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Current Research on Opioid Receptor Function

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Abstract

The use of opioid analgesics has a long history in clinical settings, although the comprehensive action of opioid receptors is still less understood. Nonetheless, recent studies have generated fresh insights into opioid receptor-mediated functions and their underlying mechanisms. Three major opioid receptors (μ -opioid receptor, MOR; δ -opioid receptor, DOR; and κ -opioid receptor, KOR) have been cloned in many species. Each opioid receptor is functionally sub-classified into several pharmacological subtypes, although, specific gene corresponding each of these receptor subtypes is still unidentified as only a single gene has been isolated for each opioid receptor.

In addition to pain modulation and addiction, opioid receptors are widely involved in various physiological and pathophysiological activities, including the regulation of membrane ionic homeostasis, cell proliferation, emotional response, epileptic seizures, immune function, feeding, obesity, respiratory and cardiovascular control as well as some neurodegenerative disorders. In some species, they play an essential role in hibernation. One of the most exciting findings of the past decade is the opioid-receptor, especially DOR, mediated neuroprotection and cardioprotection. The up-regulation of DOR expression and DOR activation increase the neuronal tolerance to hypoxic/ischemic stress. The DOR signal triggers (depending on stress duration and severity) different mechanisms at multiple levels to preserve neuronal survival, including the stabilization of homeostasis and increased pro-survival signaling (e.g., PKC-ERK-Bcl 2) and anti-oxidative capacity. In the heart, PKC and KATP channels are involved in the opioid receptor-mediated cardioprotection. The DOR-mediated neuroprotection and cardioprotection have the potential to significantly alter the clinical pharmacology in terms of prevention and treatment of life-threatening conditions like stroke and myocardial infarction.

The main purpose of this article is to review the recent work done on opioids and their receptor functions. It shall provide an informative reference for better understanding the opioid system and further elucidation of the opioid receptor function from a physiological and pharmacological point of view.

Keywords

Opioids; opioid receptors; neurotransmitters; function; brain; heart; lung; ionic homeostasis; neuroprotection; hibernation; pain; hypoxia; ischemia

1. INTRODUCTION

The use of opioid analgesics has a long history, dating back several millennia. Despite the flow of time and the energies of scientists around the world, however, the function of opioid receptors in the brain is not well understood until this day. With the limited availability of data, controversies and diametrically opposite results are inevitable. For example, *in vivo* studies [1–4] showed that opioid receptor inhibition by opioid antagonists, such as the non-selective morphinan naloxone, protected the brain from ischemia-induced injury, while other studies [5–7] suggested that opioid receptor activation with opioid agonists were protective or extended animal survival time during severe hypoxia.

Recent studies utilizing current approaches have produced new information on opioid receptor-mediated function and their underlying mechanisms. For instance, our extensive studies specifically dissected out the role of DOR in neurons under hypoxic/ischemic conditions and demonstrated that the activation of DOR is neuroprotective against hypoxic/excitotoxic insults to cortical neurons, while its inhibition causes neuronal injury [8–16, 17]. Also, many other studies have recently demonstrated that DOR activation is indeed neuroprotective against hypoxic/ischemic stress [18–31]. Besides opioid-receptor mediated neuroprotection, many new studies provide considerable evidence on involvement of opioid receptors in a multitude of functions throughout the body.

The main purpose of this article is to review the recent work done on opioids and functioning of their receptors under physiological and pathophysiological conditions. For the reader's convenience, we have briefly summarized the background information on endogenous opioids and opioid receptors, and listed the commonly used opioid ligands in research. Several previous reviews have well addressed the history of opioid research, classification of opioid receptors, signal transduction properties of these receptors with regards to G-protein coupling, adenylyl cyclase and cAMP as well as early studies of opioid receptor function (especially on opioid-induced analgesia and tolerance/dependence) [32–43].

In spite of extensive research, controversies still linger. We have attempted to present a comprehensive and objective overview on this topic, though we may not necessarily agree with all the conclusions proposed by the original articles. In this way, we believe, this review shall provide an informative reference for better understanding the opioid system in the body and for further elucidation of the opioid receptor function in a physiological and pharmacological view.

2. ENDOGENOUS AND EXOGENOUS OPIOIDS

Acheson [44] coined the term “opioids” that broadly covered all compounds with morphine-like action and distinct chemical structures ranging widely from alkaloids to peptides. Throughout history, they have been widely used as analgesics to combat pain or induce ecstasy in medical and non-medical situations. Despite the long history of usage, the underlying mechanisms the opioid action are largely unknown. In 1960's, Tsou and Jang [45] performed a pioneering work in understanding the mechanism through the direct microinjection of morphine into the brain to produce analgesia, which provided the impetus for studies on role of opioids in brain function. Unfortunately, their interesting work was

never formally published in any international journal owing to the prevailing political unrest at that time in China. By the early 1970's, Pert and Yaksh [46, 47] published their data delineating sites of morphine-induced analgesia in the primate brain. Furthermore, Liebeskind and colleagues observed that brain stimulation in certain areas, particularly the periaqueductal gray, caused pronounced analgesia [48] that was blocked by the opioid antagonist naloxone [49]. This observation strongly suggested the existence of endogenous opioids in the brain. Shortly thereafter, two groups independently reported that brain extracts mimicked the ability of morphine to inhibit electrically induced contractions of the mouse vas deferens, which was blocked by naloxone [50, 51]. These discoveries gave rise to the identification and isolation of two enkephalin pentapeptides, namely [Met⁵]enkephalin (H-Tyr-Gly-Gly-Phe-Met-OH) and [Leu⁵]enkephalin (H-Tyr-Gly-Gly-Phe-Leu-OH) [50], followed closely by the identification of β -endorphin [52, 53] and dynorphin [54] in brain tissue. In 1995, an endogenous agonist for the opioid receptor-like orphan receptor (ORL) was isolated concurrently by two independent groups, which was termed ORL-1 by Mollereau *et al.* [55] and Meunier *et al.* [56], and orphanin FQ by Reinscheid *et al.* [57]. It is commonly referred to as nociceptin. Two years later, endomorphin-1 and -2, endogenous MOR agonists with very high affinity and selectivity were synthesized and subsequently isolated by Zadina [58] in bovine and human brain extracts [58, 59]. So far at least ten endogenous opioids have been identified in the brain, which belong to distinct families of compounds (Table 1).

Endogenous opioids can originate from the same or different precursor proteins. All mammalian opioid peptides are derived from three precursors, i.e., pro-opiomelanocortin (POMC), pro-enkephalin (PENK) and pro-dynorphin (PDYN), which are translated from separate genes [60]. Although the sequence of [Met⁵]enkephalin is contained in the sequence of POMC [61], POMC is not the source of [Met⁵]enkephalin peptide. Instead, [Met⁵]enkephalin is encoded by the preproenkephalin gene. A 31-amino-acid portion of β -lipotropin was isolated and named as β -endorphin [52]. It possessed an affinity for μ -opioid receptors. Subsequently, a series of polypeptides containing the N-terminal [Leu⁵]enkephalin sequence were isolated and designated as another opioid group called dynorphins [54]. Cloning of the peptide precursors demonstrated that one precursor contained both [Met⁵]enkephalin and [Leu⁵]enkephalin transcripts, a second precursor existed for the dynorphin peptides, and a third for β -endorphin and other pro-opiomelanocortin peptides (adrenocorticotrophin and melanocyte-stimulating hormone) [62]. Many C-terminal extended enkephalins were also identified and demonstrated distinct spectra of bioactivities [63]. Till date, however, the precursor for endomorphins remains to be discovered.

Upon identification of the unique properties of opioids, especially their effectiveness in producing analgesia, many exogenous opioids were synthetically developed to enhance their properties for an eventual application in clinical research. However, among the vast plethora of compounds recognized in the literature during the last several decades, morphine still remains the most popularly used exogenous opioid for pain relief, since it is the quintessential MOR agonist and exhibits higher affinity for MOR and than for either DOR or KOR [64, 65]. While many exogenous opioids (Table 2) with similar pharmacological properties as morphine have been used both clinically and in laboratory, they however differ widely with respect to their efficacies, potency, side-effects, clearance, and passage through the blood-brain barrier [66, 67].

3. OPIOID RECEPTORS

The action of opioid compounds is mediated through activation of specific opioid receptors. Three major opioid receptor families, the μ -, κ -, and δ -opioid receptors, were cloned in

early 1990s [32, 34] and a fourth member of the opioid receptor family, nociceptin or orphanin FQ receptor (NOP) or the opioid receptor-like orphan receptor (ORL), was added to the list in 1994 [55].

Opioid receptors exist not only in the nervous system [68–73], but also in peripheral organs, such as heart, lungs, liver, gastrointestinal and reproductive tracts [74, 75]. However, the expression and distribution of these receptors vary significantly among different organs as well as among different animal species [36].

3.1. Major Opioid Receptor Family

Opioid receptors have high sequence homology and belong to the large family of seven-transmembrane G protein-coupled receptors. Because of the homologies between ORL/NOP and other opioid receptors, functional studies have also focused primarily on pain and analgesia [76–82]. Other functions of ORL/NOP receptors include dynamic homeostatic mechanisms, since they are distributed throughout the body [39, 83, 84].

In general, endogenous opioid peptides are not highly selective or specific to one particular type of opioid receptors, except the endomorphins [58]. This is due to three major factors: (1) all peptide ligands contain the N-terminal residue Tyr (except Phe in the case of nociceptin), comparable to a functional hydroxyl group in the morphinans, which is a requirement for interaction within the ligand-bind domain of opioid receptors; (2) MOR, DOR and KOR have many common structural similarities in their primary structures, in addition to function and intracellular signaling mechanisms; and (3) the formation of homomeric and heteromeric complexes between opioid receptors and non-opioid receptors modify their response to a given opioid ligand [32, 34–36, 38, 39, 85]. In other words, the outcome of opioid action could be the result of an interaction with different opioid receptor complexes. On the other hand, synthetic opioid peptides and alkaloids have a relatively high selectivity to MOR, DOR, and KOR and have been widely used to define the pharmacological properties of opioid receptors.

Studies suggest that the physical interactions between opioid receptors play a major role in defining their resultant pharmacological and physiological behaviors [86–89]. For example, δ -agonists were shown to enhance the analgesic potency and efficacy of μ -agonists, and δ -antagonists prevented or reduced the development of tolerance and physical dependence by μ -agonists [38]. Another example is LY255582, an opioid antagonist, which produced effects on feeding and body weight gain through a heteromeric combination of MOR, DOR and/or KOR [90]. Therefore, new ligands with dual μ -/ δ -agonism or μ -/ δ -antagonism, or mixed μ -agonism/ δ -antagonism or vice versa are emerging as promising unique approaches to the development of analgesic drugs [38, 91, 92].

3.2. Opioid Receptor Subtypes

The development of novel opioid analogs that elicited different biological effects gave way to the detection of pharmacological subtypes of MOR, DOR and KOR, although the molecular basis of these subtypes has not yet been established [93–96] and, to date, only one μ -opioid receptor gene (*Oprm*) has been isolated. Of the three opioid receptor families, MOR subtypes have been most extensively studied due to their role in mediating the actions of morphine and other clinically relevant analgesic agents as well as drugs of abuse. These observations gave rise to the concept of multiple μ -receptors along with the cross-tolerance to different μ -opioids [97]. Genetic and physiological variations influence the sensitivity of MOR towards different μ -opioid ligands and difference in their potency across various species and animal strains [34], which led to the proposal that receptors could be classified as MOR1, MOR2, and MOR3. Similarly, KOR multiplicity is also a complex issue under

debate. Clark *et al.* [98] presented evidence from binding studies in guinea-pig cerebellum that suggested the existence of four KOR subtypes, KOR1a, KOR1b, KOR2 and KOR3, based on pharmacological studies [99, 100]. In addition, DOR has been demonstrated to exist in at least two subtypes, DOR1 and DOR2, according to their pharmacological attributes [94, 96, 101–104]. Rothman first proposed the existence of DOR subtypes [105, 106] in which a δ -site associated with the μ - δ -opioid receptor complex was termed the δ_{cx} binding site, while non-associated or non-complexed δ -site as the δ_{ncx} site, which corresponded to DOR1 [107], however, this complex terminology is not used in the opioid literature. Although many studies have been conducted on opioid receptor subtypes, an important question that hovers over the issue of various subtypes is the lack of a specific cDNA corresponding to a receptor subtype, e.g., only one receptor gene has been isolated for each opioid receptor in spite of the existence of the multiple subtypes [108–110]. DOR has been cloned in several mammalian species including mouse [111–113], rat [114, 115] and humans [116], yet no cDNA corresponding to DOR1 and DOR2 has been found.

The emerging notion on the occurrence of pharmacological subtypes of opioid receptors as a result of receptor heteromerization that leads to new pharmacological properties is largely being accepted. The properties of these heteromerized receptors are often found to be similar to those of the previously described subtypes [85, 110]. The subtypes of opioid receptors may also be considered as splice variants of the same gene, since six new splice variants from the human μ -opioid receptor gene have been identified and characterized yielding a total of 10 human splice variants of MOR1 that differed in both potency and efficacy [117]; nonetheless, all variants were equally selective for μ -opioid ligands, thereby, confirming their classification as μ -opioid receptors [118].

3.3. Commonly Employed Opioid Agonist and Antagonist Ligands

Some common opioid agonist and antagonist ligands used clinically or in research are listed in Tables 2 and 3 for reference, but the list is by no means complete as it would be quite extensive and beyond the scope of this overview. It should be noted, however, that the selectivity mentioned here is based on the predominant spectrum of activity, concentration used for *in vivo* studies, the area of brain in which they are infused or injected, for example, naloxone and naltrexone are relatively non-selective opioid receptor antagonists similar to diprenorphine. Many integrated factors comprise receptor selectivity.

4. ADVANCES IN RESEARCH ON OPIOID RECEPTOR FUNCTIONS

Opioid peptide receptors in the CNS represent the most extensive and diverse peptidergic transmission system and are widely involved in various pleiotropic functions. They are essential for various physiological functions, including pain modulation, locomotion, mood, diuresis, thermoregulation and stress, along with regulatory functions in, respiratory, gastrointestinal and cardiovascular systems. On the other hand, abuse of opioid compounds leads to addiction, which greatly affects brain function and body homeostasis.

4.1. Ionic Homeostasis

Recent studies show that opioid receptors are involved in the regulation of ionic homeostasis. Under normal conditions, there is a steep electrochemical gradient across the plasma membrane with the extracellular fluid rich in Na^+ with concentrations up to 150 mM and relatively poor in K^+ (ca. 3 mM), and a reverse intracellular environment with up to 150 mM K^+ and 4–12 mM Na^+ . Maintenance of ionic homeostasis is vital for normal functioning of the neurons. Opioids have been shown to be involved with the regulation of ionic homeostasis under both normoxic and hypoxic/ischemic conditions. All opioid agonists either induce an elevation of intracellular Ca^{2+} or lead to an inhibition of Ca^{2+} entry

under normal conditions. However, the overall predominant effect of opioids on Ca^{2+} homeostasis is inhibitory [120–126], which seems to be consistent with classical recognition of the endogenous opioid system as an inhibitory regulator in the brain. In contrast, some studies show that opioid receptor activation activates Ca^{2+} channels. For example, the MOR agonist DAMGO (10 nM) produces a small yet consistent facilitation of Ca^{2+} current through P-type calcium channels via G-protein-independent mechanism in the rat Purkinje neurons [127]. The opioid-induced elevation of intracellular Ca^{2+} could explain the excitatory effect of opioids on some presynaptic neurons and consequent regulation of neuro-transmitter release [128, 129]. Recently, we assessed the effect of DOR and MOR activation/inhibition on K^{+} and Na^{+} homeostasis in mouse cortical slices by directly measuring the extracellular K^{+} and Na^{+} concentrations with ion-sensitive microelectrode [130–135]. The results revealed that 20 mins of δ -agonists DADLE or UFP-512 [136], or DAGO (δ -agonist) and naltrindole (δ -antagonist) perfusion under normoxia, produced no obvious change in the extracellular K^{+} and Na^{+} concentrations in cortical slices, suggesting little effect of DOR and MOR on K^{+} and Na^{+} homeostasis under normoxic conditions [130–135]. However, activation of DOR, but not MOR, greatly attenuates hypoxia/ischemia-induced increase in extracellular K^{+} and decrease in extracellular Na^{+} , which suggests that opioids are one of the important factors in the regulation of ionic homeostasis under environmental stress.

