control, including primary afferent neurons, spinal cord, midbrain, and thalamus. Though the physiological function of endogenous opioids toward the pain transmission is still unclear, under pathological conditions, the endogenous opioid system gets activated. The opioid drugs, however, produce analgesia by inhibition of neurotransmitter release from the primary afferent terminals in spinal cord and activation of descending inhibitory controls in the midbrain (Allouche et al. 2014; McDonald and Lambert 2005; Waldhoer et al. 2004).

Any modulation in the nociceptive pathways may result in profound alterations in levels of neurotransmitters in primary afferent neurons, thereby causing changes in sensitivity to opioid analgesia (Yam et al. 2018). Accordingly, neuropathic pain is related to reduced sensitivity to opioids; on the contrary, inflammatory pain is linked with increased opioid sensitivity. Moreover, the alterations that occur in pain sensitivity during the states of chronic pain have been ascribed to the activation of glutamate NMDA (*N*-Methyl-D-aspartate) receptor (Greenwald and Shafritz 2018; Latremoliere and Woolf 2009; Petrenko et al. 2003; Bennett 2000).

12.2.2.3 Activity of Opioid Peptides

Opioid peptides are produced by different tissues, including mainly pituitary and adrenal glands (Przewlocki 2013). Enkephalins, for instance, are also released by heart, skeletal muscle, kidney, and intestinal cells, thus playing an important role in behavior, pain, cardiac function, cellular growth, immunity, and ischemic tolerance (Denning et al. 2008). The expression of prodynorphin is mainly observed in the cerebral cortex and basal ganglia in addition to reproductive tissues of testis, uterus, and ovary (Collard et al. 1990; Douglass et al. 1987).

Opioid peptides are neuromodulators rather than neurotransmitters—that is, OPs can alter the release and neuronal response to neurotransmitter by changing the hyperpolarizing neuronal cell membrane (North and Williams 1983; Loose et al. 1990; Wu et al. 2007). The activation of ORs by endogenous peptides transmits or modulates signal transmission for other neurotransmitters. Therefore, the peptides have a wide range of activities that include central and peripheral antinociception, endocrine, immune, motor activity, feeding, sexual behavior, regulation of body temperature, respiration and cardiovascular and gastrointestinal functions (Przewlocki 2013).

The β-endorphin is regarded as the most important opioid peptide. The peptide is involved in interneuron communication through synapses as well as extracellular spaces and cerebrospinal fluid (volume transmission, VT) (Veening and Barendregt 2015). The peptide showed central and peripheral analgesic activities (Sprouse-Blum et al. 2010). Both ACTH and β-endorphin are stress hormones released during painful stimulations. The release of ACTH and β-endorphin from a culture of pituitary tumor cells can be evoked by epinephrine (Mains and Eipper 1981). Therefore β-endorphin is responsible for stress-induced analgesia (Rubinstein et al. 1996). The *N*-terminal amino acids of β-endorphin are likely accountable for analgesic activity, while the C-terminal amino acids are more related to potency. The removal of eight amino acids from *N*-terminal abolishes the analgesic activity of β-endorphin (Deakin et al. 1980). Although the analgesic potency of β-endorphin is higher than [Met]-enkephalin, the potency is reduced by *N*-α-acetylation (Deakin et al. 1980).

Enkephalins are another group of opioid peptides that include mainly [Met]-enkephalin and [Leu]-enkephalin. The affinity of enkephalins for MOR is similar to that of morphine and is ten times lower then affinity for DOR. Besides analgesia, enkephalins may be involved in emotional and motivational behavior (Nieto et al. 2005) and sexual activities for male (Rodríguez-Manzo et al. 2002) and controls gastrointestinal motility and secretions (Mitznegg et al. 1977; Holzer 2009).

Dynorphin is an opioid peptide which is released at the level of the spinal cord and augments the afferent pain signal (Podvin et al. 2016), thus provoking allodynia, pain sensation for usually non-painful stimuli. Therefore, dynorphin has a significant role in the mediation of chronic pain (Podvin et al. 2016) as well as tolerance to antinociceptive opioids (Vanderah et al. 2001). Moreover, dynorphin promotes anxiety, stress, and dysphoria-driven cravings for another dose in addiction through its action on KORs (Chavkin and Koob 2016; Knoll and Carlezon 2010).

Endomorphins (1 and 2) are reported to be the only discovered opioid peptide that are selective for MOR (Zadina et al. 1997). The two peptides differ from other opioid peptides in having NH_2-Tyr-Pro-Trp(Phe)-Phe-CO-NH_2, that is, having carboxamide (aminocarbonyl) terminal. Some studies showed that endomorphin-1 produces higher analgesia and without reward effect compared to morphine (Wilson et al. 2000). Although the reward effect is known to be mediated by binding MOR, it is limited to a specific conformational set of receptors; thus it is ligand-dependent property. However, the potential of respiratory depression, urinary retention, tolerance, addiction and cardiac side effects and the low intrinsic bioavailability restrict the clinical use of endomorphins (Gu et al. 2017). Glycosylation through succinamic acid linker at the *N*-terminal enhances metabolic stability and membrane permeability of endomorphins while maintaining potency and efficacy (Varamini et al. 2012).

Nociceptin is structurally related to dynorphin; however, it binds to opioid receptor-like (ORL) while having no affinity for other ORs. Similar to dynorphin, nociceptin antagonizes the analgesic effect of other opioid ligands (Mika et al. 2011). Activation of ORL inhibits adenylyl cyclase and Ca^{+2} channels while activating K^+ channels like opioid receptors (Calo et al. 2000). However, the pharmacological behavior observed upon activation by nociceptin produces potent anti-analgesic action supra-spinally and analgesic action spinally (Mogil and Pasternak 2001).

