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The Roles of Opioid Receptors and Agonists in Health and Disease Conditions

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Abstract: Opioid receptors are found in the Central Nervous System (CNS) and are classified as mu (μ), kappa (κ), delta (δ) and sigma (σ) opioid receptors. Opioid receptors belong to the large family of G Protein Coupled Receptors (GPCRs), and have diverse and important physiological roles. The aim of the present review is to discuss the roles played by opioid receptors, their agonists and antagonists in health and disease conditions. Opioid receptors are not uniformly distributed in the CNS and are found in areas concerned with pain, with the highest concentration in the cerebral cortex, followed by the amygdala, septum, thalamus, hypothalamus, midbrain and spinal cord. Activated delta opioid receptors are coupled to G_{i1} while activated mu opioid receptors are coupled to G_{i3} in neuroblastoma cells. Mu opioid receptors are activated by mu receptor agonists and are coupled through the $G\alpha_{i1}$ and $G\alpha_{oA}$. Both mu and kappa opioid receptors are coupled via both G_i and G_z and opioid receptors are important targets for thousands of pharmacological agents. GPCRs typically require activation by agonists for their signalling activity to be initiated but some of the GPCRs may display basal or spontaneous signalling activity in the absence of an agonist. The stimulation of these receptors triggers analgesic effects and affects the function of the nervous system, gastrointestinal tract and other body systems. Hundreds of analogs of opioid peptides have been synthesized in an effort to make the compounds more active, selective, and resistant to biodegradation than the endogenous ligands. All these modifications resulted in obtaining very selective agonists and antagonists with high affinity at mu-, delta-, and kappa-opioid receptors, which are useful in further studies on the pharmacology of opioid receptors in a mammalian organism.

Key words: Delta opioid, G-protein coupled receptors, κ-Opioid, μ-Opioid, opioid agonists, opioid antagonists, opioid receptors

INTRODUCTION

The term opioid refers to any natural or synthetic drugs that have morphine-like activity. They are classified as natural, semi-synthetic and synthetic opioids. Examples of natural opioids are morphine, codeine noscopine; semi-synthetic are heroin, oxymorphone and hydromorphone, while the synthetic opioids are methadone, morphinians and benzamorphans (Piestrzeniewicz *et al*., 2006). Opioid receptors are found in the Central Nervous System (CNS) and are classified as mu (μ), kappa (κ), delta (δ) and sigma (σ) opioid receptors. Opioid receptors are not uniformly distributed in the CNS but are found in areas concerned with pain receptors, with the highest concentration in the cerebral cortex, followed by the amygdala, septum, thalamus, hypothalamus, midbrain and spinal cord (Raynor *et al*., 1996; Chaturvedi *et al*., 2000). The mu receptor has been shown to be high in areas of pain perception and in the medulla, especially in the area for respiration (Reisine and Bell, 1993; Reisine and Brownstein, 1994; Massotte and Kieffer, 1998; Hasbi *et al*., 2000).

The opioid receptors (mu, delta, and kappa) belong to the large family of GPCRs and have diverse and important physiological roles (Piestrzeniewicz *et al*., 2006; Rhim and Miller, 1994). Laugwitz *et al*. (1993) have shown that activated delta opioid receptors are coupled to G_{i1} while activated mu opioid receptors are coupled to G_{i3} in neuroblastoma cells (SH-SY5Y). Mu opioid receptors have been shown to be activated by mu receptor agonists and are coupled through the $G\alpha_{i1}$ and $G\alpha_{oA}$ in human embryonic kidney (HEK 239) cells (Saidak *et al*., 2006). Tso and Wong (2000), have shown that both mu and kappa opioid receptors are coupled via both G_i and G_z in HEK 239 cells. The opioid receptors are important targets for thousands of pharmacological agents (Hasbi *et al*., 2000; Wang *et al*., 2007). The stimulation of these receptors triggers analgesic effects and affects the function of the nervous system, gastrointestinal tract and other body

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systems (Piestrzeniewicz *et al*., 2006). The discovery of opioid peptides (including delta-selective enkephalins, kappa-selective dynorphins, and mu-selective endomorphins), which are endogenous ligands of opioid receptors, initiated their structure-activity relationship studies (Fichna *et al*., 2006).