4.2. Cell Proliferation

Opioid receptors affect cell proliferation. Malendowicz *et al.* [137] observed that μ - and δ -receptor activation inhibits the growth of immature adrenals, stimulates adrenal regeneration, and does not affect proliferation of cultured adrenocortical cells. However, Narita *et al.* [138] found that the stimulation of δ -opioid receptors by the δ -opioid receptor agonist SNC80 promoted neural differentiation from multipotent neural stem cells obtained from embryonic C3H mouse forebrains. In contrast, either a selective μ -opioid receptor agonist DAMGO or a specific κ -opioid receptor agonist U-50488 hydrochloride (U50, 488H) had such effect. These findings have mooted the concept that δ -opioid receptors play a crucial role in neurogenesis and neuroprotection. Some recent studies have shown that the OGF-OGFr (opioid growth factor-opioid growth factor receptor) system is a native biological regulator of cell proliferation in some cancers including ovarian cancer, hepatocellular cancer, and so on [139, 140]. More studies are, however, needed for the validation of this interesting observation and its underlying mechanisms.

4.3. Neuroprotection

One of the most exciting findings of the past decade is the opioid-receptor, especially DOR, mediated neuroprotection against hypoxic/ischemic injury.

Historically, there have been major controversies over the role of opioids in the neuronal responses to hypoxic/ischemic insults. Some investigators [6,7, 141–143] have demonstrated that opioid receptor activation, by opioid agonists, protects brain from ischemia and extended the animal survival time during severe hypoxia, while others [1–4, 144, 145] showed opioid receptor inhibition by intravenous injection of high dose naloxone that interacts with DOR, MOR and KOR thereby protecting the brain from ischemia-induced injury.

Our serial studies since 1997 have demonstrated that DOR is neuroprotective against hypoxic/excitotoxic stress in [8–15, 43, 130, 146, the brain, especially cortical neurons 147] and clarified the historical controversies on the role of opioids and their receptors in hypoxic/ischemic neuronal injury [16, 42]. Furthermore, we have found that the mechanisms for the DOR neuroprotection involves the stabilization of ionic homeostasis [43, 130–134],

increase in intracellular transduction of pro-survival signals [13, 132] and attenuation of oxidative injury [15] as well as regulation of DOR expression [12, 13, 135].

We applied glutamate to cultured cortical neurons to mimic neuro-excitotoxicity since it is a key mediator of ischemic/hypoxic injury. The addition of glutamate induced neuronal injury and cell death in a dose-dependent manner with a major difference between the immature and mature neurons. Activation of DOR with 10 μ M DADLE reduced glutamate-induced injury by almost half and naltrindole (a DOR antagonist, 10 μ M) completely blocked this protective effect. In sharp contrast, administration of MOR and KOR agonists (DAMGO and U50, 488H respectively, 5–10 μ M) did not induce appreciable neuroprotection, and MOR or KOR antagonists had no significant effect on glutamate-induced injury. These data demonstrate that activation of DOR, but not MOR and KOR, protected neocortical neurons from exerts neuroprotection against glutamate excitotoxicity [8, 9]. DOR neuroprotection against hypoxic stress, ischemic insult or excitotoxic injury was shown in our serial studies [8–15, 43, 130, 146, 147] and has been well demonstrated in many other laboratories [18–31, 138].

4.4. Hibernation

Mammalian hibernation is a distinct energy-conserving state and a potential protective strategy for the peripheral and central nervous system, which is associated with depletion of energy stores, intracellular acidosis and hypoxia similar to the changes that occur during ischemia. Many physiological features in hibernation including analgesia and respiratory depression can be triggered by DOR activation [21]. Circulating levels of opioid peptides in hibernating animals increased dramatically, and are considered a “hibernation induction trigger” [148–151]. In the brain, the hypothalamic and septal concentrations of [Met⁵]enkephalin were found to be significantly higher in the hibernating state than that in the non-hibernating state [152], while the levels in the pons and medulla showed little change [153]. Endogenous opioid activity is seasonally affected in the lateral septal region of the brain of hibernating animals with an increase in endogenous opioid activity during hibernation, which is probably involved in regulation of hibernation cycle [154]. Accompanying the increase in the concentration of opioid peptides, opioid receptor (MOR, DOR and KOR) levels in the brain of hibernating animals decreased, which could be an adaptation to survive under thermal stress [149]. Administration of opioid antagonists effectively reversed hibernation and aroused the animals from their stupor [150, 155]. These findings clearly suggest that endogenous opioids, especially DOR, play a significant role in hibernation.

4.5. Pain Modulation

A majority of studies on opioids are associated with analgesia [156–158]. Many acute insults result in the release of endogenous opioids and increase in opioid levels in blood, which counteracts the noxious stimulus and pain, i.e., stress-induced analgesia by opioids. Circulating levels of β -endorphin are significantly elevated following muscle injury, fixed-pressure hemorrhagic shock and lipopolysaccharide (LPS) administration in animal models, which serves as an index of endogenous opioid system activation [159]. Similar stress-induced elevations in the production and release of endogenous opioids have been demonstrated in clinical studies, oral surgery [160] as well as gynaecological and abdominal surgeries [161, 162] that resulted in increased β -endorphin levels in patients. Stress-induced analgesia can be partially reversed by the broad-spectrum opioid antagonist naloxone [163], further emphasizing the involvement of endogenous opioids in this process. It is generally accepted that endogenous opioids tonically regulate nociceptive information and that all naturally occurring exogenous opioid agonists produce analgesia. Today, opiate drugs are widely used in the treatment of post-operative pain.

Opioid knockout receptor models provide a powerful tool for studying analgesia and other physiological effects attributed to the opioid system [156]. Strong evidence shows that MOR plays a central role in analgesia. Mice lacking MOR have increased sensitivity to heat, suggesting the existence of a MOR-mediated tone in thermal nociception [156] and a reduction in stress-induced analgesia [164]. In contrast, DOR- and KOR-deficient mice did not exhibit any alteration in heat perception. Many of the currently available clinical opioid analgesics exert their effects primarily through MOR [38]. After knocking out MOR, the analgesic effects of δ -agonists are either unchanged or diminished [165], while MOR agonists fail to exhibit analgesia [166, 167]. However, DOR agonists can enhance the analgesic potency and efficacy of MOR agonists and the antagonists can prevent or reduce the development of tolerance and physical dependence to MOR agonists [38]. All these observations indicate a vital role of MOR in pain modulation.

Immunohistochemical and ultrastructural analysis revealed that DOR exists in peripheral nerves in the molar dental pulp [168], and that bradykinin, an inflammatory mediator, causes a reaction in trigeminal ganglia sensory neurons, which results in a rapid increase in significant accumulation of DOR in the plasma membrane thus contributing to peripheral opioid analgesia [168, 169]. It was observed in rodent models that DOR1 and DOR2 antagonists respectively blocked the supraspinal anti-nociceptive activation by DOR agonists DPDPE and deltorphin [101–104]. In DOR knockout animals, DOR agonist-induced analgesia was either abolished, reduced, or unchanged, depending on the nociceptive assay and route of administration [170]. The recorded analgesia could be a result of the cross-reactivity of DOR agonists at MOR *in vivo* [165]. Contrary to the pre-demonstrated that, under vailing view, Scherrer *et al.* [171] resting conditions, DOR is trafficked to the cell surface independent of substance P and internalized following activation by DOR agonists. There is also evidence showing that the segregated DOR and MOR distribution is paralleled by a remarkably selective functional contribution of the two receptors to the control of mechanical and thermal pain, respectively.

KOR also plays a role in pain modulation. Though KOR-deficient did not exhibit any alteration in the perception of thermal or mechanical pain, KOR mutant mice had an enhanced pain response to the peritoneal acetic acid injection [165]. Dynorphin-deficient mice also displayed a mild increase in pain induced by inflammation [172]. Compared to MOR and DOR, KOR chiefly mediates analgesia to visceral pain [173].

In mechanistic investigations, serial studies from Caron and Lefkowitz laboratories using β -arrestin knockout mice show that β -arrestins regulate opioid receptor-mediated signal transduction and hence play an important role in opioid-induced analgesia and tolerance/dependence [174–177]. Pei and Ma [178–181] have also confirmed these findings.

4.6. Drug Abuse/Addiction

Excessive use of opioids leads to opioid addiction. Drug abuse and addiction are now considered as neurological pathology due to their effects on brain function. Neurological impairments observed in addiction reflect drug-induced neuronal dysfunction and neurotoxicity. The drugs of abuse directly or indirectly affect various neurotransmitter systems, particularly dopaminergic and glutamatergic neurons [182, 183]. The treatment of drug abuse and addiction is the most expensive of all the neuropsychiatric disorders associated with personality disorders and a diminished quality of life [182, 184, 185]. Behavioral patterns of addiction include compulsive drug-seeking, persistent abuse of substances despite the often irreparable social consequences and deterioration of physical health, and the high probability of relapse even after prolonged drug-free periods [186].

The mechanisms underlying neurological disorder caused by opioid addiction are not clear yet. Neuronal basis of positive reinforcement relies on activation of dopaminergic neurons resulting in an increased dopamine release in the mesolimbic brain structures. Certain aspects of opioid dependence and withdrawal syndrome are also related to noradrenergic and serotonergic systems, as well as to both excitatory and inhibitory amino acid and peptidergic systems. An important role in neurochemical mechanisms of opioid reward, dependence and vulnerability to addiction has been ascribed to the activation of endogenous opioid peptides, particularly those acting via the MOR and KOR.

Opioid abuse leads to opioid tolerance in the nervous system. Receptor tolerance and adaptation involve complex mechanisms of receptor regulation, including desensitization and internalization [187]. Several important processes have been identified including upregulation of cAMP/PKA and cAMP response element-binding signaling and perhaps MAPK cascades in opioid sensitive neurons, which might not only influence tolerance and withdrawal, but also synaptic plasticity during the cycles of intoxication and withdrawal [188]. Intracellular molecules of signal transmission are also involved in opioid tolerance and dependence, including G proteins, cyclic AMP, MAP kinases, and some transcription factors. The latter link in this chain of reactions modifies the expression of target genes, and it may be responsible for the long-lasting neural plasticity induced by opioids [188, 189]. In general, drug abuse induces adaptive changes in opioid receptors that occur following acute (e.g., desensitization and/or internalization) and chronic (e.g., adaptive tolerance and down-regulation) opioid administration [190–193]. Future work on prescribed drugs of abuse will include identification of clinical practices that minimize the risks of addiction, the development of guidelines for early detection and management of addiction, and the development of clinically effective agents that minimize the risks for abuse [194].

In addition, opioid abuse may predispose an individual to opportunistic infections, such as hepatitis, bacterial pneumonia, tuberculosis, abscesses, CNS infections, endocarditis and even AIDS [195–197]. One of the explanations for this phenomenon is that opioids suppress immune function (also refer to 4.9 below) including antimicrobial resistance, antibody production, monocyte-mediated phagocytosis, and neutrophil and monocyte chemotaxis [196].

4.7. Emotional Response

The role of the opioid system in controlling pain, reward and addiction is well established, but its role in regulating other emotional responses is poorly documented in pharmacology [198]. Recent studies have shown that endogenous opioid systems are associated with the regulation of emotional responses. In particular, it has been reported that δ -opioid receptors act as natural inhibitors of stress and anxiety [199]. DOR agonists have been shown to produce antidepressant and anxiolytic effects in rodent models. In addition, DOR agonists have been shown to increase expression of brain-derived neurotrophic factor (BDNF) mRNA, an effect of some antidepressants, which may be important for the clinical efficacy of antidepressant drugs [200, 201]. Zhang *et al.* [202] reported that centrally administered nor-BNI, like most clinically used antidepressants, upregulated BDNF mRNA expression in the rat hippocampus. These findings further imply that central KOR mediates antidepressant-like effects by BDNF gene upregulation. Some data demonstrate dynamic changes in MOR neurotransmission in response to an experimentally induced negative affective state [203].

In addition, stress contributes to opioid-induced neuronal activation. Mice exposed to stress and morphine showed region-specific increases in KOR [204, 205].

4.8. Epileptic Seizures

The role of opioid system in epileptogenesis and epileptic seizure is still controversial. Both anticonvulsant and proconvulsant effects of the three major opioid systems (δ -, μ -, and κ -) as well as nociceptin opioid peptide have been proposed in the literature [206–219]. For example, Rubaj *et al.* [220] showed that MOR and KOR are involved in hypoxic preconditioning against seizures in the brain. They observed that an episode of normobar hypoxia reduced the susceptibility to convulsions induced by pentylenetetrazol, which could be mimicked by MOR or KOR agonists.

In some experimental models of epilepsy, endogenous opioid (e.g. enkephalin and dynorphin) levels are greatly increased in the brain during epileptic seizures [209, 219, 221], and opioid receptors are up-regulated following spontaneous epileptic seizure [222]. It is not clear if this represents a compensatory mechanism against epilepsy because multiple factors determine the anticonvulsant or proconvulsant role of opioids in the brain. For example, morphine depresses electrographic seizure activity under a low concentration, while enhances seizure activity under high concentrations with an apparent dose-dependent manner [217, 223]. SCN80, a non-peptide DOR agonist, both in low or high dose, produced convulsions in the rat, but had little effects in rhesus monkeys [215, 224, 225]. Retarding the rate of administration of SCN80 brought a reduction in its convulsive effect in the rat [226]. Also, the action of opioids depends on the site of action. Endogenous opioids generally play an inhibitory role in modulation of neuronal excitability. However, if this inhibition occurs in inhibitory interneurons, the opioids facilitate, rather than suppressing seizures via post-synaptic de-inhibition. Therefore, increased familiarity with the effects of opioid action on epilepsy is necessary.

Data from our recent work shows that DOR inhibits sodium channels and thus suppresses epileptic activity in the cortical regions. Sodium channel mutation has been casually linked to human epilepsy [227, 228], and an up-regulation of Na⁺ channels has demonstrated to cause epileptic hyper-excitability and seizures [229, 230]. Interestingly, we observed that in the mutant brain exhibiting spontaneous epilepsy, Na⁺ channels are up-regulated [230], while DOR is down-regulated [231], implicating DOR contribution to the pathophysiology of epilepsy associated with genetic abnormality. In addition, our studies on Na⁺ channels and DOR co-expression in *Xenopus* oocytes demonstrated that DOR activation inhibits Na⁺ channel function by decreasing the amplitude/velocity of sodium currents and increasing their threshold for activation [135]. Since Na⁺ channels play a major role in neuronal excitability including epileptic hyper-excitability and most of anti-epileptic drugs are actually inhibitors of Na⁺ channels [232, 233], the phenomenon we observed can provide novel clues for better solutions of epileptic seizures.