12.3 Receptor (Types, Subtypes, Localization, Down Signaling Pathways, Functions, Agonist, Antagonist)

Endogenous opioids produce effects on the neurons by binding to three types of receptors located on neuronal cell membranes: namely, mu (μ), delta (δ) and kappa (κ) receptors. Other receptors such as opioid receptor-like-1 (ORL1) have sequence similarity to ORs, however not classified as ORs since being unresponsive to classical opioids ligands (Snyder 2004). Naturally occurring opioids, β-endorphins interact preferentially with μ-receptors, while the enkephalins and dynorphin interact respectively with δ-receptors and κ-receptors (Ghelardini et al. 2015; Al-Hasani and Bruchas 2011; Dhawan et al. 1996). The relative selectivity for endogenous and exogenous ORs ligands are listed in Table 12.2. The crystal structures for opioid receptors are available for mu, delta, and recently kappa receptors. The structures are for inactive conformations that are stabilized by bound antagonists (Manglik et al. 2012; Wu et al. 2012; Granier et al. 2012) and for active conformations that are stabilized by either bound agonist or conformation-specific nanobody or G-protein (Huang et al. 2015; Koehl et al. 2018; Che et al. 2018). The further sorting of main OR classes into subtypes is only approved from the anesthetic perspective in a way that μ1 is responsible for analgesia and dependence, μ2 is for euphoria, dependence and respiratory depression, and μ3 is for vasodilation. However, currently, there is no clear evidence for the existence of subtypes for these receptors (Dietis et al. 2011).

Table 12.2 Selectivity of naturally occurring endogenous opioids and opiates for opioid receptors

	μ-receptor	δ-receptor	κ-receptor
Opioid peptides (endogenous opioids)			
β-endorphin	+++	+++	+++
[Leu]-enkephalin	+	+++	–
[Met]-enkephalin	++	+++	–
Dynorphin	++	+	+++
Opioid drugs (agonists)			
Morphine	+++	+	++
Codeine	+	+	+
Pethidine	++	+	+
Fentanyl	+++	+	–
Opioid drugs (partial/mixed agonists)			
Pentazocine	+	+	± ±
Buprenorphine	± ± ±	–	–
Opioid drugs (antagonists)			
Naloxone	+++	++	++
Naltrexone	+++	++	++

+ indicates agonist; ± indicates partial agonist; number of + or ± indicates potency

Opioid receptors are classical G protein-coupled receptors (Fig. 12.2), thus interacting with intracellular G-protein that has GTPase activity to mediate intracellular signaling. The G-protein is a heterotrimeric protein composed of Gα, Gβ, and Gγ. The activation of ORs leads to the dissociation of G-protein. The Gβγ subunits may interact directly with the membrane ion channels, thereby causing inhibition of voltage-gated calcium channels (VGCCs) or rectifying potassium channels (Kir). The Gβγ subunits also contribute to the activation of inositol triphosphate kinase (IP3K), phospholipase C—phosphatidyl inositol triphosphate (PLC-IP3), or mitogen-activated protein kinase (MAPK) (Khan et al. 2013; Smrcka 2008). With respect to Gα subunit, it is classified into four families: $G\alpha_s$ (activates adenylyl cyclase), $G\alpha_{i/o}$ (inhibits adenylyl cyclase), $G\alpha_{q/11}$ (activation of phospholipase Cβ) and $G\alpha_{12/13}$ (activation of GTPase activating protein for Ras)(Ras, a small GTP-binding protein named after Rat sarcoma) (Neves et al. 2002). The inhibition of adenylyl cyclase by $G\alpha_{i/o}$ subunit leads to reduced production of cyclic adenosine monophosphate (cAMP). Decreased concentration of cAMP further modulates membrane sodium or calcium channels (Law 2011; Catterall 2011; Scheuer 2011). Additionally, cAMP may also interact with and modulate the inward rectifying potassium channels (Li et al. 2013; Butt and Kalsi 2006; North 1993). Chronic consumption of opiates inhibits the production of cAMP; however, this inhibition is offset in the long run by other cAMP production mechanisms (Ramaswamy and Langford 2017; Al-Hasani and Bruchas 2011; Kosten and George 2002). When no opiates are available, this increased cAMP production capacity comes to the force and results in neural hyperactivity, thus causing a sensation of craving the drug (Al-Hasani and Bruchas 2011; Bie 2005; Kosten and George 2002).

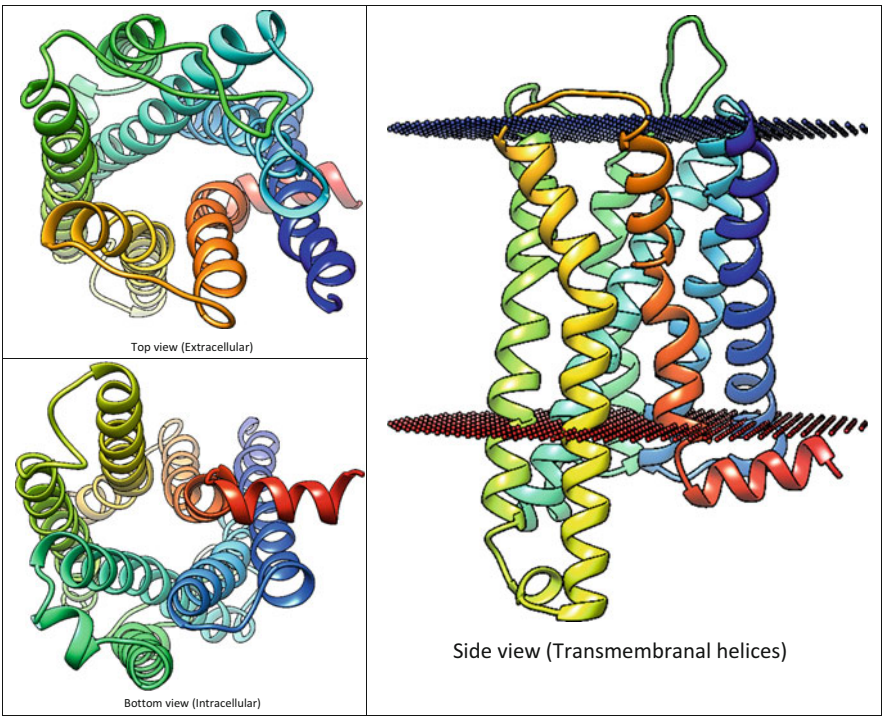


Fig. 12.2 Crystal structure of active conformation of Mu opioid receptors (PDB ID: 6DDE) with missing H8 being added from PDB 5C1M and the position within cell membrane is optimized using OPM database