Piestrzeniewicz *et al*. (2006) have shown that in the last 30 years, hundreds of analogs of opioid peptides have been synthesized in an effort to make the compounds more active, selective, and resistant to biodegradation than the endogenous ligands. Different unnatural amino acids, as well as cyclisation procedures, leading to conformationally restricted analogs, were employed. All these modifications resulted in obtaining very selective agonists and antagonists with high affinity at mu-, delta-, and kappa-opioid receptors, which are extremely useful tools in further studies on the pharmacology of opioid receptors in a mammalian organism (Piestrzeniewicz *et al*., 2006; Xiong *et al*., 2007). GPCRs typically require activation or stimulation by agonists for their signalling activity to be initiated but Wang *et al*. (2007), have shown that some of the GPCRs display basal or spontaneous signalling activity in the absence of an agonist. This basal or spontaneous signalling activity is also called constitutive activity (Wang *et al*., 2007; Piiper and Zeuzem, 2004).

As mentioned, opioids exert their biological activity through the activation by GPCRs, and their effects can be blocked by receptor antagonists. Opioid antagonists with different inverse agonist properties have different effects in precipitating withdrawal in acute morphine dependent mice, and constitutive opioid receptor activation is critically involved in acute opioid withdrawal (Freye and Levy, 2005; Wang *et al*., 2007; Xiong *et al*., 2007). It has been shown that the pharmacological properties and activities of the three opioid receptor classes are distinct and can be clearly differentiated (Raynor *et al*., 1996). Opioid receptors have high affinity for both agonists and antagonists. DAMGO and its antagonists do not bind to delta or kappa receptors, and morphine and its derivatives are much less potent at the delta or kappa receptors. All the three opioid receptors are sensitive to the antagonist naloxone (Raynor *et al*., 1996; Raynor *et al*., 1994; Wang *et al*., 2007). The aim of the present review is to discuss the roles played by opioid receptors, their agonists and antagonists in health and disease conditions

Uses of opioids: Opioids have long been used to treat acute pain, such as post-operative pain (Raynor *et al*., 1994). They are commonly prescribed, and used, because of their effective analgesic properties. Studies have shown that properly managed medical use of opioid analgesic compounds is safe and rarely causes addiction. Taken exactly as prescribed, opioids can be used to manage pain effectively. They have also been found to be invaluable in palliative care to alleviate the severe, chronic and disabling pain of terminal conditions such as cancer and AIDS (Doyle *et al*., 2004). Contrary to popular belief, high doses are not required to control the pain of advanced or end-stage disease. In recent years there has been an increased use of opioids in the management of non-malignant chronic pain. This practice has grown from over 30 years experience in palliative care of long-term use of strong opioids, which has shown that dependence is rare when the drug is being used for pain relief (Doyle *et al*., 2004)

In addition to analgesia, clinical uses of opioids include codeine and hydrocodone for cough, natural opioids for diarrhoea, oxymorphone for anxiety due to shortness of breath and methadone and buprenorphine for heroin detoxification and maintenance programs during heroin replacement therapy (Eap *et al*., 1999, 2002). Despite the fact that opioids have been extensively reported to have psychological benefits, they are never officially prescribed to treat psychological illnesses, even in circumstances where researchers have reported opioids to be especially effective for example in the treatment of senile dementia, geriatric depression, and psychological distress due to chemotherapy or terminal diagnosis (Berridge, 2006).