4.9. Immune Function

Opioids may behave like cytokines to modulate the immune response through an interaction with their receptors in central and peripheral neurohumoral systems [234–237]. In general, opioids mediate immunosuppression although their actions are complicated, often indirect and not well understood. Nonetheless, acute and chronic opioid administration is known to have inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity [235, 236, 238–240]. *In vivo* and *in vitro* studies indicated that opioid receptor stimulation exerts suppression of multiple components of the immune defense response including natural killer (NK) cell activity [241], neutrophil complement and immunoglobulin receptor expression [242], chemokine-induced chemotaxis [243] and phagocytosis [244]. Bai *et al.* [245] found that after intracerebroventricular injection of β -endorphin in rats, the mitogen-induced spleen lymphocyte DNA synthesis, hemolysin formation and IgG production were reduced

significantly, suggesting a role of the central opioid system in immune regulation. Pretreatment with U50 488 - a κ -opioid ligand, significantly reduced lipopolysaccharide (LPS)-stimulated interleukin-6 (IL-6) production. This effect was mediated by the KOR through inhibition by KOR antagonist-nor-binaltorphimine (nor-BNI) [246]. Treatment of normal human astrocytes with morphine leads to significant down-regulation of gene expression for β -chemokines, MCP-1, and MIP-1 β , while reciprocal up-regulation of the expression of their specific receptors, CCR2b, CCR3, and CCR5, respectively, and reversed by naloxone [247]. In addition, acute administration of morphine significantly decreased NK cell cytotoxicity and interferon-gamma mRNA levels, and increased the mortality rate of mice infected with herpes simplex virus 1 [240]. DOR agonist, DPDPE, triggers monocyte adhesion [248]. Ordaz-Sanchez *et al.* [196] observed that SNC80, another DOR agonist, significantly stimulated rat thymic and human leukocyte chemotaxis. The effects of SNC80 on the chemotaxis of rat and human leukocytes were antagonized by naloxone, indicating that the modulation of chemotaxis via opioid receptors. It has been suggested that activation of the KOR induces an anti-inflammatory response through the down-regulation of cytokine, chemokine and chemokine receptor expression, while activation of MOR favors a pro-inflammatory response [249]. Investigation into the ORL1/nociceptin system demonstrated a down-regulation of immune function secondary to the activation of this receptor [39, 249].

In summary, opioid modulation of the immune response in animals is mediated through the direct interaction with opioid receptors expressed by immune cells. The influence of the opioids on the immune response *in vivo* is likely to be a result of involvement of both the central nervous system and the hypothalamic-pituitary-adrenal axis [250]. Sharp *et al.* [251] demonstrated that the β -endorphin and dynorphin stimulate the superoxide production by neutrophils and peritoneal macrophages. Inhibition of superoxide production by morphine is likely to be mediated via soluble factors, such as growth factor β , produced by the lymphoid cells present in the peripheral blood [252].

Pharmacological evidence has demonstrated the presence of MOR, KOR and DOR, as well as non-classical opioid-like receptors, in cells of the immune system. Studies have shown that the phagocytic activity of non-elicited macrophages is inhibited by *in vitro* administration with μ -, κ -, or δ -opioid agonists [253]. An antagonist blocks the inhibitory activity of each agonist with the appropriate opioid receptor selectivity.

TNF- α and IL-6 are the two of the major cytokines secreted by activated macrophages. One study [254] showed that morphine differentially modulates LPS induced expression of IL-6 and TNF- α , and Greenelch *et al.* [255] found that naltrexone was capable of preventing LPS-induced septic shock mortality by indirect inhibition of TNF- α production *in vivo*. Although Alicea *et al.* [256] reported that macrophage function is significantly modulated following activation of the KOR, morphine and the endogenous opioids (β -endorphin, [Met⁵]enkephalin, and dynorphin) also induce chemotaxis of human monocytes and neutrophils [243, 257–259]. Morphine modulation of several immune functions, including macrophage phagocytosis and macrophage secretion of TNF- α , was not observed in the MOR knock-out animals suggesting that these functions are mediated by the classical MOR receptor [254].

4.10. Feeding

Opioid receptors also participate in the regulation of feeding. Opioid agonists and antagonists have corresponding stimulatory and inhibitory effects on feeding. In addition to studies aimed at identifying the relevant receptor subtypes and sites of action in brain, there has been an increasing interest in the role of opioids on diet/taste preferences, food reward, and the overlap of food reward with others types of reward. Some data suggest a role for opioids in the control of appetite for specific macronutrients, but there is also evidence for

their role in the stimulation of intake based on already-existing diet or taste preferences and in controlling intake motivated by hedonics rather than by energy needs [260].

Agonist stimulation of opioid receptors increases feeding in rodents, while opioid antagonists inhibit food intake and weight gain in ob/ob mice [261]. The pan-opioid antagonist, LY255582, produces a sustained reduction in food intake and body weight in rodent models of obesity. The study on mouse indicated that LY2555823 produces its effects on feeding and body weight gain likely through a combination of μ -, δ - and κ -receptor activity [90]. The κ -antagonist, nor-binaltorphimine, significantly increased food intake, while naltrexone (general antagonist) and naloxonazine (μ -antagonist) both reduced feeding [262]. Research suggested that syndyphalin-33 (SD33) - a μ -opioid receptor ligand, increases food intake in sheep after intravenous injection, and its effects are mediated via opioid receptors [263].

4.11. Obesity

Opioid receptors as obesity-related factor affect body weight and obesity. Studies showed that stimulation of μ -opioid receptors preferentially increases the intake of a high fat diet. The increased levels of hypothalamic μ -opioid receptors in Osborne-Mendel rats could contribute to their preference for a high fat diet and increased susceptibility to obesity [264, 265]. The μ -opioid receptor signaling in the nucleus accumbens core and shell is necessary for palatable diet-induced hyperphagia and obesity to fully develop in rats [266]. Czyzyk *et al.* [267] fed KOR-knockout (KO) and wild-type (WT) mice with high-energy diet (HED) for 16 wk. They found that the KO mice had 28% lower body weight and 45% lower fat mass when compared to WT mice fed an HED. Furthermore, KOR deficiency led to an attenuation of triglyceride synthesis in the liver. This study provides the evidence that KOR plays an essential physiological role in the control of hepatic lipid metabolism, and KOR activation is a permissive signal toward fat storage. Marczak *et al.* [261] administered H-Dmt-Tic-Lys-NH-CH₂-Ph (MZ-2), a potent μ -/ δ -opioid receptor antagonist, in mice and found that MZ-2 exhibited the following: (1) reduction in weight gain in sedentary obese mice that persisted beyond the treatment period without any significant effect on leaner mice; (2) stimulation of voluntary running behavior on exercise wheels of both groups of mice; (3) decrease in fat content, enhanced bone mineral density (BMD), and decreased serum insulin and glucose levels in obese mice; and (4) MZ-2 (30 μ M) increased BMD in human osteoblast cells (MG-63) comparable to naltrexone, while morphine inhibited mineral nodule formation. Thus, MZ-2 offers potential for application in the clinical management of obesity, insulin and glucose levels, and osteoporosis.

4.12. Respiratory Control

Opioids affect ventilation, leading to respiratory depression in both animals and humans [268, 269]. This effect occurs in part due to a direct action of opioids on respiratory-generating structures in the brain [269]. It has been known that there are high densities of opioid receptors in the brain areas related to respiration [270, 271] and local application of opioid agonists to these areas depressed the activity of respiratory related neurons [271, 272]. Opioid receptors show a heterogeneous variation in the depression of respiration by opioids, as MOR activation shows a marked decrease in respiratory frequency and complete apnea, less pronounced respiratory depressant effect by DOR, and the absence of an effect on respiration upon KOR activation [271]. Also, there appears to be “crosstalk” among opioid receptors regarding their depression on respiratory response. For example, it has been shown that respiratory depression produced by DOR agonists is suppressed, while the respiratory response to the activation of KOR is maintained in MOR knockout mice [273]. The phenomenon could be a result of μ -/ δ -receptor heteromeric interactions, which exhibit regional selectivity across different areas of the brain [274].

Owing to an extensive clinical use of opioid drugs for pain relief (e.g., cancer-induced or post-operative), the accompanying undesirable side-effect of opioid-induced respiratory depression has become an important concern. Though associated mortality is low, respiratory depression poses a significant clinical problem for patients treated with opioids, especially in the post-operative period [269]. Opioid drugs depress the rate and depth of breathing, blunt respiratory responsiveness to CO₂ and hypoxia, increase upper airway resistance and reduce pulmonary compliance. Opiate respiratory disturbances are mainly due to the agonist activation of μ - and δ -receptor subtypes and involves specific types of respiratory-related neurons in the ventrolateral medulla and the dorsolateral pons [275, 276].

Under certain conditions, this adverse effect may be lethal. For instance, severe stress (hemorrhagic shock, trauma, bacterial infection) resulting in a massive release of endogenous opioids, or an overdose of opioid analogues (drug abuse, addiction, and uncontrolled use for pain relief) can cause a severe respiratory depression, hypotension, and even death.

4.13. Cardiovascular Regulation

Opioid peptides, including β -endorphin [277], enkephalins [278–281] and dynorphins/dynorphin-like peptides [280, 282], are present in the heart. Myocardial cells are sites of opioid peptide synthesis, storage and release [283]. Myocardial opioid peptide levels are elevated during episodes of stress, such as ischemia [150, 284]. In addition to heart myocardial cells, δ - and κ -opioid peptides have been shown to exist in sympathetic nerve fibers and ganglion cells [279, 285]. Short-term cholestasis is associated with resistance against ischemia/reperfusion-induced arrhythmia, which depends on availability of endogenous opioids [286]. Both the KOR agonists, ethylketocyclazocine and enadoline, elicited an increase heart rate with a little effect on blood pressure through a combined action on central and peripheral receptors in conscious squirrel monkeys that could be blocked by the opioid antagonist naltrexone. This effect appeared to be specific for KOR, since the MOR agonist morphine did not mimic the effects of the KOR agonists [287]. In addition, both DOR [172, 288] and KOR [172, 289] have been shown to mediate cardioprotection by preconditioning with myocardial ischemia and metabolic inhibition, one of the consequences of ischemia.

Animal experiments have demonstrated that the opioid system can modulate hemodynamic and cardiovascular activity. In an animal model of hemorrhagic shock, opioid receptor antagonists ameliorated hemodynamic instability [290, 291]. Microinjection of DOR antagonist naltrindole into the ventrolateral periaqueductal gray, a region importantly involved in opioid analgesia, inhibited hemorrhagic hypotension significantly in both conscious and anesthetized rats, while MOR and KOR antagonists were ineffective [292]. However, it is reported that after hemorrhage and during the re-compensatory period, stimulation of δ_2 -opioid receptors led to improved mean arterial pressure in conscious, freely moving male rats, and this recovery involved a change in baroreflex sensitivity [293]. Similar effects of enhanced mean arterial blood pressure were also observed in shock patients undergoing treatment with opioid antagonists [294].

MOR has been shown to be involved in the regulation of cardiovascular function. For example, cyclo[*N* ϵ ,*N* β -carbonyl-D-Lys²,Dap⁵]enkephalinamide (cUENK6), a MOR agonist, was found to stimulate excretion of urine, sodium, potassium and cGMP, suppressed the stress-induced elevation in blood pressures and heart rate [295]. Intrathecal injection of endomorphins, elicited a decrease in systemic arterial pressure and heart rate in a dose-dependent manner [296]. As naloxone significantly antagonized the effects of vaso-depression and bradycardia, it is possible that they were elicited by the activation of MOR in the rat spinal cord [296]. In contrast, Mao and Wang [297] reported that microinjection of

endomorphin-1 (EM-1) or nociceptin into nucleus tractus solitarius increased blood pressure and heart rate. These contrary results indicate that the cardiovascular effects are likely to be dependent on the site of action of opioid peptides. Opioid receptors, especially DOR and KOR, are also involved in cardio-protection against ischemic injury. Gross *et al.* [298–300] observed that opioid receptors are important in mediating ischemic preconditioning (IPC) in the heart of dogs. DOR stimulation with selective agonists could mimic the cardio-protective effects of IPC [300]. In an animal model of severe hemorrhagic shock, following DADLE treatment improved hemodynamic stability and a prolonged survival was observed [142]. Although some investigators believe that DOR1 plays an important role in the DOR-mediated cardiac protection, others maintain an opposite view. For instance, Lasukova *et al.* [301] showed that DOR agonist, DPDPE, induced antiarrhythmic and cardio-protective effects in the condition of coronary artery occlusion and reperfusion, and concluded that this protection manifested secondary to stimulation of cardiac DOR1. On the other believes that DOR2 plays the vital hand, Maslov *et al.* [302] role in cardio-protection. They reported that a pretreatment with peripheral and DOR2 antagonists completely abolished the cardioprotective effects of deltorphin II, while DOR1 antagonist 7-benzylidenenaltrexone (BNTX) had no effect. In addition, protein kinase C (PKC) inhibitor chelerythrine and the NO-synthase inhibitor L-NAME (*N*-nitro-L-arginine methyl ester) also reversed the effects of deltorphin II. The nonselective ATP-sensitive K⁺ (K_{ATP}) channel inhibitor glibenclamide and the selective mitochondrial K_{ATP} channel inhibitor 5-hydroxydecanoic acid abolished the infarct-sparing effect of deltorphin II. Inhibition of tyrosine kinase (TK) with genistein, the ganglion blocker hexamethonium and the depletion of endogenous catecholamine storage with guanethidine reversed the antiarrhythmic action of deltorphin II but did not change its infarct-sparing action. Based on all these findings, they concluded that the cardioprotective mechanism of deltorphin II is mediated via stimulation of DOR-2. PKC and NOS are involved in both its infarct-sparing and antiarrhythmic effects. Infarct-sparing effect is dependent upon mitochondrial K_{ATP} channel activation while the antiarrhythmic effect is dependent upon TK activation. Endogenous catecholamine depletion reduced antiarrhythmic effects but did not alter the infarct-sparing effect of deltorphin II. This controversy provides additional evidence on the uncertainty over the existence of DOR subtypes. In studies on KOR, Wu *et al.* [289] showed that KOR plays a role in cardioprotection during the delayed phase of protection, while Wang *et al.* [172] demonstrated that KOR activation mediated both the anti-arrhythmic and infarct limiting effects of IPC. Furthermore, Rong *et al.* [303] found that KOR activation attenuated myocardial apoptosis and infarction after ischemia/reperfusion.

4.14. Role in Neurodegenerative and other Diseases

Substantial data shows that opioids inhibit the onset and progression of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis [304]. Several lines of evidence suggest that DOR agonists have a therapeutic effect on Parkinson's disease [305, 306]. Also, activation of KOR effectively ameliorates L-DOPA-induced dyskinesia symptoms in a rat model of Parkinson's disease [307]. Even in the treatment of uremic pruritus, an opioid receptor agonist - nalfurafine, effectively reduced itching, itching intensity, and sleep disturbances [308]. Although the side-effects of opioid receptor activation under certain conditions represents the other side of the coin, For example, a recent study showed that intrathecal injection of morphine after a short interval of aortic occlusion in the rodent model induced transient spastic paraparesis via opioid receptor-coupled effects in the spinal cord [309].

Abundant clinical evidence shows that various movement disorders such as dystonia can develop in patients, with or without pre-existing Parkinson's disease, while emerging from general anesthesia and it can be dramatically reversed by the administration of naloxone.

This indicates an underlying contribution of the fentanyl and morphine that the patient had received to the development of these movement disorders [310]. Zesiewicz *et al.* [311] described a case of 58-year-old man with advanced Parkinson disease who underwent battery replacement for a deep brain stimulator and experienced severe postoperative bradykinesia and rigidity that lasted for 36 hours. The patient was administered fentanyl as an anesthetic during the procedure and as an analgesic periodically during the day after surgery. The severe bradykinesia and rigidity persisted despite reactivation of the deep brain stimulator and immediate reinstitution of Parkinson disease medications, but resolved completely couple of hours after discontinuation of fentanyl. These observations suggest a potential role of MOR in the movement disorders of patients with Parkinson disease. Indeed, a recent study shows that a selective MOR antagonist, ADC5510, can reduce L-DOPA induced dyskinesia in a Parkinson's disease model [312]. It is apparent that MOR has a very different role compared to DOR and KOR in Parkinson's disease.

However, there is lack of in-depth and mechanistic studies for most functions in which they are involved because the majority of the previous, especially early, studies focused on pain modulation and drug addiction via μ -agonist and MOR in the CNS.