Besides interaction with G-protein, ORs interact with other regulatory proteins and may end up with its sequestration or desensitization. Specific phosphorylation of ORs by GPCR kinases leads to interaction with β-arrestin and subsequent internalization of the receptor. Probably, $G_{i/o}$ mediates the antinociceptive effect produced by activation of MOR (Lamberts et al. 2011; Connor and Christie 1999), while respiratory depression and tolerance is mediated by activation of β-arrestin. Specific phosphorylation of ORs by GPCR kinases leads to interaction with β-arrestin and subsequent internalization of the receptor further causes tolerance to morphine analgesia (Bohn et al. 1999). Avoiding activation of β-arrestin-2 pathway reduces internalization of MOR and consequently tolerance; however, it has little effect on the up-regulation of adenylyl cyclase activity that is correlated to physical dependence (Bohn et al. 2000).

Opioid receptors may exist as homo- or heteromers to provide a cellular specific response for the same ligand. The ORL-1 or nociceptin/orphanin FQ (N/OFQ) receptor undergoes heteromerization to form heteromers with μ-opioid receptor (MOR), δ-opioid receptor (DOR), and κ-opioid receptor (KOR) (Evans et al. 2010). Additionally, MOR may also form heteromers with DOR in small dorsal

root ganglion neurons (DRGn) and in homologous expression systems (Gendron et al. 2015).

All three ORs produce analgesia when opioid binds to them; however, it is higher for μ then κ and δ subtypes and is associated with euphoria, dysphoria, and anxiolytic effects, respectively (Lutz and Kieffer 2013). Activation of κ-receptors produces comparatively less physical dependence as activation of μ-receptors (Machelska and Celik 2018; Feng et al. 2012). Each of these receptors is coupled to intracellular mechanisms *via* G-protein and mediates its effect through the second messengers, thereby influencing the probability of opening of the ion channels, which in some instances may reduce the excitability of the neurons (Machelska and Celik 2018, Feng et al. 2012). This reduced excitability contributes as a potential source of the euphoric effect of opiates and probably appears to be mediated by μ- and δ-receptors (Machelska and Celik 2018; Reisine and Bell 1993).

Like many GPCRs, ORs have binding sites for orthosteric and allosteric ligands. While orthosteric ligand can modulate receptor conformation independently, allosteric ligand depends on orthosteric ligand for modulating receptor conformation. The orthosteric active opioid peptides (Livingston and Traynor 2018) share a common *N*-terminal sequence of Tyr-Gly-Gly-Phe that starts with an ionized amine. The peptides are proposed to have two pharmacophores named as message and address pharmacophores. In other words, the address leads the peptide for opioid receptor subtype, while the message stabilizes particular receptor conformations to mediate specific set of intracellular signals. This proposal has been used to design highly potent and selective non-peptide DOR antagonists (Portoghese et al. 1988). The extracellular loops of opioid receptors have long been thought to involve in controlling ligand selectivity to receptor subtypes by interaction with the address part of the ligand (Metzger and Ferguson 1995). On the other hand, allosteric ligands (or modulators) are classified as positive (PAM), negative (NAM) and neutral/silent allosteric (SAM) modulators, which increases, decreases, and has no effect on orthosteric ligand activity, respectively (Mahmod Al-Qattan and Mordi 2019). Most of the allosteric ligands require bound orthosteric ligand in order to exert activity.

The conformational ensembles stabilized by orthosteric ± allosteric ligand(s) modulate the downstream signaling of the receptor (i.e. interaction with intracellular second messengers). Therefore, any ligand binding to ORs has a 2D fingerprint of intracellular signaling paradigm as affinities versus efficacies. Accordingly, some ligands are biased toward activating a particular group of second messengers over others, which is referred to as biased agonism. Biased signaling (also known as differential efficacy or functional selectivity) is the way of separating wanted pharmacological effect from other unwanted effects mediated by the same receptor (Bologna et al. 2017). The biased activation of ORs was observed among endogenous as well as exogenous ligands. Unlike other endogenous OPs, α-neoendorphin, [Met]-enkephalin, [Met]-enkephalin-RF, endomorphin-1 and endomorphin-2- showed biased agonistic activities compared to reference DAMGO (a synthetic peptide with high μ-opioid receptor specificity and its structure is H-Tyr-D-Ala-Gly-N-MePhe-Gly-ol) across multiple signaling pathways as shown in Fig. 12.3 (Thompson et al. 2015).