Doyle *et al*. (2004) have shown that opioids are used to treat pain of moderate or greater severity, irrespective of the underlying pathophysiological mechanism. Morphine has been used to treat breathlessness of which several mechanisms have been suggested for its action. Codeine and loperamide are the most widely used opioids for diarrhoea. Loperamide has the advantage of acting only on the gut, since very little is absorbed and topical morphine in an aqueous gel can be an effective agent for treatment of painful wounds. Their use is based on the discovery of activated opioid receptors in damaged tissue (Doyle *et al*., 2004). Opioid medications can affect regions of the brain, resulting in the initial euphoria that many opioids produce. They can also produce drowsiness, because constipation and depending upon the amount taken, depress breathing. When taken as a large single dose, opioids could cause severe respiratory depression or death (Wang *et al*., 2007).

Opioid receptor activation: Milligan (2004) has shown that the opioid receptors form homomeric as well as heteromeric receptor complexes. Opioid receptors are capable of forming a heterodimer with each other and certain non-opioid receptors, for example, mu with alpha$_{2a}$-adrenoceptors (Devi, 2001). This heterodimerisation between opioid receptors has been shown to result in changes in the pharmacology of the receptors as well as changes in receptor coupling to second messengers and trafficking (Corbett *et al*., 2006). It has been shown that both mu and delta receptors internalise on exposure to agonists, whereas kappa

Table 1: Some agonists and antagonists of opioid receptor subtypes

Opioid receptor subtype	Agonists	Antagonists
Delta	Deltorphin- Penicillamine- 2,Penicillamine-5- enkephalin (DPDPE) [D-serine 2, O-Leu5]- enkephalin-Thr (DSLET) TAN-67 D-Ala^2]-Deltorphin II	Naltrindole ICI 174,864 Dalargin SDM25N hydrochloride Naltriben mesylate ICI 154,129 Benzylnaltrindole- hydrochloride
Kappa	U50,488 [3H]U69,593 ([3H]U69) ICI 204,448 (ICI) ICI-199441hydrochloride U-54494A hydrochloride BRL 52537- hydrochloride	nor-binaltorphimine (nor-BNI) 7-benzylidenenaltrexone (BNTX) [3H]diprenorphine ([3H]DIP) GNTI dihydrochloride
Mu	(D-Ala^2-MePhe^4, Gly-ol^5) enkephalin (DAMGO) Morphine Loperamide-hydrochloride Endomorphin-1 Endomorphin-2	D-Phe-Cys-Tyr-D-Trp-Orn-Pen-Thr-NH2 (CTOP) Naloxonazine Cyprodime hydrochloride H-D-Phe-Cys-Tyr-D-Trp- Arg-Thr-Pen-Thr-NH_2. (CTAP)

receptors do not and when such dimers such as delta/kappa dimers are formed, the trafficking properties of the kappa receptor predominates, while the heterodimer does not internalise on exposure to agonists of either receptors (Corbett *et al*., 2006; Koch and Hollt, 2008). Opioid receptor subtypes have been proposed largely on the basis of radioligand binding studies and as such there is little or no evidence for the presence of the different genes encoding these subtypes but in some cases, receptor heterodimerisation of opioid receptors has been proposed as a possible explanation (Corbett *et al*., 2006). Table 1 shows some of the agonists and antagonists of the opioid receptor subtypes.

All of the opioid receptors are GPCRs and couple to their cellular effectors primarily through G_i/G_o proteins, and thus the majority of opioid responses are pertussis toxin-sensitive (Milligan and Kostenis, 2006). Corbett *et al*. (2006) have shown that the different behaviours mediated by each of the receptor subtype in the intact animal such as euphoria for mu and dysphoria for kappa, result not from each type of receptor evoking different cellular responses but from the different anatomical distributions of each receptor (Corbett *et al*., 2006). Although the predominant action of opioids in the nervous system is inhibitory, in several brain regions such as Periaqueductal Grey (PAG), important for supraspinal analgesia or ventral tegmental area (VTA), for euphoria/ reward, opioids are excitatory (Corbett *et al*., 2006). It has been shown that opioid-induced excitations are due, not to a direct excitatory action of opioids, but to disinhibition (Corbett *et al*., 2006). The apparent excitation of a neuron by opioids is as a result of inhibition of the release of inhibitory neurotransmitters such as Gamma Amino Butyric Acid (GABA) from the interneurons into the cell (Corbett *et al*., 2006).