5. CONCLUDING REMARKS

The opioid system is considered as one of the most complex and interwoven neurotransmitter systems in the body. The functional effects of opioids are mediated by three distinct opioid receptors with over-lapping distribution and functions in the brain and other major organs. Although opioids are predominantly used for therapeutic pain relief in a clinical setting, other potential roles of the opioid system throughout the body, especially in the brain, are coming into focus with an emergence of new and specific analogues that have brought forth their subtle differences and enabled the investigators to unravel this issue. Since the cloning of the three major opioid receptors, many studies have been performed to elucidate their function and show that besides the involvement of pain modulation, opioid receptors are widely involved in various pleiotropic functions throughout the body, including ionic homeostasis, cell proliferation, emotional response, epileptic seizures, immune function, feeding, obesity, respiratory and cardiovascular control. They also play a critical role in hibernation. One of the most exciting findings in the past decade possibly is neuroprotection and cardioprotection mediated by opioid receptors, especially DOR. The underlying mechanisms involve the stabilization of ionic homeostasis in acute stage of hypoxic/ischemic stress, up-regulation of survival molecules and anti-oxidative capacity, and the down-regulation of apoptosis during the long-term stress of hypoxia/ischemia. These recent findings can have significant clinical implications with regards to the role of opioids, either endogenous or exogenous, in limiting the pathogenesis of brain and heart from hypoxic/ischemic damage.

Many important issues such as the difference between MOR and DOR, despite structural similarity among them, in terms of neuroprotection still remain to be clarified. Morphine protects purkinje cells against cell death under *in vitro* simulated ischemia-reperfusion conditions, which is mediated by DOR, but not MOR [18]. In rat hippocampal slices, however, exposure to morphine aggravates the neurotoxic effects of a subsequent hypoxia/hypoglycemia in a concentration-dependent manner [313, 314]. It seems that opioid receptors have differential roles in neuronal responses to hypoxic/ischemic stress across different brain regions/cells (e.g., cortical vs. hippocampal cells). MOR may induce a toxic effect on neurons in some brain regions under hypoxic/ischemic condition. It is still unclear whether this is a reason why some investigators observed neuroprotection induced by opioid blockers such as naltrexone under certain conditions [315]. More intricate and in-depth studies are needed to address many complex issues like this. Although the role of DOR in

neuroprotection is relatively clear, it is important to develop more specific and potent DOR-agonists with lesser side-effects to strengthen their neuroprotection as they might prove useful for patients with stroke, cardiac ischemia, and hypoxic encephalopathy.

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References

1. Hosobuchi Y, Baskin DS, Woo SK. Reversal of induced ischemic neurologic deficit in gerbils by the opiate antagonist naloxone. *Science*. 1982; 215(4528):69–71. [PubMed: 6274019]
2. Adams HP Jr, Olinger CP, Barsan WG, et al. A dose-escalation study of large doses of naloxone for treatment of patients with acute cerebral ischemia. *Stroke*. 1986; 17(3):404–9. [PubMed: 3715936]
3. Skarphedinsson JO, Thoren P. Endorphin mechanisms are responsible for the beneficial effects of opioid antagonists on cerebral function during relative cerebral ischaemia in rats. *Acta Physiologica Scandinavica*. 1988; 132(3):281–8. [PubMed: 2852436]
4. Olinger CP, Adams HP Jr, Brott TG, et al. High-dose intravenous naloxone for the treatment of acute ischemic stroke. *Stroke*. 1990; 21(5):721–5. [PubMed: 2339451]
5. Hayward NJ, McKnight AT, Woodruff GN. Neuroprotective effect of the kappa-agonist enadoline (CI-977) in rat models of focal cerebral ischaemia. *Eur J Neurosci*. 1993; 5(7):961–7. [PubMed: 8281306]
6. Mayfield KP, D'Alecy LG. Delta-1 opioid agonist acutely increases hypoxic tolerance. *J Pharmacol Exp Ther*. 1994; 268(2):683–8. [PubMed: 8113979]
7. Endoh H, Taga K, Yamakura T, et al. Effects of naloxone and morphine on acute hypoxic survival in mice. *Crit Care Med*. 1999; 27(9):1929–33. [PubMed: 10507620]
8. Zhang JH, Xia Y, Haddad GG. Activation of delta-opioid receptors protects cortical neurons from glutamate excitotoxic injury. *Soc Neurosci*. 1999; 28:Abstract 736.
9. Zhang JH, Haddad GG, Xia Y. delta-, but not mu- and kappa-opioid receptor activation protects neocortical neurons from glutamate-induced excitotoxic injury. *Brain Res*. 2000; 885(2):143–53. [PubMed: 11102568]
10. Zhang JH, Gibney GT, Xia Y. Effect of prolonged hypoxia on expression of Na⁺ channel mRNA subtypes in the developing rat cortex. *Brain Res Mol Brain Res*. 2001; 91(1–2):154–8. [PubMed: 11457503]
11. Zhang JH, Gibney GT, Xia Y. Neuroprotective role of delta-opioid receptors in cortical neurons. *Am J Physiol Cell Physiol*. 2002; 282(6):C1225–34. [PubMed: 11997236]
12. Zhang J, Qian H, Zhao P, Hong SS, Xia Y. Rapid hypoxia preconditioning protects cortical neurons from glutamate toxicity through δ -opioid receptor. *Stroke*. 2006; 37(4):1094–9. [PubMed: 16514101]
13. Ma MC, Qian H, Ghassemi F, Zhao P, Xia Y. Oxygen sensitive δ -opioid receptor-regulated survival and death signals: novel insights into neuronal preconditioning and protection. *J Biol Chem*. 2005; 280(16):16208–18. [PubMed: 15687501]
14. Tian XS, Zhou F, Yang R, Xia Y, Wu GC, Guo JC. Effects of intracerebroventricular injection of delta-opioid receptor agonist TAN-67 or antagonist naltrindole on acute cerebral ischemia in rat. *Acta Physiol Sin*. 2008; 60(4):475–84.
15. Yang Y, Xia X, Zhang Y, et al. Delta-opioid receptor activation attenuates oxidative injury in the ischemic rat brain. *BMC Biol*. 2009; 7:55. [PubMed: 19709398]
16. Chao D, Xia Y. Ionic storm in hypoxic/ischemic stress: can opioid receptors subside it? *Prog Neurobiol*. 2010; 90(4):439–70. [PubMed: 20036308]
17. Feng Y, He X, Yang Y, Chen J, Yin K, Xia Y. Effect of delta-opioid receptor over-expression on cortical expression of GABAA receptor α 1-subunit in hypoxia. *Chin J Physiol*. 2011; 54(2): 118–23. [PubMed: 21789893]

18. Lim YJ, Zheng S, Zuo Z. Morphine preconditions purkinje cells against cell death under *in vitro* simulated ischemia-reperfusion conditions. *Anesthesiology*. 2004; 100(3):562–8. [PubMed: 15108969]
19. Horiuchi T, Kawaguchi M, Sakamoto T, et al. The effects of the delta-opioid agonist SNC80 on hind-limb motor function and neuronal injury after spinal cord ischemia in rats. *Anesth Analg*. 2004; 99(1):235–40. [PubMed: 15281536]
20. Horiuchi T, Kawaguchi M, Kurita N, et al. Effects of delta-opioid agonist SNC80 on white matter injury following spinal cord ischemia in normothermic and mildly hypothermic rats. *J Anesth*. 2008; 22(1):32–7. [PubMed: 18306011]
21. Borlongan CV, Wang Y, Su TP. Delta opioid peptide (D-Ala²,D-Leu⁵) enkephalin: linking hibernation and neuroprotection. *Front Biosci*. 2004; 9:3392–8. [PubMed: 15353366]
22. Borlongan CV, Hayashi T, Oeltgen PR, Su TP, Wang Y. Hibernation-like state induced by an opioid peptide protects against experimental stroke. *BMC Biol*. 2009; 7:31. [PubMed: 19534760]
23. Zhao P, Huang Y, Zuo Z. Opioid preconditioning induces opioid receptor-dependent delayed neuroprotection against ischemia in rats. *J Neuropathol Exp Neurol*. 2006; 65(10):945–52. [PubMed: 17021399]
24. Su DS, Wang ZH, Zheng YJ, Zhao YH, Wang XR. Dose-dependent neuroprotection of delta opioid peptide [D-Ala²,D-Leu⁵] enkephalin in neuronal death and retarded behavior induced by forebrain ischemia in rats. *Neurosci Lett*. 2007; 423(2):113–7. [PubMed: 17689189]
25. Iwata M, Inoue S, Kawaguchi M, Nakamura M, Konishi N, Furuya H. Effects of delta-opioid receptor stimulation and inhibition on hippocampal survival in a rat model of forebrain ischaemia. *Br J Anaesth*. 2007; 99(4):538–46. [PubMed: 17704092]
26. Charron C, Messier C, Plamondon H. Neuroprotection and functional recovery conferred by administration of kappa- and delta- opioid agonists in a rat model of global ischemia. *Physiol Behav*. 2008; 93(3):502–11. [PubMed: 18031772]
27. Kao TK, Ou YC, Liao SL, Chen WY, Wang CC, Chen SY, Chiang AN, Chen CJ. Opioids modulate post-ischemic progression in a rat model of stroke. *Neurochem*. 2008; 52(6):1256–65.
28. Govindaswami M, Brown SA, Yu J, et al. Delta 2-specific opioid receptor agonist and hibernating woodchuck plasma fraction provide ischemic neuroprotection. *Acad Emerg Med*. 2008; 15(3): 250–7. [PubMed: 18304055]
29. Pamenter ME, Buck LT. δ -Opioid receptor antagonism induces NMDA receptor-dependent excitotoxicity in anoxic turtle cortex. *J Exp Biol*. 2008; 211(21):3512–7. [PubMed: 18931323]
30. Peng PH, Huang HS, Lee YJ, Chen YS, Ma MC. Novel role for the δ -opioid receptor in hypoxic preconditioning in rat retinas. *J Neurochem*. 2009; 108(3):741–54. [PubMed: 19054276]
31. Zhu M, Li M, Tian X, Ou X, Zhu C, Guo J. Neuroprotective role of δ -opioid receptors against mitochondrial respiratory chain injury. *Brain Res*. 2009; 1252:183–91. [PubMed: 19056363]
32. Law PY, Loh HH. Regulation of Opioid Receptor Activities. *J Pharmacol Exp Ther*. 1999; 289(2): 607–24. [PubMed: 10215631]
33. Wiesenfeld-Hallin Z, de Araújo Lucas G, Alster P, Xu XJ, Hökfelt T. Cholecystokinin/opioid interactions. *Brain Res*. 1999; 848(1–2):78–89. [PubMed: 10612699]
34. Pasternak GW. Multiple opiate receptors: déjà vu all over again. *Neuropharmacology*. 2004; 47(Suppl 1):312–23. [PubMed: 15464147]
35. Waldhoer M, Bartlett SE, Whistler JL. Opioid receptors. *Annu Rev Biochem*. 2004; 73:953–90. [PubMed: 15189164]
36. Barry U, Zuo Z. Opioids: old drugs for potential new applications. *Curr Pharm Des*. 2005; 11(10): 1343–50. [PubMed: 15853689]
37. Bohn LM, Racheal KM. Opioid receptor signaling: relevance for gastrointestinal therapy. *Curr Opin Pharmacol*. 2006; 6(6):559–63. [PubMed: 16935560]
38. Ananthan S. Opioid ligands with mixed μ /delta opioid receptor interactions: an emerging approach to novel analgesics. *AAPS J*. 2006; 8(1):E118–25. [PubMed: 16584118]
39. Lambert DG. The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential. *Nature Rev Drug Disc*. 2008; 7(8):694–711.

40. Kieffer BL, Evans CJ. Opioid receptors: from binding sites to visible molecules *in vivo*. *Neuropharmacology*. 2009; 56(Suppl 1):205–12. [PubMed: 18718480]
41. Kreek MJ, Zhou Y, Butelman ER, Levran O. Opiate and cocaine addiction: from bench to clinic and back to the bench. *Curr Opin Pharmacol*. 2009; 9(1):74–80. [PubMed: 19155191]
42. Feng Y, Chao D, He X, et al. A novel insight into neuroprotection against hypoxic/ischemic stress. *Acta Physiol Sin*. 2009; 61(6):585–92.
43. Zhao P, Guo JC, Xia Y, et al. Electro-acupuncture and brain protection from cerebral ischemia: the role of delta-opioid receptor. *Soc Neurosci Abstract Program*. 2002:490.13.
44. Martin WR. Opioid antagonists. *Pharmacol Rev*. 1967; 19(4):463–521. [PubMed: 4867058]
45. Tsou K, Jang CS. Studies on the site of analgesic action of morphine by intracerebral micro-injection. *Sci Sin*. 1964; 13:1099–109. [PubMed: 14196479]
46. Pert A, Yaksh T. Sites of morphine induced analgesia in the primate brain: relation to pain pathways. *Brain Res*. 1974; 80(1):135–40. [PubMed: 4424093]
47. Pert A, Yaksh T. Localization of the antinociceptive action of morphine in primate brain. *Pharmacol Biochem Behav*. 1975; 3(1):133–8. [PubMed: 1129350]
48. Mayer D, Liebeskind JC. Pain reduction by focal electrical stimulation of the brain: an anatomical and behavioral analysis. *Brain Res*. 1974; 68(1):73–93. [PubMed: 4549764]
49. Akil H, Mayer DJ, Liebeskind JC. Antagonism of stimulation-produced analgesia by naloxone, a narcotic antagonist. *Science*. 1976; 191(4230):961–2. [PubMed: 1251210]
50. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature*. 1975; 258(5536):577–9. [PubMed: 1207728]
51. Snyder SH, Matthyse S. Opiate Receptor Mechanisms. *Neurosci Res Program Bull*. 1975; 13(1):1–66.
52. Li CH, Chung D, Doneen BA. Isolation, characterization and opiate activity of beta-endorphin from human pituitary glands. *Biochem Biophys Res Commun*. 1976; 72(4):1542–7. [PubMed: 999687]
53. Doneen BA, Chung D, Yamashiro D, Law PY, Loh HH, Li CH. Beta-Endorphin: structure-activity relationships in the guinea pig ileum and opiate receptor binding assays. *Biochem Biophys Res Commun*. 1977; 74(2):656–62. [PubMed: 189770]
54. Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L. Dynorphin-(1–13), an extraordinarily potent opioid peptide. *Proc Natl Acad Sci USA*. 1979; 76(12):6666–70. [PubMed: 230519]
55. Mollereau C, Parmentier M, Mailleux P, et al. ORL1, a novel member of the opioid receptor family: cloning, functional expression and localization. *FEBS Lett*. 1994; 341(1):33–8. [PubMed: 8137918]
56. Meunier JC, Mollereau C, Toll L, et al. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. *Nature*. 1995; 377(6549):532–5. [PubMed: 7566152]
57. Reinscheid RK, Nothacker HP, Bourson A, et al. Orphanin FQ: a neuropeptide that activates an opioid like G protein-coupled receptor. *Science*. 1995; 270(5237):792–4. [PubMed: 7481766]
58. Zadina JE, Hackler L, Ge L-J, Kastin AJ. A potent and selective endogenous agonist for the mu-opiate receptor. *Nature*. 1997; 386(6624):499–502. [PubMed: 9087409]
59. Hackler L, Zadina JE, Ge L-J, Kastin AJ. Isolation of relatively large amounts of endomorphin-1 and endomorphin-2 from human brain cortex. *Peptides*. 1997; 18(10):1635–9. [PubMed: 9437727]
60. Höllt V. Precursors of opioid peptides and their gene regulation. *Clin Neuropharmacol*. 1992; 15(Suppl 1 Pt A):50A–1A. [PubMed: 1576598]
61. Li CH, Chung D. Primary structure of human β -lipotropin. *Nature*. 1976; 260(5552):622–4. [PubMed: 1264228]
62. Comb M, Seeburg PH, Adelman J, Eiden L, Herbert E. Primary structure of the human met- and leu-enkephalin precursor and its mRNA. *Nature*. 1982; 295(5851):663–6. [PubMed: 7057924]
63. Barr JM, Van Stipdonk MJ. Multi-stage tandem mass spectrometry of metal cationized leucine enkephalin and leucine enkephalin amide. *Rapid Commun Mass Spectrom*. 2002; 16(6):566–78. [PubMed: 11870894]