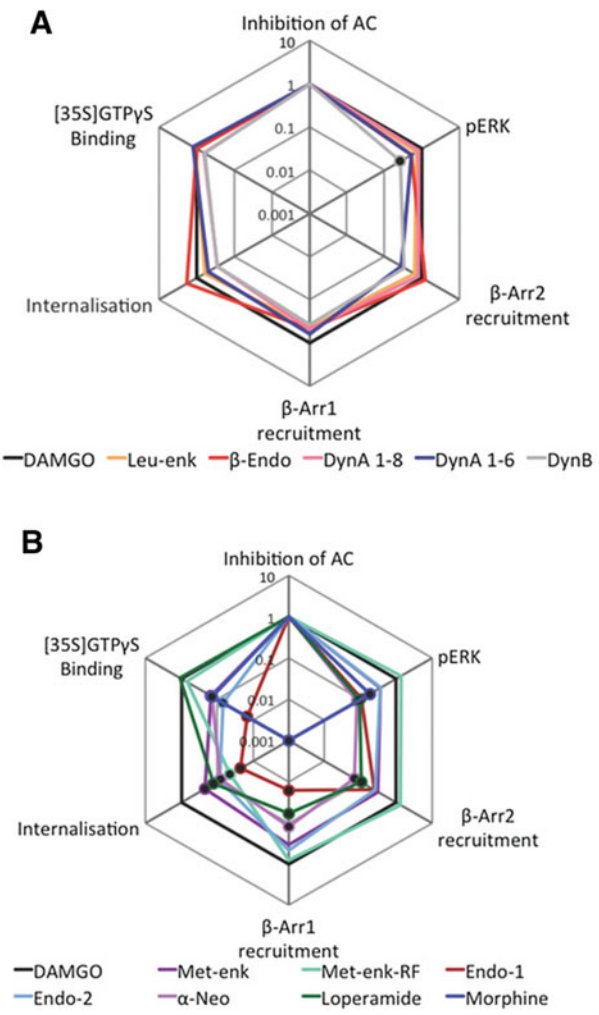


Fig. 12.3 Webs of bias of endogenous opioid peptides and reference ligands at the MOP. (**a**) Ligands with profiles similar to DAMGO. (**b**) Ligands with profiles that differ from that of DAMGO. The score of τ/K_A (or efficacy/affinity) values was normalized to the reference ligand DAMGO and to the cAMP assay. Statistically significant differences ($P \leq 0.05$) are denoted by black circles as determined by two-tailed t test. For the purposes of visualization only, a τ/K_A for Met-enk-RF in the internalization assay was estimated using the incomplete concentration response curve for plasma membrane marker (Thompson et al. 2015)

With respect to exogenous ligands, biased activation of MOR toward G-protein was observed for a fungal peptide, which is opposite to the biased activity produced by endogenous endomorphin-2 that is toward β-arrestin-2 (Dekan et al. 2019). Biased agonist at MOR opens a new opportunity of agonists with lower side effects (Madariaga-MazÓN et al. 2017). Oliceridine is a biased agonist at MOR, which provides lower β-arrestin binding leading to lower receptor internalization and thus lower respiratory depression and tolerance compared to unbiased morphine agonist (Dewire et al. 2013). Similar natural products such as mitragynine and 7-hydroxymitragynine (Kruegel et al. 2016) and salvinorin-analogues (Groer et al. 2007) also showed a biased effect with lower β-arrestin binding. The PZM21, a molecule obtained by structure-based screening and design, showed selective MOR agonistic effect with minimal β-arrestin activation (Manglik et al. 2016). Biased agonist at KOR was developed to produce antinociception and anti-itching activities

without the concomitant dysphoria and sedation usually associated with this receptor (Brust et al. 2016). Several biased agonists at KOR were successfully developed, and some are being used clinically (Mores et al. 2019; Brust et al. 2016). Despite the previous successes, there are unresolved experimental limitations of measuring differences in biased factor among various ligands in addition to the implications of cellular environments (Mores et al. 2019; Ho et al. 2018). Although beneficial results observed by using biased agonists to stabilize receptor conformational ensembles that said to activate intracellular Gαi over β-arrestin-2 recruitment (Ranjan et al. 2017), such simplification of the story might not be precise (Conibear and Kelly 2019; Bermudez et al. 2019).

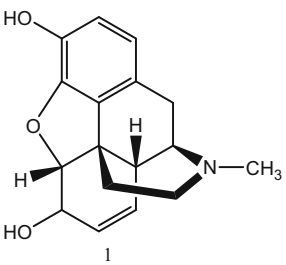
Like other GPCRs, the allosteric sites of ORs are therapeutically promising to get biased signaling (Livingston and Traynor 2018; Livingston et al. 2018). Moreover, allosteric ligands can enhance efficacy/affinity for endogenous opioid peptides as well as provide selectivity toward particular OR type, which usually is difficult to achieve using orthosteric ligands (Livingston et al. 2018). Interestingly, some endogenous compounds act as PAM for ORs, for example, oxytocin which is a peptide hormone principally involved in labor and lactation act as PAM for orthosteric endomorphin-1, β-endorphin, and morphine by enhancing efficacy and not affinity toward MOR (Meguro et al. 2018). The tuber of the species Aconitum is traditionally used in Japan to relieve pain, currently shown to have ignavine, that has selectivity for MOR over KOR and acts as PAM for endomorphin-1 and morphine (Ohbuchi et al. 2016). Biased signaling can also be produced using allosteric modulators. The BMS-986187, a synthetic compound discovered by high-throughput screening (HTS), can function as PAM selectively for DOR (Burford et al. 2015) and produce biased signaling toward G-protein over β-arrestin-2, which is elicited by lower receptor internalization (Stanczyk et al. 2019).

12.4 Opioid System as Potential Target for Neurological Disorders

The ongoing developments, including a plethora of available drugs and various promising investigational molecules, suggest the potentiality of opioid receptors as viable drug targets for therapeutic interventions of numerous disorders. Targeting and modulating these molecular switches mediates the alleviation of Alzheimer's disease (AD) (Torres-Berrio and Nava-Mesa 2019), mood disorder (Lutz and Kieffer 2013; Lalanne et al. 2014; Ehrich et al. 2014; Browne and Lucki 2019) and psychiatric disorders (Tejeda et al. 2011; Carlezon and Krystal 2016; Guerrero et al. 2019) and treatment of alcohol and opioid use disorder (AUD and OUD) (Niciu and Arias 2013; Schuckit 2016). Besides, the target-specific treatment intervention related to bowel disorders (Lacy et al. 2016; Corsetti et al. 2019), chronic pain (Günther et al. 2017; Markman et al. 2019), ischemic stroke (Wang and Subedi 2020) and respiratory disorders (Zebraski et al. 2000) have also been demonstrated amongst others. This section focuses on the current updates on targeting the opioidergic system in an effort to treat neurological disorders.