Opioids have been shown to act via receptors interacting with heterotrimeric pertussis toxin (PTX) sensitive G proteins. The mu-selective agonist, DAMGO, and the delta-selective agonist, [D-Pen^2,D-Pen^5]-enkephalin (DPDPE) stimulated the incorporation of the photo-reactive GTP analogue into proteins co-migrating with the alpha subunits of G_{i1}, G_{i2}, G_{i3}, G_{o1}, and G_{o2} in the membranes of neuroblastoma SH-SY5Y cells while in the membranes of PTX-treated cells, both agonists were ineffective, because mu and delta opioid receptors appear to discriminate between PTX-sensitive G proteins which lead to activation of distinct G protein subtypes (Laugwitz *et al*., 1993). Subtype-specific immuno-precipitation of G protein alpha subunits photo-labelled in the absence or presence of agonists revealed profound differences between mu and delta opioid receptors in coupling to PTX-sensitive G proteins (Milligan, 2004).

Opioid inhibition of neuronal excitability resulting in the down-regulation of pain occurs largely by activation of potassium channels in the plasma membrane (Samways and Henderson, 2006). Opioid receptors are now known to activate a variety of potassium channels, including G-protein-activated inwardly rectifying (GIRK), calcium-activated inwardly rectifying, dendrotoxin-sensitive and M-type channels (Williams *et al*., 2001). Opioid receptors have been shown to inhibit high threshold voltage-activated calcium channels, like other members of the G_i/G_o-coupled receptor family such as cannabinoid (CB_1) receptors (Corbett *et al*., 2006). In some cell types, such as neuronal cells, opioid receptor activation can also cause an elevation of the free calcium concentration inside cells by releasing calcium from intracellular stores or by enhancing calcium entry by a dihydropyridine-sensitive mechanism (Samways and Henderson, 2006). It has been shown that the activation of opioid receptors stimulates a variety of intracellular signalling mechanisms including activation of inwardly rectifying potassium channels, and inhibition of both voltage-operated N-type Ca^{2+} channels and adenylyl cyclase activity (Samways and

Henderson, 2006). It is now apparent that like many other G_i/G_o-coupled receptors, opioid receptor activation can significantly elevate intracellular free Ca^{2+}, although the mechanism underlying this phenomenon is not well understood (Samways and Henderson, 2006). In some cases opioid receptor activation alone appears to elevate intracellular Ca^{2+}, but in many cases it requires concomitant activation of G_q-coupled receptors, which themselves stimulate Ca^{2+} release from intracellular stores via the inositol phosphate pathway (Samways and Henderson, 2006).

Opioid receptors, like other G_i/G_o-coupled receptors, inhibit adenylyl cyclase resulting in a fall in intracellular cAMP (Corbett *et al*., 2006). Williams *et al*., (2001), have shown that in primary afferent neurons, opioid receptors activate and regulate multiple second messenger pathways associated with effector coupling, receptor trafficking, nuclear signalling and modulates the activation of hyperpolarization-activated cation channels. In opioid withdrawal, cAMP levels are elevated and enhanced protein kinase A (PKA) activity increases neurotransmitter release (Corbett *et al*., 2006). Opioid receptors, like many other GPCRs, cycle to and from the plasma membrane from intracellular compartments (Corbett *et al*., 2006). This cycling is caused by agonist activation of the receptors which results in the cycling of the receptors to the plasma membrane in response to various stimuli (Williams *et al*., 2001). The generally accepted mechanism underlying mu and delta receptor desensitization, is that agonist-activated receptors on the plasma membrane are phosphorylated by G-protein-coupled receptor kinases (GRKs), which facilitates arrestin binding and prevents the receptor from coupling to G-proteins (Bailey and Connor, 2005). Arrestin-bound receptors are rapidly concentrated in clathrin-coated pits and undergo dynamin-dependent internalisation into early endosomes (Corbett *et al*., 2006). Delta receptors are trafficked into lysosomes and are down-regulated, whereas mu receptors are trafficked into endosomes, where they are dephosphorylated and recycled back to the plasma membrane in a re-sensitised state (Corbett *et al*., 2006). Thus, for mu receptor, internalisation can be considered to be involved in re-sensitisation, but not in desensitisation and there is evidence that different C-terminus splice variants of the mu receptor re-sensitise at different rates while the kappa receptors do not appear to internalise in response to agonist activation (Corbett *et al*., 2006).