64. Martin WR. Pharmacology of opioids. *Pharmacol Rev.* 1983; 35(4):283–323. [PubMed: 6144112]
65. Paterson SJ, Robson LE, Kosterlitz HW. Classification of opioid receptors. *Br Med Bull.* 1983; 39(1):31–6. [PubMed: 6301606]
66. Zöllner C, Schäfer M. Opioids in anesthesia. *Anaesthesist.* 2008; 57(7):729–40. [PubMed: 18685878]
67. Zöllner C, Stein C. Opioids. *Handb Exp Pharmacol.* 2007; 177:31–63. [PubMed: 17087119]
68. Mansour A, Fox CA, Akil H, Watson SJ. Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. *Trends Neurosci.* 1995; 18(1):22–9. [PubMed: 7535487]
69. Vogt BA, Wiley RG, Jensen EL. Localization of mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of mu regulation. *Exp Neurol.* 1995; 135(2):83–92. [PubMed: 7589327]
70. Xia Y, Haddad GG. Ontogeny and distribution of opioid receptors in the rat brainstem. *Brain Res.* 1991; 549(2):181–93. [PubMed: 1653081]
71. Xia Y, Haddad GG. Major difference in the expression of delta- and mu-opioid receptors between turtle and rat brain. *J Comp Neurol.* 2001; 436(2):202–10. [PubMed: 11438924]
72. Abbadie C, Pan YX, Pasternak GW. Immunohistochemical study of the expression of exon11-containing mu opioid receptor variants in mouse brain. *Neuroscience.* 2004; 127(2):419–30. [PubMed: 15262332]
73. Beadles-Bohling AS, Wiren KM. Alteration of kappa-opioid receptor system expression in distinct brain regions of a genetic model of enhanced ethanol withdrawal severity. *Brain Res.* 2005; 1046(1–2):77–89. [PubMed: 15869750]
74. Wittert G, Hope P, Pyle D. Tissue distribution of opioid receptor gene expression in the rat. *Biochem Biophys Res Commun.* 1996; 218(3):877–81. [PubMed: 8579608]
75. Villemagne PS, Dannals RF, Ravert HT, Frost JJ. PET imaging of human cardiac opioid receptors. *Eur J Nucl Med Mol Imaging.* 2002; 29(10):1385–8. [PubMed: 12271423]
76. Darland T, Heinricher MM, Grandy DK. Orphanin FQ/nociceptin: a role in pain and analgesia, but so much more. *Trends Neurosci.* 1998; 21(5):215–21. [PubMed: 9610886]
77. Meis S. Nociceptin/orphanin FQ: actions within the brain. *Neuroscientist.* 2003; 9(2):158–68. [PubMed: 12708619]
78. Heinricher MM. Nociceptin/orphanin FQ: pain, stress and neural circuits. *Life Sci.* 2005; 77(25):3127–32. [PubMed: 15985270]
79. Rizzi A, Nazzaro C, Marzola GG, et al. Endogenous nociceptin/orphanin FQ signalling produces opposite spinal antinociceptive and supraspinal pronociceptive effects in the mouse formalin test: pharmacological and genetic evidences. *Pain.* 2006; 124(1–2):100–8. [PubMed: 16697109]
80. Reiss D, Wichmann J, Tekeshima H, Kieffer BL, Ouagazzal AM. Effects of nociceptin/orphanin FQ receptor (NOP) agonist, Ro64-6198, on reactivity to acute pain in mice: comparison to morphine. *Eur J Pharmacol.* 2008; 579(1–3):141–8. [PubMed: 18031727]
81. Scoto GM, Aricò G, Ronsisvalle S, Parenti C. Blockade of the nociceptin/orphanin FQ/NOP receptor system in the rat ventrolateral periaqueductal gray potentiates DAMGO analgesia. *Peptides.* 2007; 28(7):1441–6. [PubMed: 17628212]
82. Chen Y, Somme C. Activation of the nociceptin opioid system in rat sensory neurons produces antinociceptive effects in inflammatory pain: involvement of inflammatory mediators. *J Neurosci Res.* 2007; 85(7):1478–88. [PubMed: 17387690]
83. Stevens CW, Brasel CM, Mohan S. Cloning and bioinformatics of amphibian mu, delta, kappa, and nociceptin opioid receptors expressed in brain tissue: evidence for opioid receptor divergence in mammals. *Neurosci Lett.* 2007; 419(3):189–94. [PubMed: 17452077]
84. Doggrell SA. Cardiovascular and renal effects of nociceptin/orphanin FQ: a new mediator to target? *Curr Opin Investig Drugs.* 2007; 8(9):742–9.
85. Zhang S, Yekkiral A, Tang Y, Portoghese PS. A bivalent ligand (KMN-21) antagonist for mu/kappa heterodimeric opioid receptors. *Bioorg Med Chem Lett.* 2009; 19(24):6978–80. [PubMed: 19892550]
86. Garzon J, Jen M, Sanchez-Blazquez P, Lee N. Dynorphin (1–13), a long-lasting inhibitor of opiate receptor binding *in vitro*. *Life Sci.* 1982; 31(16–17):1789–92. [PubMed: 6130441]

87. Demoliou-Mason CD, Barnard EA. Distinct subtypes of the opioid receptor with allosteric interactions in brain membranes. *J Neurochem.* 1986; 46(4):1118–28. [PubMed: 3005504]
88. Miaskowski C, Taiwo Y, Levine J. Kappa- and delta-opioid agonists synergize to produce potent analgesia. *Brain Res.* 1990; 509(1):165–8. [PubMed: 2155044]
89. Dawson-Basoa M, Gintzler AR. Gestational and ovarian sex steroid antinociception: synergy between spinal kappa and delta opioid systems. *Brain Res.* 1998; 794(1):61–7. [PubMed: 9630517]
90. Gackenheim SL, Suter TM, Pinter JE, et al. Localization of opioid receptor antagonist [3H]-LY255582 binding sites in mouse brain: comparison with the distribution of mu, delta and kappa binding sites. *Neuropeptides.* 2005; 39(6):559–67. [PubMed: 16289278]
91. Fujita Y, Tsuda Y, Li T, et al. Development of potent bifunctional endomorphin-2 analogues with mixed mu/delta-opioid agonist and delta-opioid antagonist properties. *J Med Chem.* 2004; 47(14):3591–9. [PubMed: 15214786]
92. Balboni G, Onnis V, Cenzo C, et al. Effect of lysine at C-terminus of the Dmt-Tic opioid pharmacophore. *J Med Chem.* 2006; 49(18):5610–7. [PubMed: 16942034]
93. Traynor J. Trends. Subtypes of k-opioid receptor: fact or fiction? *Trends Pharmacol Sci.* 1989; 10(2):52–3. [PubMed: 2541524]
94. Traynor J, Elliot J. δ -opioid receptor subtypes and cross talk with μ -receptors. *Trends Pharmacol Sci.* 1993; 14(3):84–5. [PubMed: 8387705]
95. Borsodi A, Tóth G. Characterization of opioid receptor types and subtypes with new ligands. *Ann NY Acad Sci.* 1995; 757:339–52. [PubMed: 7611691]
96. Zaki PA, Bilskey EJ, Vanderah TW, Lai J, Evans CJ, Porreca F. Opioid receptor types and subtypes: the delta receptor as a model. *Annu Rev Pharmacol Toxicol.* 1996; 36:379–401. [PubMed: 8725395]
97. Wolozin BL, Pasternak GW. Classification of multiple morphine and enkephalin binding sites in the central nervous system. *Proc Natl Acad Sci USA.* 1981; 78(10):6181–5. [PubMed: 6273857]
98. Clark JA, Liu L, Price M, Hersh B, Edelson M, Pasternak GW. Kappa opiate receptor multiplicity: evidence for two U50, 488-sensitive kappa 1 subtypes and a novel kappa 3 subtype. *J Pharmacol Exp Ther.* 1989; 251(2):461–8. [PubMed: 2553920]
99. Butelman ER, Ko MC, Sobczyk-Kojiro K, et al. Kappa-Opioid Receptor Binding Populations in Rhesus Monkey Brain: relationship to an Assay of Thermal Antinociception. *J Pharmacol Exp Ther.* 1998; 285(2):595–601. [PubMed: 9580603]
100. Caudle RM, Finegold AA, Mannes AJ, Tobias MD, Kenshalo DR, Iadarola MJ. Spinal kappa1 and kappa2 opioid binding sites in rats, guinea pigs, monkeys and humans. *Neuroreport.* 1998; 9(11):2523–5. [PubMed: 9721926]
101. Jiang Q, Takemori AE, Sultana M, et al. Differential antagonism of opioid delta antinociception by [D-Ala2,Leu5,Cys6]enkephalin and naltrindole 5'-isothiocyanate: evidence for delta receptor subtypes. *J Pharmacol Exp Ther.* 1991; 257(3):1069–75. [PubMed: 1646319]
102. Sofuoglu M, Portoghese PS, Takemori AE. Differential antagonism of delta opioid agonists by naltrindole and its benzofuran analog (NTB) in mice: evidence for delta opioid receptor subtypes. *J Pharmacol Exp Ther.* 1991; 257(2):676–80. [PubMed: 1851833]
103. Sofuoglu M, Portoghese PS, Takemori AE. 7-Benzylidenenaltrexone (BNTX): A selective δ 1 opioid receptor antagonist in the mouse spinal cord. *Life Sci.* 1993; 52(8):769–75. [PubMed: 8383271]
104. Mattia A, Vanderah T, Mosberg HI, Porreca F. Lack of antinociceptive cross-tolerance between [D-Pen2,D-Pen5]enkephalin and [D-Ala2]deltorphin II in mice: evidence for delta receptor subtypes. *J Pharmacol Exp Ther.* 1991; 258(2):583–7. [PubMed: 1650835]
105. Rothman RB, Bowen WD, Herkenham M, Jacobson AE, Rice KC, Pert CB. A quantitative study of [3H]D-Ala2-D-Leu5-enkephalin binding to rat brain membranes. Evidence that oxymorphone is a noncompetitive inhibitor of the lower affinity delta-binding site. *Mol Pharmacol.* 1985; 27(3):399–409. [PubMed: 2579319]
106. Rothman RB, Bowen WD, Bykov V, et al. Preparation of rat brain membranes greatly enriched with either type-I-delta or type-II-delta opiate binding sites using site directed alkylating agents: evidence for a two-site allosteric model. *Neuropeptides.* 1984; 4(3):201–15. [PubMed: 6087189]

107. Rothman RB, Bykov V, Jacobson AE, Rice KC, Long JE, Bowen WD. A study of the effect of the irreversible delta receptor antagonist [D-Ala²,Leu⁵,Cys⁶]-enkephalin on delta μ and delta κ opioid binding sites *in vitro* and *in vivo*. *Peptides*. 1992; 13(4):691–4. [PubMed: 1331996]
108. Giros B, Pohl M, Rochelle JM, Seldin MF. Chromosomal localization of opioid peptide and receptor genes in the mouse. *Life Sci*. 1995; 56(18):PL369–75. [PubMed: 7752808]
109. Liang Y, Mestek A, Yu L, Carr LG. Cloning and characterization of the promoter region of the mouse μ opioid receptor gene. *Brain Res*. 1995; 679(1):82–88. [PubMed: 7648268]
110. Jordan BA, Cvejic S, Devi LA. Opioids and their Complicated Receptor Complexes. *Neuropsychopharmacology*. 2000; 23(4 Suppl):S5–18. [PubMed: 11008063]
111. Evans CJ, Keith DE, Morrison H, Magendzo K, Edwards RH. Cloning of a delta opioid receptor by functional expression. *Science*. 1992; 258(5090):1952–5. [PubMed: 1335167]
112. Kieffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG. The delta-opioid receptor: isolation of a cDNA clone by expression cloning and pharmacological characterization. *Proc Natl Acad Sci USA*. 1992; 89(24):12048–52. [PubMed: 1334555]
113. Augustin LB, Felsheim RF, Min BH, Fuchs SM, Fuchs JA, Loh HH. Genomic structure of the mouse delta opioid receptor gene. *Biochem Biophys Res Commun*. 1995; 207(1):111–9. [PubMed: 7857252]
114. Chen Y, Mestek A, Liu J, Yu L. Molecular cloning of a rat κ -opioid receptor reveals sequence similarities to the μ and δ opioid receptors. *Biochem J*. 1993; 295(pt3):625–8. [PubMed: 8240267]
115. Abood ME, Noel MA, Farnsworth JS, Tao Q. Molecular cloning and expression of a delta-opioid receptor from rat brain. *J Neurosci Res*. 1994; 37(6):714–9. [PubMed: 7519274]
116. Simonin F, Befort K, Gaveriaux-Ruff C, et al. The human delta-opioid receptor: Genomic organization, cDNA cloning, functional expression, and distribution in human brain. *Mol Pharmacol*. 1994; 46(6):1015–21. [PubMed: 7808419]
117. Pan L, Xu J, Yu R, Xu MM, Pan YX, Pasternak GW. Identification and characterization of six new alternatively spliced variants of the human μ opioid receptor gene. *Neuroscience*. 2005; 133(1):209–20. [PubMed: 15893644]
118. Pasternak GW. Molecular biology of opioid analgesia. *J Pain Symptom Manage*. 2005; 29(5 Suppl):S2–S9. [PubMed: 15907642]
119. Shimohigashi Y, Takano, Kamiya H, Costa T, Herz A, Stammer CH. A highly selective ligand for brain delta opiate receptors, a cyclopropyl(E)Phe(4)-enkephalin analog, suppresses μ receptor-mediated thermal analgesia by morphine. *FEBS Lett*. 1988; 233 (2):289–93. [PubMed: 2838332]
120. Jin W, Lee NM, Loh HH, Thayer SA. Dual excitatory and inhibitory effects of opioids on intracellular calcium in neuroblastoma x glioma hybrid NG108-15 cells. *Mol Pharmacol*. 1992; 42(6):1083–9. [PubMed: 1336113]
121. Wang JF, Shun XJ, Yang HF, Ren MF, Han JS. Suppression by [D-Pen², D-Pen⁵] enkephalin on cyclic AMP dependent protein kinase-induced, but not protein kinase C-induced increment of intracellular free calcium in NG108-15 cells. *Life Sci*. 1993; 52(19):1519–25. [PubMed: 8387139]
122. Vlaskovska M, Schramm M, Nylander I, et al. Opioid effects on $^{45}\text{Ca}^{2+}$ uptake and glutamate release in rat cerebral cortex in primary culture. *J Neurochem*. 1997; 68(2):571–24.
123. Thorlin T, Eriksson PS, Persson PAI, Aberg ND, Hansson E, Rönnbäck L. Delta-opioid receptors on astroglial cells in primary culture: mobilization of intracellular free calcium via a pertussis sensitive G protein. *Neuropharmacology*. 1998; 37(3):299–311. [PubMed: 9681928]
124. Spadoni F, Martella G, Martorana A, et al. Opioid-mediated modulation of calcium currents in striatal and pallidal neurons following reserpine treatment: focus on κ response. *Synapse*. 2004; 51(3):194–205. [PubMed: 14666517]
125. Komai H, McDowell TS. Effects of local anesthetics on opioid inhibition of calcium current in rat dorsal root ganglion neurons. *Neurosci Lett*. 2007; 418(3):298–303. [PubMed: 17412500]
126. Rola R, Jarkiewicz M, Szulczyk P. Modulation of Ca^{2+} channel current by μ opioid receptors in prefrontal cortex pyramidal neurons in rats. *Acta Neurobiol Exp*. 2008; 68(1):10–25.