12.4.1 Alzheimer's Disease (AD)

Numerous evidential researches suggest the possible association of the opioidergic system and pathogenesis of AD. The opioid receptors are innervated extensively in the specific region of the central nervous system that is vital for cognition and memory and includes hippocampus and cortex. Any abnormality within the opioid system homeostasis may result in the hyperphosphorylation of *tau* proteins and subsequent generation of amyloid-beta (Aβ) proteins. This event cause neuroinflammation followed by cholinergic neurons' deterioration and impairment of cognitive functions (Mathieu-Kia et al. 2001). Alterations in the level of G-protein coupled opioid receptors (μ, δ, and κ) indicate a significant association of the endogenous opioid in AD pathology (Nandhu et al. 2010). The ORs can modulate the imbalance of various neurotransmitters of cholinergic, adrenergic, GABAergic, serotonergic, and glutaminergic systems that are involved with the progression of AD (Cai and Ratka 2012). Studies on morphine (**1**) and endogenous opioids such as endomorphin-1 (**2**) and endomorphin-2 (**3**) showed substantial protection against intracellular Aβ toxicity in both human and rat brains *in vivo*. Morphine mediated its activity by stimulating estradiol release in the hippocampus and increases the activity of P450 cytochrome aromatase. This chain of events stimulates the heat shock protein 70 (Hsp70) and confers protection against neurodegeneration (Cui et al. 2011). Furthermore, morphine attenuates the Aβ induced neurotoxicity by activation of MOR and upregulates the mammalian target of rapamycin (mTOR) signaling as evaluated by cell viability and neurite outgrowth assay (Wang et al. 2014).



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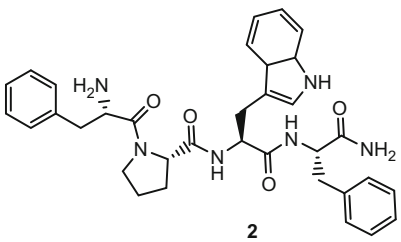

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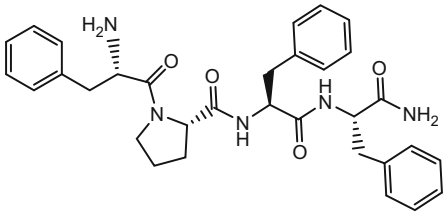

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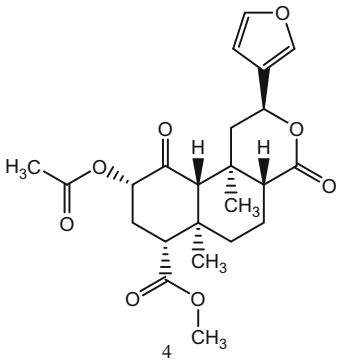

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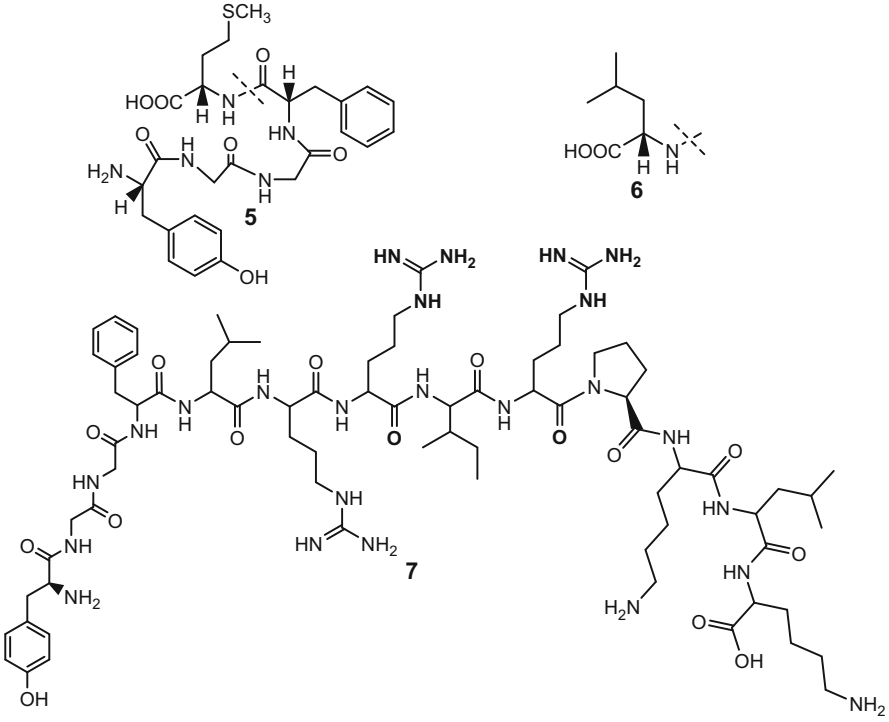
Unlike morphine, salvinorin A (**4**), a novel non-nitrogenous hallucinogenic neoclerodane diterpene isolated from *Salvia divinorum* (Roth et al. 2002), exhibited potent hallucinogenic property by selective agonism at κ-opioid receptor (KOR). This activity opens up new avenues and insights for the development of selective KOR antagonists. Targeting and blocking KOR will reverse the hallucinosis and altered perception as observed in AD and Pick's and Huntington's diseases (Cunningham et al. 2011; Sheffler and Roth 2003). Besides, salvinorin A also displayed modulatory activity on cholinergic systems and may signify a valuable molecular entity for alleviating the progression of AD (Motel et al. 2013). Research on an elevated level of dynorphin A (**5**) (Yakovleva et al. 2007) and enkephalins, namely [Met]-enkephalin (**6**) and [Leu]-enkephalin (**7**), observed that they induce neurodegeneration in transgenic mouse models and AD patients (Meilandt et al. 2008).



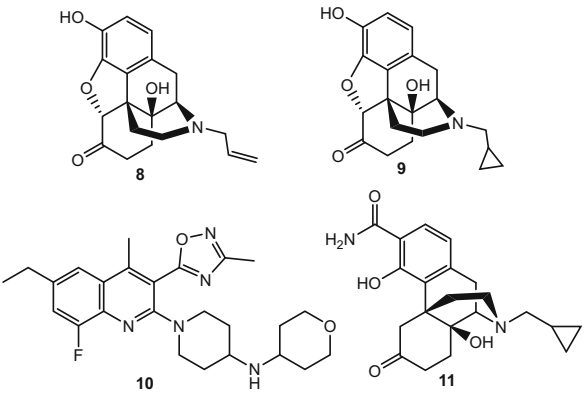
The dynorphins were profoundly expressed during the aging process and AD and have been reported to stimulate the KOR and thought to induce stress-related memory impairments. Additionally, they also affect glutamate neurotransmission and perturb their function of synaptic plasticity essential for memory (Ménard et al. 2013).