Chakrabarti *et al*. (1995) have suggested that different G-proteins can be activated with different potencies by mu receptor agonists in Chinese-hamster ovary cell membranes, which agrees with studies on delta- and kappa-opioid receptors, suggesting that commonly used agonists of these receptors can activate multiple G-protein subtypes with similar potency (Burford *et al*., 2000). Carter and Medzihradsky (1993) have shown that mu-selective agonist, DAMGO inhibited cAMP formation in membranes of human neuroblastoma cells (SH-SY5Y), differentiated with retinoic acid. Antibodies to G_i alpha 1, 2 or G_i alpha 3 reduced the mu-opioid signal insignificantly and inhibition of adenylyl cyclase by the delta-opioid agonist (DPDPE) was very sensitive to the G_i alpha 1, 2 antibodies (Carter and Medzihradsky, 1993).

Interaction of opioids and cannabinoids: Opioids and cannabinoids are among the most widely consumed drugs of abuse in the world (Manzanares *et al*., 1999; Smart and Ogborne, 2000). Both drugs have been shown to share some pharmacological properties including antinociception, hypothermia, sedation, hypotension, inhibition of both intestinal motility and locomotor activity (Manzanares *et al*., 1999). It has been reported that there is a cross-tolerance or mutual potentiation of these pharmacological effects. These phenomena have supported the possible existence of functional linkage in the mechanisms of action of both drugs especially in antinociception and drug addiction (Manzanares *et al*., 1999; Manzanares *et al*., 2005).

The cannabinoid and opioid compounds mimic endogenous ligands and act through the GPCRs, cannabinoid and opioid receptors (Felder and Glass, 1998; Kieffer, 1995). It has been shown that chronic administration of Δ^9-THC increases opioid gene expression while, acute administration of Δ^9-THC increases extracellular levels of endogenous enkephalins in the nucleus accumbens of mice (Corchero *et al*., 1997; Valverde *et al*., 2001). Some studies have also demonstrated the existence of cross-tolerance between opioid and cannabinoid agonists and such, morphine-tolerant animals show decreased Δ^9-THC antinociceptive responses, whereas Δ^9-THC-tolerant rodents show a decrease in morphine antinociception (Thorat and Bhargava, 1994; Ghozland *et al*., 2002). There is cross-dependence between opioid and cannabinoid compounds and opioid antagonist naloxone precipitated a withdrawal syndrome in Δ^9-THC-tolerant rats, whereas cannabinoid antagonist SR171416A was able to precipitate abstinence in morphine-dependent rats (Navarro *et al*., 1998; Ghozland *et al*., 2002). The severity of opioid withdrawal was reduced by the administration of Δ^9-THC or anandamide (Vela *et al*., 1995; Valverde *et al*., 2001). This bidirectional cross-dependence was confirmed by using knock-out mice and opioid dependence was reduced in mice lacking the CB_1 receptor whereas, cannabinoid dependence was reduced in mice lacking the preproenkephalin gene (Ledent *et al*., 1999; Valverde *et al*., 2000).