127. Iegorova O, Fisyunov A, Krishtal O. G-protein-independent modulation of P-type calcium channels by mu-opioids in Purkinje neurons of rat. *Neurosci Lett*. 2010; 480(2):106–11. [PubMed: 20541588]
128. Bao L, Jin SX, Zhang C, et al. Activation of delta opioid receptors induces receptor insertion and neuropeptide secretion. *Neuron*. 2003; 37(1):121–33. [PubMed: 12526778]
129. Samways DSK, Henderson G. Opioid elevation of intracellular free calcium: possible mechanisms and physiological relevance. *Cell Signal*. 2006; 18(2):151–61. [PubMed: 16199136]
130. Chao D, Qian H, Ghassemi F, Chen JS, Xia Y. Transgenic over-expression of δ -opioid receptors protects the cortex from anoxic disruption of ionic homeostasis. *Soc Neurosci Abstract Program*. 2006; (87):19/MM68.
131. Chao D, Bazy-Asaad A, Balboni G, Xia Y. δ -, but not μ -, opioid receptor stabilizes K⁺ homeostasis by reducing Ca²⁺ influx in the cortex during acute hypoxia. *J Cell Physiol*. 2007a; 212(1):60–7. [PubMed: 17373650]
132. Chao D, Donnelly DF, Feng Y, Bazy-Asaad A, Xia Y. Cortical δ -opioid receptors potentiate K⁺ homeostasis during anoxia and oxygen–glucose deprivation. *J Cereb Blood Flow Metab*. 2007b; 27(2):356–68. [PubMed: 16773140]
133. Chao D, Bazy-Asaad A, Balboni G, Salvadori S, Xia Y. Activation of DOR attenuates anoxic K⁺ derangement via inhibition of Na⁺ entry in mouse cortex. *Cereb Cortex*. 2008; 18(9):2217–27. [PubMed: 18203692]
134. Chao D, Balboni G, Lazarus LH, Salvadori S, Xia Y. Na⁺ mechanism of δ -opioid receptor induced protection from anoxic K⁺ leakage in the cortex. *Cell Mol Life Sci*. 2009; 66(6):1105–15. [PubMed: 19189047]
135. Kang X, Chao D, Gu Q, et al. δ -opioid receptors protect from anoxic disruption of Na⁺ homeostasis via Na⁺ channel regulation. *Cell Mo Life Sci*. 2009; 66(21):3505–16.
136. Balboni G, Salvadori S, Guerrini R, et al. Potent delta-opioid agonists containing the Dmt-Tic pharmacophore. *J Med Chem*. 2002; 45(25):5556–63. [PubMed: 12459023]
137. Malendowicz LK, Rebuffat P, Tortorella C, Nussdorfer GG, Ziolkowska A, Hochol A. Effects of met-enkephalin on cell proliferation in different models of adrenocortical-cell growth. *Int J Mol Med*. 2005; 15(5):841–5. [PubMed: 15806307]
138. Narita M, Kuzumaki N, Miyatake M, et al. Role of delta-opioid receptor function in neurogenesis and neuroprotection. *J Neurochem*. 2006; 97(5):1494–505. [PubMed: 16696856]
139. Donahue RN, McLaughlin PJ, Zagon IS. Cell proliferation of human ovarian cancer is regulated by the opioid growth factor-opioid growth factor receptor axis. *Am J Physiol Regul Integr Comp Physiol*. 2009; 296(6):R1716–25. [PubMed: 19297547]
140. Avella DM, Kimchi ET, Donahue RN, et al. The opioid growth factor-opioid growth factor receptor axis regulates cell proliferation of human hepatocellular cancer. *Am J Physiol Regul Integr Comp Physiol*. 2010; 298(2):R459–66. [PubMed: 19923357]
141. Hayward NJ, McKnight AT, Woodruff GN. Neuroprotective effect of the kappa-agonist enadoline (CI-977) in rat models of focal cerebral ischaemia. *Eur J Neurosci*. 1993; 5(7):961–7.
142. Summers RL, Li Z, Hildebrandt D. Effect of a delta receptor agonist on duration of survival during hemorrhagic shock. *Acad Emerg Med*. 2003; 10(6):587–93. [PubMed: 12782517]
143. Yang L, Wang H, Shah K, Karamyan VT, Abbruscato TJ. Opioid receptor agonists reduce brain edema in stroke. *Brain Res*. 2011; 1383:307–16. [PubMed: 21281614]
144. Chen CJ, Cheng FC, Liao SL, Chen WY, Lin NN, Kuo JS. Effects of naloxone on lactate, pyruvate metabolism and antioxidant enzyme activity in rat cerebral ischemia/reperfusion. *Neurosci Lett*. 2000; 287(2):113–6. [PubMed: 10854725]
145. Chen CJ, Liao SL, Chen WY, Hong JS, Kuo JS. Cerebral ischemia/reperfusion injury in rat brain: effects of naloxone. *Neuroreport*. 2001; 12(6):1245–9.
146. Tian XS, Zhou F, Yang R, Xia Y, Wu GC, Guo JC. Electroacupuncture protects the brain against acute ischemic injury via up-regulation of delta-opioid receptor in rats. *J Chin Integr Med*. 2008b; 6(6):632–8.
147. Tian XS, Zhou F, Yang R, Xia Y, Wu GC, Guo JC. Role of δ -opioid receptors in cumulative electro-acupuncture induced protection from ischemic injury in the rat brain. *Shanghai J TCM*. 2008; 42:71–4.

148. Bruce DS, Bailey EC, Setran DP, et al. Circannual variations in bear plasma albumin and its opioid-like effects on guinea pig ileum. *Pharmacol Biochem Behav.* 1996; 53(4):885–9. [PubMed: 8801593]
149. Bourhim N, Kabine M, Elkebbaj MS. Characterization of opioid peptides and opioid receptors in the brain of jerboa (*Jaculus orientalis*), a hibernating rodent. *Brain Res Bull.* 1997; 44(5):615–20. [PubMed: 9365806]
150. Peart JN, Gross ER, Gross GJ. Opioid-induced preconditioning: recent advances and future perspectives. *Vascul Pharmacol.* 2005; 42(5–6):211–8. [PubMed: 15922254]
151. Wu T, Dong P, Chen C, Yang J, Hou X. The myocardial protection of polarizing cardioplegia combined with delta-opioid receptor agonist in swine. *Ann Thorac Surg.* 2011; 91(6):1914–20. [PubMed: 21619990]
152. Cui Y, Lee TF, Wang LC. State-dependent changes of brain endogenous opioids in mammalian hibernation. *Brain Res Bull.* 1996; 40(2):129–33. [PubMed: 8724431]
153. Ye ZC, Cai YP. Changes of opioid contents in brain and plasma through the hibernation bout cycle of ground squirrels. *Acta Physiol Sinica.* 1995; 47(6):610–4. [PubMed: 8762454]
154. Nurnberger F, Lee TF, Jourdan ML, Wang LC. Seasonal changes in methionine-enkephalin immunoreactivity in the brain of a hibernator, *Spermophilus columbianus*. *Brain Res.* 1991; 547(1):115–21. [PubMed: 1860064]
155. Yu LC, Cai YP. Arousal following intra-preoptic area administration of naltrexone, ICI 174864 or nor-BNI in hibernating ground squirrels. *Behav Brain Res.* 1993; 57(1):31–5. [PubMed: 8292252]
156. Kieffer BL, Gavériaux-Ruff C. Exploring the opioid system by gene knockout. *Prog Neurobiol.* 2002; 66(5):285–306. [PubMed: 12015197]
157. Eisinger DA, Schulz R. Mechanism and consequences of delta-opioid receptor internalization. *Crit Rev Neurobiol.* 2005; 17(1):1–26. [PubMed: 16307525]
158. Hanlon KE, Herman DS, Agnes RS, et al. Novel peptide ligands with dual acting pharmacophores designed for the pathophysiology of neuropathic pain. *Brain Res.* 2011; 1395:1–11. [PubMed: 21550594]
159. Molina PE. Stress-specific opioid modulation of haemodynamic counter-regulation. *Clin Exp Pharmacol Physiol.* 2002; 29(3):248–53. [PubMed: 11906493]
160. Troullos E, Hargreaves KM, Dionne RA. Ibuprofen elevates immunoreactive beta-endorphin levels in humans during surgical stress. *Clin Pharmacol Ther.* 1997; 62(1):74–81. [PubMed: 9246021]
161. Kho HG, Kloppenborg PW, van Egmond J. Effects of acupuncture and transcutaneous stimulation analgesia on plasma hormone levels during and after major abdominal surgery. *Eur J Anaesthesiol.* 1993; 10(3):197–208. [PubMed: 8388332]
162. Ozarda Ilcol Y, Ozyurt G, Kilicturgay S, Uncu G, Ulus IH. The decline in serum choline concentration in humans during and after surgery is associated with the elevation of cortisol, adrenocorticotrophic hormone, prolactin and beta-endorphin concentrations. *Neurosci Lett.* 2002; 324(1):41–4. [PubMed: 11983290]
163. Yamada K, Nabeshima T. Stress-induced behavioral responses and multiple opioid systems in the brain. *Behav Brain Res.* 1995; 67(2):133–45. [PubMed: 7779288]
164. LaBuda CJ, Sora I, Uhl GR, Fuchs PN. Stress-induced analgesia in mu-opioid receptor knockout mice reveals normal function of the delta-opioid receptor system. *Brain Res.* 2000; 869(1–2):1–5. [PubMed: 10865052]
165. Gavériaux-Ruff C, Kieffer BL. Opioid receptor genes inactivated in mice: the highlights. *Neuropeptides.* 2002; 36(2–3):62–71. [PubMed: 12359497]
166. Matthes HW, Maldonado R, Simonin F, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature.* 1996; 383(6603):819–23. [PubMed: 8893006]
167. Yamada H, Shimoyama N, Sora I, et al. Morphine can produce analgesia via spinal kappa opioid receptors in the absence of mu opioid receptors. *Brain Res.* 2006; 1083(1):61–9. [PubMed: 16530171]

168. Frisstad I, Berggreen E, Haug SR. Delta opioid receptors in small and medium-sized trigeminal neurons supporting the dental pulp of rats. *Arch Oral Biol*. 2006; 51(4):273–81. [PubMed: 16266688]
169. Patwardhan AM, Berg KA, Akopain AN, et al. Bradykinin-Induced functional competence and trafficking of the δ -opioid receptor in trigeminal nociceptors. *J Neurosci*. 2005; 25(39):8825–32. [PubMed: 16192372]
170. Zhu Y, King MA, Schuller AGP, et al. Retention of supraspinal delta-like analgesia and loss of morphine tolerance in delta opioid receptor knockout mice. *Neuron*. 1999; 24(1):243–52. [PubMed: 10677041]
171. Scherrer G, Imamachi N, Cao YQ, et al. Dissociation of the opioid receptor mechanisms that control mechanical and heat pain. *Cell*. 2009; 137(6):1148–59. [PubMed: 19524516]
172. Wang GY, Wu S, Pei JM, Yu XC, Wong TM. Kappa- but not delta-opioid receptors mediate effects of ischemic preconditioning on both infarct and arrhythmia in rats. *Am J Physiol Heart Circ Physiol*. 2001; 280(1):H384–91. [PubMed: 11123255]
173. Gebhart GF, JJ. Bonica lecture-2000: Physiology, pathophysiology, and pharmacology of visceral pain. *Reg Anesth Pain Med*. 2000; 25(6):632–8. [PubMed: 11097673]
174. Bohn LM, Lefkowitz RJ, Gainetdinov RR, Peppel K, Caron MG, Lin FT. Enhanced morphine analgesia in mice lacking beta-arrestin 2. *Science*. 1999; 286(5449):2495–8. [PubMed: 10617462]
175. Bohn LM, Gainetdinov RR, Lin FT, Lefkowitz RJ, Caron MG. Mu-opioid receptor desensitization by beta-arrestin-2 determines morphine tolerance but not dependence. *Nature*. 2000; 408(6813):720–3. [PubMed: 11130073]
176. Bohn LM, Lefkowitz RJ, Caron MGJ. Differential mechanisms of morphine antinociceptive tolerance revealed in (beta) arrestin-2 knock-out mice. *J Neurosci Neurosci*. 2002; 22(23):10494–500.
177. Bohn LM, Gainetdinov RR, Sotnikova TD, et al. Enhanced rewarding properties of morphine, but not cocaine, in beta (arrestin)-2 knock-out mice. *J Neurosci*. 2003; 23(32):10265–73. [PubMed: 14614085]
178. Cen B, Yu Q, Guo J, et al. Direct binding of beta-arrestins to two distinct intracellular domains of the delta opioid receptor. *J Neurochem*. 2001; 76(6):1887–94. [PubMed: 11259507]
179. Xiang B, Yu GH, Guo J, et al. Heterologous activation of protein kinase C stimulates phosphorylation of delta-opioid receptor at serine 344, resulting in beta-arrestin- and clathrin-mediated receptor internalization. *J Biol Chem*. 2001; 276(7):4709–16. [PubMed: 11085981]
180. Kang J, Shi Y, Xiang B, et al. A nuclear function of beta-arrestin1 in GPCR signaling: regulation of histone acetylation and gene transcription. *Cell*. 2005; 123(5):833–47. [PubMed: 16325578]
181. Zhang X, Wang F, Chen X, et al. Beta-arrestin1 and beta-arrestin2 are differentially required for phosphorylation-dependent and -independent internalization of delta-opioid receptors. *J Neurochem*. 2005; 95(1):169–78. [PubMed: 16181421]
182. Cunha-Oliveira T, Rego AC, Oliveira CR. Cellular and molecular mechanisms involved in the neurotoxicity of opioid and psychostimulant drugs. *Brain Res Rev*. 2008; 58(1):192–208. [PubMed: 18440072]
183. LaLumiere RT, Kalivas PW. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *J Neurosci*. 2008; 28(12):3170–7. [PubMed: 18354020]
184. Birnbaum HG, White AG, Reynolds JL, et al. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clin J Pain*. 2006; 22(8):667–76. [PubMed: 16988561]
185. Karow A, Verthein U, Krausz M, Schafer I. Association of personality disorders, family conflicts and treatment with quality of life in opiate addiction. *Eur Addict Res*. 2008; 14(1):38–46. [PubMed: 18182771]
186. Ivanov IS, Schulz KP, Palmero RC, Newcorn JH. Neurobiology and evidence-based biological treatments for substance abuse disorders. *CNS Spectr*. 2006; 11(11):864–77. [PubMed: 17075558]
187. Koch T, Höllt V. Role of receptor internalization in opioid tolerance and dependence. *Pharmacol Ther*. 2008; 117(2):199–206. [PubMed: 18076994]