The rate-determining step in the production of Aβ is the proteolytic breakdown of Amyloid Precursor Protein (APP) by β-secretase (BACE1). The activation of DOR

by an agonist has been shown to increase the secretase activity probably through the post-translational mechanism and causing an increased formation of Aβ (Sarajarvi et al. 2015). The cascade of reaction makes DOR and BACE1 as prospective targets in the design of DOR antagonist (Zhao et al. 2015) and BACE1 inhibitors (Coimbra et al. 2018) for ameliorating the neurodegeneration underlying AD. The hypermethylation of opioid receptor δ 1 (OPRD1) promoter was also linked with the risk of AD (Ji et al. 2017). Subsequent studies suggest that in addition to OPRD1, elevated methylation of opioid receptor κ1 and opioid receptor μ1 genes are also involved in the progression of AD. Therefore, the genes of the opioid receptors could serve as potential biomarkers for AD diagnosis (Xu et al. 2018).

12.4.2 Schizophrenia

Schizophrenia is a multifaceted, diverse mental disorder that affects the behavior and cognitive function and has genetic or environmental predisposition, or both. Antipsychotics, along with psychological therapies, are the primary line of management available to alleviate the disorder. In recent years, much research to gain insight into the pathophysiology of schizophrenia has been undertaken (Owen et al. 2016; Patel and Shulman 2015) and identification of novel targets is under investigation (Gill et al. 2018; Yang and Tsai 2017). The cardinal features of schizophrenia are negative symptoms (reduced enthusiasm and withdrawal from society), cognitive symptoms (disruption of attentiveness and dementia), and positive symptoms (hallucinations accompanied by delusions). KOR agonists could elicit these specific symptoms and drugs blocking this receptor might result in a fruitful therapeutic outcome. Antipsychotics are capable of effectively combating the positive symptoms; however, presently, efficient therapeutic managements for controlling the symptoms (negative or cognitive) of schizophrenia are not available. The potentiality of a pan-opioid antagonist either naloxone (**8**) or naltrexone (**9**) could make KOR a promising target option for overall treatment benefits in schizophrenia (Clark and Abi-Dargham 2019; Shekhar 2019). Alongside, contemporary research on the discovery of novel KOR antagonist by Guerrero et al. has shown encouraging results. The promising drug candidate BTRX-335140/CYM-53093 (**10**) exhibited potent (IC_{50}-0.8 nM) and selective KOR antagonistic activity with a favorable pharmacokinetic profile. Currently, the compound is undergoing phase I clinical trials for the possible treatment of various psychiatric disorders (Guerrero et al. 2019). A recent double-blind phase II study found that a combination of olanzapine and fixed dose of MOR antagonist samidorphan (**11**) demonstrated clinically and statistically significant reduction of weight gain and adverse metabolic effect of olanzapine without compromising the antipsychotic efficacy of olanzapine. The combination was considerably tolerated and comparable to that of olanzapine-placebo in terms of safety (Chaudhary et al. 2019; Martin et al. 2019).

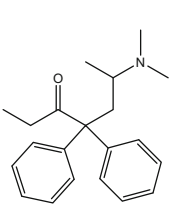


12.4.3 Post-traumatic Stress Disorder (PTSD), Opioid Use Disorder (OUD), and Alcohol Use Disorder (AUD)

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that may arise after a single encounter or exposures to life-threatening chronic events. PTSD deteriorates physical health and is mostly accompanied by cardiorespiratory, musculoskeletal, gastrointestinal, immunological, endocrine, and metabolic problems. It is also associated with psychiatric comorbidity and an increased suicidal tendency (Bisson et al. 2015; Yehuda et al. 2015). Existing approaches in the treatment of PTSD involve cognitive behavioral therapy and the use of anxiolytic/antidepressant agents to ameliorate the symptoms (Shalev et al. 2017). Interestingly, studies suggest that endogenous opioid peptides exhibited a placebo effect in PTSD, and the mood-enhancing effects of the peptides may be initiated by exercise and light therapy to relieve the stress. It is suggested that the interaction between dopaminergic pathways and the endogenous opioids may be responsible for the placebo effect (Sher 2004), although it would not be a stand-alone option and may be concomitantly utilized along with standard drugs. As discussed earlier, the dynorphin mediates its action *via* KOR and the dynorphin/KOR interrelationship is associated in several brain disorders (De Lanerolle et al. 1997; Mathieu-Kia et al. 2001; Mello and Negus 2006). Various works of the literature suggest that in PTSD, there is a substantial expression of the KOR and mediate the symptoms of anxiety. Therefore, in line of the evidence, targeting the KOR might be a viable option in the management of PTSD (Bailey et al. 2013). The opioid analgesics prescribed in PTSD often result in comorbidity between PTSD and OUD, and they are frequently considered as two sides of the same coin (Elman and Borsook 2019; Hassan et al. 2017).

Centrally acting competitive MOR antagonist opioid receptor antagonists such as naloxone is the ideal choice in emergencies related to opioid overdose. On the contrary, naltrexone, which mediates its action *via* KOR antagonism, is employed mainly in OUD and AUD for maintaining abstinence by decreasing the cravings

(Theriot et al. 2019). However, both opioid agonist and antagonist are utilized in substance abuse therapies to combat the withdrawal syndromes and for the inhibition of return usage. Agonists such as morphine and methadone (**12**), partial agonist buprenorphine (**13**) and opioid antagonist such as extended-release injectable naltrexone are recommended for overall treatment and tackling the relapsing of OUD. The mechanism by which opioid antagonist maintain abstinence in OUD and AUD is by reducing the mesolimbic dopaminergic neurotransmission (McCarty et al. 2018; Williams et al. 2008).



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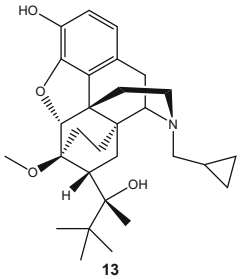

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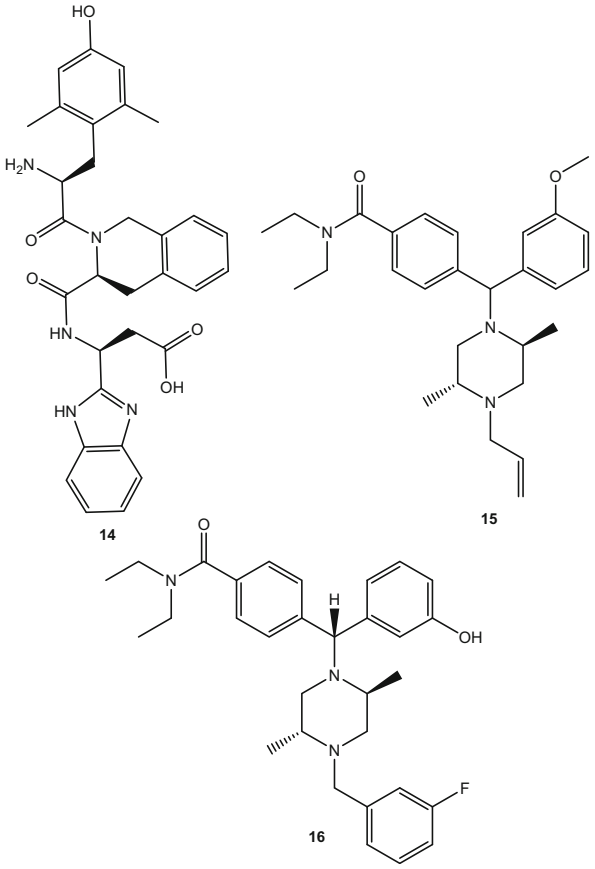
12.4.4 Parkinson's Disease (PD)

It is a chronic neurodegenerative disease having marked motor (rigidity, tremor, bradykinesia, firmness, and defective gait) and nonmotor features (hyposmia, sleep disorders, depression, etc.) (Schapira et al. 2017; Xia and Mao 2012). The disease is related to formation of Lewy bodies and dopaminergic neuronal damage in the substantia nigra. The main challenge in the treatment of Parkinson's disease (PD) is the failure to make a conclusive diagnosis at the earliest stages and difficulties in late-stage management of symptoms. Presently, there are no effective treatments for slowing down the neurodegenerative process and involve significal physical and mental co-morbidity (Demaagd and Philip 2015; Kalia and Lang 2015). The currently available pharmacotherapeutic options in PD are dopamine precursor (first line), dopamine agonist and monoamine oxidase B inhibitors (second line), the antiviral drug amantadine (third line) and a newer United States Food and Drug Administration (USFDA)-approved second-generation antipsychotic pimavanserin (Young and Mendoza 2018). The increasing perspective of the opioid receptors as a promising target in numerous brain disorders is well established. The treatment with levodopa is almost always associated with dyskinesia. Recent data suggest that selective opioid antagonists (MOR and DOR) can efficiently improve the dyskinetic side effect in animal models (Pan and Cai 2017; Sgroi and Tonini 2018).

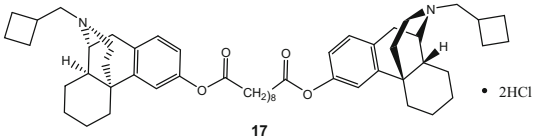
Nevertheless, a study on DOR agonist UFP-512 to mitigate motor insufficiencies in hemilesioned rodents resulted in a mixed response. At a low dose involving rotarod test, it largely improved the gait, whereas at high dose UFP-512 (**14**) was found inefficacious or to exacerbate the symptoms of Parkinsonism. Further, when

locally microinjected in the globus pallidus (GP), increased akinesia was observed, and vice versa, when injected in the substantia nigra pars reticulate. Adverse effects such as convulsions may restrict the use of DOR agonist in Parkinsonism. The convulsion was avoided by a synergistic combination of a DOR agonist, SNC-80, (**15**) and J-113397, an N/OFQ antagonist (Mabrouk et al. 2009; Mabrouk et al. 2014). Conversely, UF-512 showed encouraging activities as anxiolytic/antidepressant and treatment against chronic and neuropathic pain (Polo et al. 2019; Vergura et al. 2008). Recently, a new mixed DOR agonist/MOR antagonist, DPI-289 (**16**), in combination with levodopa elicited improved activity without increasing dyskinesia, and it was superior when compared to high dose levodopa (Johnston et al. 2018).



12.4.5 Mood Disorder

Mental illness such as bipolar disorder (BD) and major depressive disorder (MDD) are recalcitrant to treat due to the chronic nature and due to inter-individual variation (Jeon et al. 2016). Studies found that opioid analgesic demonstrated potent mood-elevating effect on patients with bipolar disorder and involve positive interaction between the opioid and the dopaminergic systems (Schaffer et al. 2007). Preclinical evaluations revealed that the dynorphin system is related to mood, motor, cognitive, and endocrine functionality and subjects with MDD and BD showed a decreased level of prodynorphin mRNA expression (Hurd 2002). Besides, a novel KOR antagonist MCL-144B (**17**) displayed antidepressant activity in the forced swim test (Reindl et al. 2008). Berrocoso et al. reported that a combination of a selective serotonin reuptake inhibitor (SSRI) with a weak MOR agonist, (+)-tramadol (**18**), produced better antidepressant activity than SSRI alone (Berrocoso and Mico 2009). As previously discussed, UF-512, a DOR agonist, showed anxiolytic/antidepressant properties (Polo et al. 2019). However, a combination of opioid-based samidorphan (MOR antagonist) and buprenorphine (ALKS 5461) in phase III trials was recently rejected by USFDA because of inadequate data to prove its effectiveness.