188. Christie MJ. Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. *Br J Pharmacol.* 2008; 154(2):384–96. [PubMed: 18414400]
189. Przewlocki R. Opioid abuse and brain gene expression. *Eur J Pharmacol.* 2004; 500(1–3):331–49. [PubMed: 15464044]
190. Harrison LM, Kastin AJ, Zadina JE. Opiate tolerance and dependence: receptors, G-proteins, and antiopiates. *Peptides.* 1998; 19(9):1603–30. [PubMed: 9864069]
191. Kreek MJ, Nielsen DA, LaForge KS. Genes associated with addiction: alcoholism, opiate, and cocaine addiction. *Neuromolecular Med.* 2004; 5(1):85–108. [PubMed: 15001815]
192. Mayer P, Höllt V. Pharmacogenetics of opioid receptors and addiction. *Pharmacogenet Genomics.* 2006; 16(1):1–7. [PubMed: 16344716]
193. Iskandar SB, Abi-Saleh BS, Mechleb BK, Fahrig SA. Methadone and torsade de pointes: case report and review of the literature. *Tenn Med.* 2007; 100(2):35–7. [PubMed: 17378505]
194. Compton WM, Volkow ND. Abuse of prescription drugs and the risk of addiction. *Drug Alcohol Depend.* 2006; 83(Suppl 1):S4–7. [PubMed: 16563663]
195. Quaglio GL, Lugoboni F, Pajusco B, et al. GICS. Hepatitis C virus infection: prevalence, predictor variables and prevention opportunities among drug users in Italy. *J Viral Hepat.* 2003; 10(5):394–400. [PubMed: 12969192]
196. Ordaz-Sanchez I, Weber RJ, Rice KC, et al. Chemotaxis of human and rat leukocytes by the delta-selective non-peptidic opioid SNC 80. *Rev Latinoam Microbiol.* 2003; 45(1–2):16–23. [PubMed: 17061517]
197. Korolenko TA, Goncharova IA, Anterejkina LI, Levina OA, Korolenko CP. Influence of opiate addiction on liver cell damage of patients with viral hepatitis C. *Alaska Med.* 2007; 49(2 Suppl): 75–8. [PubMed: 17929611]
198. Filliol D, Ghozland S, Chluba J, et al. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. *Nat Genet.* 2000; 25(2):195–200. [PubMed: 10835636]
199. Saitoh A, Yoshikawa Y, Onodera K, Kamei J. Role of delta-opioid receptor subtypes in anxiety-related behaviors in the elevated plus-maze in rats. *Psychopharmacology (Berl).* 2005; 182(3): 327–34. [PubMed: 16075288]
200. Torregrossa MM, Jutkiewicz EM, Mosberg HI, Balboni G, Watson SJ, Woods JH. Peptidic delta opioid receptor agonists produce antidepressant-like effects in the forced swim test and regulate BDNF mRNA expression in rats. *Brain Res.* 2006; 1069(1):172–81. [PubMed: 16364263]
201. Naidu PS, Lichtman AH, Archer CC, May EL, Harris LS, Aceto MD. NIH 11082 produces antidepressant-like activity in the mouse tail-suspension test through a delta-opioid receptor mechanism of action. *Eur J Pharmacol.* 2007; 566(1–3):132–6. [PubMed: 17459369]
202. Zhang H, Shi YG, Woods JH, Watson SJ, Ko MC. Central kappa-opioid receptor-mediated antidepressant-like effects of nor-Binaltorphimine: behavioral and BDNF mRNA expression studies. *Eur J Pharmacol.* 2007; 570(1–3):89–96. [PubMed: 17601558]
203. Zubieta J-K, Ketter TA, Bueller JA, et al. Regulation of human affective responses by anterior cingulate and limbic μ -opioid neurotransmission. *Arch Gen Psychiatry.* 2003; 60(11):1145–53. [PubMed: 14609890]
204. Taracha E, Mierzejewski P, Lehner M, et al. Stress-opioid interactions: a comparison of morphine and methadone. *Pharmacol Rep.* 2009; 61(3):424–35. [PubMed: 19605941]
205. Vien N, Gleason CA, Hays SL, McPherson RJ, Chavkin C, Juul SE. Effects of neonatal stress and morphine on kappa opioid receptor signaling. *Neonatology.* 2009; 96(4):235–43. [PubMed: 19478529]
206. Pinsky C, Bose R, Frederickson RC. Mu- and delta-opioid modulation of electrically-induced epileptic seizures in mice. *NIDA Res Monogr.* 1986; 75:543–6. [PubMed: 2829000]
207. Tortella FC, Robles L, Holaday JW. The anticonvulsant effects of DADLE are primarily mediated by activation of delta opioid receptors: interactions between delta and mu receptor antagonists. *Life Sci.* 1985; 37(6):497–503. [PubMed: 2991684]
208. Tortella FC, Echevarria E, Robles L, Mosberg HI, Holaday JW. Anticonvulsant effects of mu (DAGO) and delta (DPDPE) enkephalins in rats. *Peptides.* 1988; 9(5):1177–81. [PubMed: 2854247]

209. Tortella FC, Long JB. Endogenous anticonvulsant substance in rat cerebrospinal fluid after a generalized seizure. *Science*. 1985; 228(4703):1106–8. [PubMed: 2986292]
210. Grecksch G, Becker A, Schroeder H, Höllt V. Involvement of delta-opioid receptors in pentylenetetrazol kindling development and kindling-related processes in rats. *Naunyn Schmiedebergs Arch Pharmacol*. 1999; 360(2):151–6. [PubMed: 10494884]
211. Yajima Y, Narita M, Takahashi-Nakano Y, et al. Effects of differential modulation of mu-, delta- and kappa-opioid systems on bicuculline- induced convulsions in the mouse. *Brain Res*. 2000; 862(1–2):120–6. [PubMed: 10799676]
212. Bregola G, Zucchini S, Frigati L, et al. Involvement of the neuropeptide orphanin FQ/nociceptin in kainate and kindling seizures and epileptogenesis. *Epilepsia*. 2002; 43(Suppl 5):18–9. [PubMed: 12121289]
213. Feng Y, Chao DM, Li WM, Cao YX, Wang YQ, Wu GC. Inhibition of nociceptin/orphanin FQ on penicillin-induced seizures in rats. *Brain Res*. 2004; 1020(1–2):214–9. [PubMed: 15312806]
214. Bausch B, Garland JP, Yamada J. The delta opioid receptor agonist, SNC80, has complex, dose-dependent effects on pilocarpine-induced seizures in Sprague-Dawley rats. *Brain Res*. 2005; 1045(1–2):38–44. [PubMed: 15910761]
215. Danielsson I, Gasior M, Stevenson GW, Folk JE, Rice KC, Negus SS. Electroencephalographic and convulsant effects of the delta opioid agonist SNC80 in rhesus monkeys. *Pharmacol Biochem Behav*. 2006; 85(2):428–34. [PubMed: 17112570]
216. Solbrig MV, Adrian R, Baratta J, Lauterborn JC, Koob GF. Kappa opioid control of seizures produced by a virus in an animal model. *Brain*. 2006; 129(pt3):642–54. [PubMed: 16399805]
217. Saboori E, Derchansky M, Ismaili M, et al. Mechanisms of morphine enhancement of spontaneous seizure activity. *Anest Analg*. 2007; 105(6):1729–35.
218. Zhang HN, Ko MC. Seizure activity involved in the up-regulation of BDNF mRNA expression by activation of central mu opioid receptors. *Neuroscience*. 2009; 161(1):301–10. [PubMed: 19303919]
219. Schwarzer S. 30 Years of Dynorphins—new insights on their functions in neuropsychiatric diseases. *Pharmacol Ther*. 2009; 123(3):353–70. [PubMed: 19481570]
220. Rubaj A, Gustaw K, Zgodziński W, Kleinrok Z, Sieklucka-Dziuba M. The role of opioid receptors in hypoxic preconditioning against seizures in brain. *Pharmacol Biochem Behav*. 2000; 67(1):65–70. [PubMed: 11113485]
221. Madar I, Lesser RP, Krauss G, et al. Imaging of delta- and mu-opioid receptors in temporal lobe epilepsy by positron emission tomography. *Ann Neurol*. 1997; 41(3):358–67. [PubMed: 9066357]
222. Hammers A, Asselin M, Hinz R, et al. Upregulation of opioid receptor binding following spontaneous epileptic seizures. *Brain*. 2007; 130(pt4):1009–16. [PubMed: 17301080]
223. Honar H, Riazi K, Homayoun H, et al. Ultra-low dose naltrexone potentiates the anticonvulsant effect of low dose morphine on clonic seizures. *Neuroscience*. 2004; 129(3):733–42. [PubMed: 15541894]
224. Negus SS, Gatch MB, Mello NK, Zhang X, Rice K. Behavioral effects of the delta-selective opioid agonist SNC80 and related compounds in rhesus monkeys. *J Pharmacol Exp Ther*. 1998; 286(1):362–75. [PubMed: 9655881]
225. Jutkiewicz EM, Baladi MG, Folk JE, Rice KC, Woods JH. The convulsive and electroencephalographic changes produced by nonpeptidic delta-opioid agonists in rats: comparison with pentylenetetrazol. *J Pharmacol Exp Ther*. 2006; 317(3):1337–48. [PubMed: 16537798]
226. Jutkiewicz EM, Rice KC, Traynor JR, Woods JH. Separation of the convulsions and antidepressant-like effects produced by the delta-opioid agonist SNC80 in rats. *Psychopharmacology (Berl)*. 2005; 182(4):588–96. [PubMed: 16163520]
227. Yamakawa K. Na⁺ channel gene mutations in epilepsy--the functional consequences. *Epilepsy Res*. 2006; 70:S218–22. [PubMed: 16806834]
228. Xu R, Thomas EA, Jenkins M, et al. A childhood epilepsy mutation reveals a role for developmentally regulated splicing of a sodium channel. *Mol Cell Neurosci*. 2007; 35(2):292–301. [PubMed: 17467289]

229. Agrawal N, Alonso A, Ragsdale DS. Increased persistent sodium currents in rat entorhinal cortex layer V neurons in a post-status epilepticus model of temporal lobe epilepsy. *Epilepsia*. 2003; 44(12):1601–4. [PubMed: 14636336]
230. Xia Y, Zhao P, Xue J, et al. Na⁺ channel expression and neuronal function in the Na⁺/H⁺ exchanger 1 null mutant mouse. *J Neurophysiol*. 2003; 89(1):229–36. [PubMed: 12522174]
231. Zhao P, Ma MC, Qian H, Xia Y. Down-regulation of delta-opioid receptors in Na⁺/H⁺ exchanger 1 null mutant mouse brain with epilepsy. *Neurosci Res*. 2005; 53(4):442–6. [PubMed: 16297477]
232. Remy S, Urban BW, Elger CE, Beck H. Anticonvulsant pharmacology of voltage-gated Na⁺ channels in hippocampal neurons of control and chronically epileptic rats. *Eur J Neurosci*. 2003; 17(12):2648–58. [PubMed: 12823472]
233. Armijo JA, Shushtarian M, Valdizan EM, Cuadrado A, de las Cuevas I, Adín J. Ion channels and epilepsy. *Curr Pharm Des*. 2005; 11(15):1975–2003. [PubMed: 15974971]
234. Sheng WS, Hu S, Gekker G, Zhu S, Peterson PK, Chao CC. Immunomodulatory role of opioids in the central nervous system. *Arch Immunol Ther Exp (Warsz)*. 1997; 45(5–6):359–66. [PubMed: 9437491]
235. Welters ID. Is immunomodulation by opioid drugs of clinical relevance? *Curr Opin Anaesthesiol*. 2003; 16(5):509–13. [PubMed: 17021504]
236. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. *Am J Ther*. 2004; 11(5):354–65. [PubMed: 15356431]
237. Cheĭdo MA, Idoval GV. Role of serotonin receptors in the delta-opioid immunosuppression. *Russ Fiziol Zh Im I M Sechenova*. 2010; 96(12):1234–40. [PubMed: 21473110]
238. Eisenstein TK, Rahim RT, Feng P, Thingalaya N, Meissler JJ. Effects of opioid tolerance and withdrawal on the immune system. *J Neuroimmune Pharmacol*. 2006; 1(3):237–49. [PubMed: 18040801]
239. Zou W, Guo Q, Wang E, Cai J, Cheng Z. Intrathecal morphine suppresses immune function in rats with inflammatory-induced pain. *J Int Med Res*. 2007; 35(5):626–36. [PubMed: 17900402]
240. Jamali A, Bamdad T, Soleimanjahi H, Pakdel FG, Arefian E. Acute morphine administration reduces white blood cells' capability to induce innate resistance against HSV-1 infection in BALB/c mice. *Neuroimmunomodulation*. 2007; 14(1):16–23. [PubMed: 17700036]
241. Carr D, Gebhart B, Paul D. Alpha adrenergic and mu-2 opioid receptors are involved in morphine-induced suppression of splenocyte natural killer activity. *J Pharmacol Exp Ther*. 1993; 264(3):1179–86. [PubMed: 8383741]
242. Welters ID, Menzebach A, Goumon Y, et al. Morphine suppresses complement receptor expression, phagocytosis, and respiratory burst in neutrophils by a nitric oxide and mu(3) opiate receptor-dependent mechanism. *J Neuroimmunol*. 2000; 111(1–2):139–45. [PubMed: 11063831]
243. Grimm MC, Ben-Baruch A, Taub DD, et al. Opiates transdeactivate chemokine receptors: delta and mu opiate-receptor mediated heterologous desensitization. *J Exp Med*. 1998; 188(2):317–25. [PubMed: 9670044]
244. Menzebach A, Hirsch J, Nost R, Mogk M, Hempelmann G, Welters ID. Morphine inhibits complement receptor expression, phagocytosis and oxidative burst by a nitric oxide dependent mechanism. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2004; 39(4):204–11. [PubMed: 15098168]
245. Bai HB, Du JZ, Zheng XX. Beta-endorphin involved in the regulation of humoral immune function of rats during acute hypoxia. *Acta Physiol Sinica*. 1999; 51(3):258–62. [PubMed: 11498986]
246. Parkhill AL, Bidlack JM. Reduction of lipopolysaccharide-induced interleukin-6 production by the kappa opioid U50, 488 in a mouse monocyte-like cell line. *Int Immunopharmacol*. 2006; 6(6):1013–9. [PubMed: 16644488]
247. Mahajan SD, Schwart SA, Aalinkeel R, Chawda RP, Sykes DE, Nair MP. Morphine modulates chemokine gene regulation in normal human astrocytes. *Clin Immunol*. 2005; 115(3):323–32. [PubMed: 15893700]
248. Pello OM, Duthey B, García-Bernal D, et al. Opioids trigger α5-β1 integrin-mediated monocyte adhesion. *J Immunol*. 2006; 176(3):1675–85. [PubMed: 16424197]

249. Finley MJ, Happel CM, Kaminsky DE, Rogers TJ. Opioid and nociceptin receptors regulate cytokine and cytokine receptor expression. *Cell Immunol.* 2008; 252(1–2):146–54. [PubMed: 18279847]
250. McCarthy L, Wetzel M, Sliker JK, Eisenstein TK, Rogers TJ. Opioids, opioid receptors, and the immune response. *Drug Alcohol Depend.* 2001; 62(2):111–23. [PubMed: 11245967]
251. Sharp BM, Keane WF, Suh HJ, Gekker G, Tsukayama D, Peterson PK. Opioid peptides rapidly stimulate superoxide production by human polymorphonuclear leukocytes and macrophages. *Endocrinol.* 1985; 117(2):793–5.
252. Chao CC, Hu S, Molitor TW, et al. Morphine potentiates transforming growth factor-beta release from human peripheral blood mononuclear cell cultures. *J Pharmacol Exp Ther.* 1992; 262(1):19–24. [PubMed: 1625199]
253. Szabo I, Rojavin M, Bussiere JL, Eisenstein TK, Adler MW, Rogers TJ. Suppression of peritoneal macrophage phagocytosis of *Candida albicans* by opioids. *J Pharmacol Exp Ther.* 1993; 267(2):703–6. [PubMed: 8246144]
254. Roy S, Cain KJ, Chapin RB, Charboneau RG, Barke RA. Morphine modulates NF kappa B activation in macrophages. *Biochem Biophys Res Commun.* 1998; 245(2):392–6.
255. Greeneltch KM, Haudenschild CC, Keegan AD, Shi Y. The opioid antagonist naltrexone blocks acute endotoxic shock by inhibiting tumor necrosis factor-alpha production. *Brain Behav Immun.* 2004; 18(5):476–84. [PubMed: 15265541]
256. Alicea C, Belkowski S, Eisenstein TK, Adler MW, Rogers TJ. Inhibition of primary murine macrophage cytokine production *in vitro* following treatment with the kappa- opioid agonist U50,488H. *J Neuroimmunol.* 1996; 64(1):83–90. [PubMed: 8598393]
257. Van Epps DE, Saland L. Beta-endorphin and met-enkephalin stimulate human peripheral blood mononuclear cell chemotaxis. *J Immunol.* 1984; 132(6):3046–53. [PubMed: 6327817]
258. Makman MH, Bilfinger TV, Stefano GB. Human granulocytes contain an opiate alkaloid-selective receptor mediating inhibition of cytokine-induced activation and chemotaxis. *J Immunol.* 1995; 154(3):1323–30. [PubMed: 7822801]
259. Ruff MR, Wahl SM, Mergenhagen S, Pert CB. Opiate receptor-mediated chemotaxis of human monocytes. *Neuropeptides.* 1985; 5(4–6):363–6. [PubMed: 2860594]
260. Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. *Int J Obes (Lond).* 2009; 33:S54–8. [PubMed: 19528981]
261. Marczak ED, Jinsmaa Y, Myers PH, et al. Orally administered H-Dmt-Tic-Lys-NH-CH₂-Ph (MZ-2), a potent mu/delta-opioid receptor antagonist, regulates obese-related factors in mice. *Eur J Pharmacol.* 2009; 616(1–3):115–21. [PubMed: 19576206]
262. Cooper PD, Dennis SR, Woodman JD, Cowlings A, Donnelly C. Effect of opioid compounds on feeding and activity of the cockroach, *Periplaneta americana*. *Comp Biochem Physiol C Toxicol Pharmacol.* 2010; 151(3):298–302. [PubMed: 20005975]
263. Obese FY, Whitlock BK, Steele BP, Buonomo FC, Sartin JL. Long-term feed intake regulation in sheep is mediated by opioid receptors. *J Anim Sci.* 2007; 85(1):11–7. [PubMed: 17179535]
264. Barnes MJ, Holmes G, Primeaux SD, York DA, Bray GA. Increased expression of mu opioid receptors in animals susceptible to diet-induced obesity. *Peptides.* 2006; 27(12):3292–8. [PubMed: 16996647]
265. Zuberi AR, Townsend L, Patterson L, Zheng H, Berthoud HR. Increased adiposity on normal diet, but decreased susceptibility to diet-induced obesity in mu-opioid receptor-deficient mice. *Eur J Pharmacol.* 2008; 585(1):14–23. [PubMed: 18396272]
266. Lenard NR, Zheng H, Berthoud HR. Chronic suppression of mu-opioid receptor signaling in the nucleus accumbens attenuates development of diet-induced obesity in rats. *Int J Obes (Lond).* 2010; 34(6):1001–10. [PubMed: 20065959]
267. Czyzyk TA, Nogueiras R, Lockwood JF, et al. kappa-Opioid receptors control the metabolic response to a high-energy diet in mice. *FASEB J.* 2010; 24(4):1151–9. [PubMed: 19917675]
268. Yeadon M, Kitchen I. Opioids and respiration. *Prog Neurobiol.* 1989; 33(1):1–16. [PubMed: 2548229]
269. Pattinson KT. Opioids and the control of respiration. *Br J Anaesth.* 2008; 100:747–58. [PubMed: 18456641]