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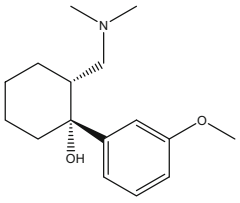

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12.5 Effect of Opioids on Various Ion Channels

The body of human beings normally generates substances similar to opiates and utilizes them as neuromodulators. These opiate-like substances comprise of β-endorphins, dynorphins, and enkephalins, and are frequently conjointly called as opioid peptides or endogenous opioids (Corder et al. 2018; Li et al. 2012; Pathan and Williams 2012). Opioid peptides are implicated in the regulation and/or control of various body functions such as tolerance and drug dependency, stress and pain,

cognition, immunological, muscle-related, cardiovascular (CVS) and endocrine. Not only these, endogenous opioids also play a vital role in monitoring various sensory functions (Bodnar 2018). Opioids are enormously expressed in several parts of the brain including non-neuronal tissues as well, namely central nervous system (CNS) and peripheral nervous system (PNS). Within the CNS, opioids exert their actions in spinal cord; while in PNS, they have been found to act not only in myenteric but also in submucous plexus situated within the stomach wall and are accountable for producing vigorous constipation. Besides, opioids have been entailed in reduction of pain stimuli and inflammation in several peripheral tissues like joints (Iwaszkiewicz et al. 2013).

12.5.1 Calcium Channels

The entry of Ca^{2+} ions through the voltage-gated Ca^{2+} channels (VGCCs) results in depolarization of nerve terminals that further causes the discharge of neurotransmitters from the nerve cells. Three types of voltage-gated Ca^{2+} channels are reported, namely, T-type channels which are capable of showing small conductance, N-type channels which are inept to demonstrate intermediate conductance, and L-type channels which illustrate large conductance. Opioids act through the inhibition of N-type voltage-gated Ca^{2+} channels and reduce the passage of Ca^{2+} ions inside the cell, thereby inhibiting the release of neurotransmitters (Zamponi et al. 2015; Seseña et al. 2014; Catterall et al. 2013; Zamponi and Currie 2013). However, this action of opioids exclusively is not accountable for the total cumulative effect of opioids on neurotransmitter release (Chieng and Bekkers 2001).

12.5.2 GABA Channels

The euphoric effect of opioids may be due to another mechanism in which the GABA inhibitory interneurons of the ventral tegmental area (VTA) are involved (Listos et al. 2019; Creed et al. 2014; Xi 2002). By attaching to the μ-receptors, the exogenous opioids like morphine and heroine decrease the amount of GABA (a neurotransmitter) released. More often than not, GABA reduces the amount of dopamine released in the nucleus accumbens (NAcc). Hence, by inhibiting GABA, the opiates eventually increase the concentration of dopamine produced and consequently the amount of pleasure felt (Dubhashi 2018; Nuechterlein 2016; Shirayama and Chaki 2006). Opiates also have dopamine-independent effects within the NAcc, which play an important role in opiate reward (Ting-A-Kee and Van Der Kooy 2012; Tomkins and Sellers 2001; O'malley et al. 1992; Shippenberg and Elmer 1998; Koob and Bloom 1988).

Besides this, the periaqueductal gray (PAG) in the midbrain region being rich in endogenous opioids and opioid receptors is a major target of analgesic action in CNS (Tsagareli et al. 2012; Pathan and Williams 2012; Mansour et al. 1995). The analgesic action of opioids on PAG is exerted by the suppression of inhibitory

influence of neurotransmitter GABA on neurons that form part of a descending antinociceptive pathway (Tsagareli et al. 2012; Basbaum and Fields 1984). Opioids inhibit GABA-mediated (GABAergic) synaptic transmission in the PAG and other brain regions by reducing the probability of presynaptic neurotransmitter release (Wilson-Poe et al. 2017; Vaughan and Christie 1997), but the mechanisms involved remain uncertain. Literatures have reported that opioid inhibition of GABAergic synaptic currents in the PAG is controlled by a presynaptic voltage-dependent potassium conductance. Opioid receptors of μ-type in GABAergic presynaptic terminals are specifically coupled to this potassium conductance by a pathway involving phospholipase A_2, arachidonic acid and 12-lipoxygenase. Additionally, opioid inhibition of GABAergic synaptic transmission is also found to be potentiated by inhibitors of the enzymes cyclooxygenase and 5-lipoxygenase, presumably because more arachidonic acid is available for conversion to 12-lipoxygenase products (Zhang and Pan 2011; Heinke et al. 2011; Finnegan et al. 2006; Ingram et al. 1998). These mechanisms account for the analgesic action of cyclooxygenase inhibitors in the PAG and their synergism with opioids (Leith et al. 2007; Vaughan 1998; Vaughan et al. 1997; Tortorici and Vanegas 1995; Maves et al. 1994).

12.5.3 Sodium Channels

Voltage-gated sodium channel plays a critical role in nociception by interacting with the δ-opioid receptor. The dorsal root ganglia (DRG) neurons being rich in voltage-gated sodium channels (Wang et al. 2011; Rush et al. 2007; Wang and Wessendorf 2001; Zhang et al. 1997) can be correlated with the emergence of pain-related behavior characteristic of painful diabetic neuropathy (PDN). Activation of presynaptic δ-opioid receptor by enkephalin prevents the increase in neuronal Na^+ in DRG through inhibition of protein kinase C (PKC) and p38 mitogen-activated protein kinase. This can be implicating presynaptic receptors of primary sensory afferents in modulating the amount of voltage-gated sodium channels and can be a useful therapy for PDN (Chattopadhyay et al. 2008).

12.6 Conclusion

Opioid peptides are endogenous ligands for opioid receptors. Proteolytic processing of larger precursor proteins generates the peptides. The peptides are stored in dense vesicles within neurons and released upon activation. The release is not restricted to synaptic space; thus peptides may signal other neurons by volume transmission. Opioid peptides inhibit the release of neurotransmitters by the affected neurons, thus modulating their signal propagations. The action of opioid peptides is mediated by binding GPCR group of receptors (opioid receptors) by binding to the orthosteric binding site. However, the affinity/efficacy of orthosteric ligand is affected by cooperation with ligand at allosteric site. Interestingly, many orthosteric and allosteric ligands show biased activation of intracellular second messengers, which

provide an opportunity of separating the desired pharmacological properties from a myriad of unwanted effects. Due to the interaction between opioid receptors and other types of receptors and ion channels, opioid peptides find a wide range of applications in managing several types of neurological disorders besides their primary use as analgesics.

12.7 Remark

The authors declare that theory of biological evolution and its related terms mentioned in this chapter and in references are not considered per se by them.

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