270. Mansour, A.; Watson, SJ. Anatomical distribution of opioid receptors in mammals: an overview. In: Herz, A., editor. *Handbook of Experimental Pharmacology*. Vol. 104. 1993. p. 79-105.
271. Mutolo D, Bongianni F, Einum J, Dubuc R, Pantaleo T. Opioid-induced depression in the lamprey respiratory network. *Neuroscience*. 2007; 150(3):720–9. [PubMed: 17949922]
272. Haji A, Takeda R, Okazaki M. Neuropharmacology of control of respiratory rhythm and pattern in mature mammals. *Pharmacol Ther*. 2000; 86(3):277–304. [PubMed: 10882812]
273. Matthes HW, Smadja C, Valverde O, et al. Activity of the δ receptor is partially reduced, whereas activity of the κ -receptor is maintained in mice lacking the μ -receptor. *J Neurosci*. 1998; 18(18): 7285–95. [PubMed: 9736649]
274. Morin-Surun MP, Boudinot E, Dubois C, et al. Respiratory function in adult mice lacking the mu-opioid receptor: role of delta-receptors. *Eur Neurobiol*. 2001; 13(9):1703–10.
275. Xia Y. Pressor effect of naloxone in acute experimental rabbits. *Chin Pharmacol Bull*. 1989; 5:162–4.
276. Lalley PM. Opioidergic and dopaminergic modulation of respiration. *Respir Physiol Neurobiol*. 2008; 164(1–2):160–7. [PubMed: 18394974]
277. Forman LJ, Estilow S, Hock CE. Localization of beta-endorphin in the rat heart and modulation by testosterone. *Proc Soc Exp Biol Med*. 1989; 190(3):240–5. [PubMed: 2522227]
278. Lang RE, Hermann K, Dietz R, et al. Evidence for the presence of enkephalins in the heart. *Life Sci*. 1983; 32(4):399–406. [PubMed: 6827901]
279. Weihe E, McKnight AT, Corbett AD, Hartschuh W, Reinecke M, Kosterlitz HW. Characterization of opioid peptides in guinea-pig heart and skin. *Life Sci*. 1983; 33(Suppl 1): 711–4. [PubMed: 6363857]
280. Weihe E, McKnight AT, Corbett AD, Kosterlitz HW. Proenkephalin- and prodynorphin- derived opioid peptides in guinea-pig heart. *Neuropeptides*. 1985; 5(4–6):453–6. [PubMed: 3839054]
281. Barron BA, Gu H, Gaugl JF, Caffrey JL. Screening for opioids in dog heart. *J Mol Cell Cardiol*. 1992; 24(1):67–77. [PubMed: 1564731]
282. Spampinato S, Goldstein A. Immunoreactive dynorphin in rat tissues and plasma. *Neuropeptides*. 1983; 3(3):193–212. [PubMed: 16229162]
283. Barron BA, Jones CE, Caffrey JL. Pericardial repair depresses canine cardiac catecholamines and met-enkephalin. *Regul Pept*. 1995; 59(3):313–20. [PubMed: 8577936]
284. Eliasson T, Mannheimer C, Waagstein F, et al. Myocardial turnover of endogenous opioid and calcitonin-gene-related peptide in the human heart and the effects of spinal cord stimulation on pacing-induced angina pectoris. *Cardiology*. 1998; 89(3):170–7. [PubMed: 9570430]
285. Steele PA, Aromataris EC, Riederer BM. Endogenous opioid peptides in parasympathetic, sympathetic and sensory nerves in the guinea-pig heart. *Cell Tissue Res*. 1996; 284(2):331–9. [PubMed: 8625399]
286. Hajrasouliha AR, Tavakoli S, Jabehdar-Maralani P, et al. Cholestatic liver disease modulates susceptibility to ischemia/reperfusion -induced arrhythmia, but not necrosis and hemodynamic instability: the role of endogenous opioid peptides. *J Hepatol*. 2005; 43(3):491–8. [PubMed: 16023251]
287. Schindler CW, Graczyk Z, Gilman JP, et al. Effects of kappa opioid agonists alone and in combination with cocaine on heart rate and blood pressure in conscious squirrel monkeys. *Eur J Pharmacol*. 2007; 576(1–3):107–13. [PubMed: 17707792]
288. Schultz JJ, Hsu AK, Gross GJ. Ischaemic preconditioning and morphine-induced cardioprotection involve the delta (δ)-opioid receptor in the intact rat heart. *J Mol Cell Cardiol*. 1997; 29(8):2187–95. [PubMed: 9281450]
289. Wu S, Li HY, Wong TM. Cardioprotection of Preconditioning by metabolic inhibition in the rat ventricular myocyte. Involvement of kappa-opioid receptor. *Circ Res*. 1999; 84(12):1388–95. [PubMed: 10381890]
290. Faden AI, Holaday JW. Opiate antagonists: a role in the treatment of hypovolemic shock. *Science*. 1979; 205(4403):317–8. [PubMed: 451606]
291. Holaday JW. Opiate antagonists in shock and trauma. *Am J Emerg Med*. 1984; 2(1):8–12. [PubMed: 6097276]

292. Cavun S, Resch GE, Evenc AD, Rapacon-Baker MM, Millington WR. Blockade of delta opioid receptors in the ventrolateral periaqueductal gray region inhibits the fall in arterial pressure evoked by hemorrhage. *J Pharmacol Exp Ther*. 2001; 297(2):612–9. [PubMed: 11303050]
293. McBride SM, Smith-Sonneborn J, Oeltgen P, Flynn FW. Delta2 opioid receptor agonist facilitates mean arterial pressure recovery after hemorrhage in conscious rats. *Shock*. 2005; 23(3):264–8. [PubMed: 15718926]
294. Boeuf B, Poirier V, Gauvin F, et al. Naloxone for shock. *Cochrane Database Syst Rev*. 2003; 4:CD004443. [PubMed: 14584016]
295. Gutkowska J, Jankowski M, Pawlak D, Mukaddam-Daher S, Izdebski J. The cardiovascular and renal effects of a highly potent mu-opioid receptor agonist, cyclo [Ne,Nb-carbonyl-D-Lys2,Dap5] enkephalinamide. *Eur J Pharmacol*. 2004; 496(1–3):167–74. [PubMed: 15288587]
296. Wang J, Gao Q, Shen J, Ye TM, Xia Q. Kappa-opioid receptor mediates the cardioprotective effect of ischemic postconditioning. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2007; 36(1):41–7. [PubMed: 17290490]
297. Mao L, Wang JQ. Cardiovascular responses to microinjection of nociceptin and endomorphin-1 into the nucleus tractus solitarius in conscious rats. *Neuroscience*. 2005; 132(4):1009–15. [PubMed: 15857705]
298. Gross GJ. Role of opioids in acute and delayed preconditioning. *J Mol Cell Cardiol*. 2003; 35(7):709–18. [PubMed: 12818560]
299. Gross ER, Hsu AK, Gross GJ. Opioid-induced cardioprotection occurs via glycogen synthase kinase beta inhibition during reperfusion in intact rat hearts. *Circ Res*. 2004; 94(7):960–6. [PubMed: 14976126]
300. Peart JN, Patel HH, Gross GJ. Delta-opioid receptor activation mimics ischemic preconditioning in the canine heart. *J Cardiovasc Pharmacol*. 2003; 42(1):78–81. [PubMed: 12827030]
301. Lasukova TV, Krylatov AV, Maslov LN, et al. Antiarrhythmic and cardioprotective effect of stimulation of delta1-opiate receptors in myocardial ischemia and reperfusion. *Patol Fiziol Eksp Ter*. 2004; (3):12–5. [PubMed: 15446414]
302. Maslov LN, Lishmanov YB, Oeltgen PR, et al. Activation of peripheral delta2 opioid receptors increases cardiac tolerance to ischemia/reperfusion injury Involvement of protein kinase C, NO-synthase, KATP channels and the autonomic nervous system. *Life Sci*. 2009; 84(19–20):657–63. [PubMed: 19245818]
303. Rong F, Peng Z, Ye MX, et al. Myocardial apoptosis and infarction after ischemia/reperfusion are attenuated by kappa-opioid receptor agonist. *Arch Med Res*. 2009; 40(4):227–34. [PubMed: 19608010]
304. Zagon IS, Rahn KA, Bonneau RH, Turel AP, McLaughlin PJ. Opioid growth factor suppresses expression of experimental autoimmune encephalomyelitis. *Brain Res*. 2010; 1310:154–61. [PubMed: 19931226]
305. Hill MP, Hille CJ, Brotchie JM. Delta-opioid receptor agonists as a therapeutic approach in Parkinson's disease. *Drug News Perspect*. 2000; 13(5):261–8. [PubMed: 12937640]
306. Mabrouk OS, Volta M, Marti M, Morari M. Stimulation of delta opioid receptors located in substantia nigra reticulata but not globus pallidus or striatum restores motor activity in 6-hydroxydopamine lesioned rats: new insights into the role of delta receptors in parkinsonism. *J Neurochem*. 2008; 107(6):1647–59. [PubMed: 19094058]
307. Ikeda K, Yoshikawa S, Kurokawa T, Yuzawa N, Nakao K, Mochizuki H. TRK-820, a selective kappa opioid receptor agonist, could effectively ameliorate L-DOPA-induced dyskinesia symptoms in a rat model of Parkinson's disease. *Eur J Pharmacol*. 2009; 620(1–3):42–8. [PubMed: 19686730]
308. Wikstrom B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol*. 2005; 16(12):3742–7. [PubMed: 16251241]
309. Kakinohana M. Spinal cord protection and opioids. *Masui*. 2007; 56(3):298–304. [PubMed: 17366917]

310. Iselin-Chaves IA, Gröttsch H, Besson M, Burkhard PR, Savoldelli GL. Naloxone- responsive acute dystonia and parkinsonism following general anaesthesia. *Anaesthesia*. 2009; 64(12):1359–62. [PubMed: 19839983]
311. Zesiewicz TA, Hauser RA, Freeman A, Sullivan KL, Miller AM, Halim T. Fentanyl-induced bradykinesia and rigidity after deep brain stimulation in a patient with Parkinson disease. *Clin Neuropharmacol*. 2009; 32(1):48–50. [PubMed: 19471184]
312. Koprich, JB.; Fox, SH.; Johnston, TH., et al. The selective mu-opioid receptor antagonist, ADC5510, reduces L-DODA induced dyskinesia in the MPTP macaque model of Parkinson's disease. Abstract of International Narcotics Research Conference; 2010. p. 85
313. Ammon-Treiber S, Stolze D, Schröder H, Loh H, Höllt V. Effects of opioid antagonists and morphine in a hippocampal hypoxia/hypoglycemia model. *Neuropharmacology*. 2005; 49(8): 1160–9. [PubMed: 16098996]
314. Ammon-Treiber S, Stolze D, Höllt V. Differential effects of mu-opioid receptor agonists in a hippocampal hypoxia/hypoglycemia model. *Brain Res*. 2007; 1183:60–5. [PubMed: 17936735]
315. San-Emeterio EP, Hurlé MA. Modulation of brain apoptosis-related proteins by the opioid antagonist naltrexone in mice. *Neurosci Lett*. 2006; 403(3):276–9. [PubMed: 16716514]

Table 1

Common Endogenous Opioids and their Preferred Receptors

Endogenous Ligands	Selectivity
Endorphins	μ
Enkephalins	δ
Dynorphins	κ
Nociceptin/orphanin FQ	NOP/ORL
Endomorphins	μ
Morphiceptin	μ

Table 2

Some Common Opioid Agonists and their Primary Receptor Selectivity

Ligand	Selectivity	Ligand	Selectivity
cUENK6	μ	TAN-67	δ_1
DALDA	μ	BW373U86	δ
DAMGO	μ	Deltorphins I, II, III	δ
DIPP-NH ₂ ψ	μ	CP-OH **	δ_{cx}
Endomorphin-1, -2	μ	DSLET	δ_2, δ_{cx}
Fentanyl	μ	DPDPE	$\delta_1, \delta_{cx}, \delta_{nex}$
Methadone	μ	Bremazocine	κ
Morphine	μ	BRL 52537	κ
Remifentanyl	μ	CI-977	κ
Sufentanyl	μ	Dynorphin A	κ
Oxymorphone	μ	ICI-197067	κ
Morphiceptins	μ	Ketocyclazocine	κ
Dermorphin	μ	Nalfurafine	κ
c[YGwFG]	μ	PD-117302	κ
CYT-1010	μ	Salvinorin A	κ
Ac-D-Trp-Phe-GlyNH ₂	μ	U-62066	κ
HIT *	δ	U-50488H	κ
JOM-13	δ	U-69593	κ_1
SNC80	δ	Pentazocine	μ, κ
SNC-121	δ	EKC	μ, δ, κ
UFP-502	δ	Etorphine	μ, δ, κ
UFP-512	δ	DADLE	$\delta, \delta_{cx} > \delta_{nex}, \mu$

* Hibernation Induction Trigger

** [D-Ala² (2R,3S)- Δ (E)Phe⁴,Leu⁵]enkephalin [119].

Table 3

Some Notable Opioid Antagonists and Predominant Receptor Selectivity

Ligand	Selectivity	Ligand	Selectivity
β -FNA	μ	BNTX	δ_1
Naltrexone	μ	Naltriben	δ_2
CTAP	μ	[<i>N</i> -allyl-Dmt ¹]endomorphin-1,2	μ
CTOP	μ	ICI 174,864	δ , δ_{nex}
Cyprodime	μ	DALCE	δ_1 , δ_{cx}
Naloxonazine	μ	GNTI	κ
Naloxone	μ	TRK-820	κ
ADL5510	μ	5-AMN	κ
ADC5510	μ	5-MABN	κ
DIPP-NH ₂ ψ	δ	Nor-BNI	κ
ICI-174864	δ	U50488H	κ
Naltrindole	δ	Diprenorphine	μ , δ , κ
<i>N</i> , <i>M</i> (Me) ₂ -Dmt-Tic-OH	δ	MZ-2	μ , δ
TIPP	δ	LY255582	μ , δ , κ
UFP-501	δ		