Cannabinoids produce their rewarding effects by stimulating mesolimbic dopaminergic transmission which has been shown to be a common substrate for the rewarding effects of other substances of abuse (Tanda *et al*., 1997). The activation of mu-opioid receptors could be involved in the bidirectional interaction between the endogenous cannabinoid and opioid systems in reward that extends to central mechanisms underlying relapsing phenomena (Fattore *et al*., 2004). This is because the endogenous cannabinoid system participates in the rewarding effects of opioids (Ghozland *et al*., 2002), and both morphine self-administration and place preference are decreased in mice lacking the CB_1 receptors (Ledent *et al*., 1999; Martin *et al*., 2000). The possible involvement of the endogenous opioid system in the different motivational responses induced by cannabinoids is not yet well understood, however, GABAergic and corticotrophin-releasing factor systems, have been suggested to be involved in the anxiogenic responses induced by cannabinoids and these anxiogenic behaviours could have some influence in the dysphoric effects of cannabinoids (Rodríguez de Fonseca *et al*., 1996; Ghozland *et al*., 2002).

Ghozland *et al*. (2002), have shown that the disruption of mu-, delta-, or kappa-opioid receptor gene does not modify acute Δ^9-THC responses while the expression of Δ^9-THC withdrawal, and the development of Δ^9-THC tolerance is only slightly altered in Kappa Opioid Receptor (KOR) knockout mice. Both mu- and kappa-opioid ligands have been reported to modulate cannabinoid antinociception (Manzanares *et al*., 1999). The Δ^9-THC antinociception was blocked in mice by the kappa-selective opioid antagonist norbinaltorphimine, and by high doses of the non-selective opioid antagonist naloxone (Smith *et al*., 1998; Ghozland *et al*., 2002). The synergistic effects of morphine and Δ^9-THC on antinociception were also blocked by norbinaltorphimine, a mu selective antagonist (Reche *et al*., 1996) and high doses of opioid antagonists are usually required to block Δ^9-THC antinociception (Manzanares *et al*., 1999). Laboratory reports have shown that kappa receptors could contribute to the development of adaptive responses to chronic Δ^9-THC administration, in agreement with the demonstration of cross-tolerance between Δ^9-THC and kappa-opioid agonists (Smith *et al*., 1994).

A non-selective opioid antagonist naloxone, precipitates an opioid-like withdrawal syndrome in cannabinoid-dependent rodents while, the CB_1 cannabinoid receptor antagonist SR 141716A, induces withdrawal in morphine-dependent rats (Navarro *et al*., 1998). This suggests that simultaneous activation of the two endogenous systems could participate in both opioid and cannabinoid dependence (Ghozland *et al*., 2002; Manzanares *et al*., 2005). Pre-treatment with Δ^9-THC and anandamide, have been shown to decrease morphine withdrawal (Valverde *et al*., 2001), and the morphine-induced rewarding effects were suppressed in mice deficient in CB_1 cannabinoid receptors, suggesting a bidirectional influence of µ-opioid and CB_1 receptors on reward processes (Ledent *et al*., 1999; Ghozland *et al*., 2002).

Ghozland *et al*. (2002), have proposed that the opposing µ-opioid and κ-opioid receptor activities mediate the dual euphoric-dysphoric effects of Δ^9-THC and a possible mechanism for this could be that cannabinoid receptor activation modifies endogenous opioid peptide levels in mesolimbic areas, that would in turn, modulate dopaminergic activity (Viganò *et al*., 2005). The release of opioid peptides by cannabinoids or endocannabinoids by opioids and their interactions at the level of receptor and their signal transduction mechanisms supports the finding of increased opioid peptide levels in the hypothalamus after cannabinoid treatment (Corchero *et al*., 1997; Viganò *et al*., 2005).

Cannabinoids and opioids can also interact at the level of their signalling activities. This is because reports have shown that both cannabinoid and opioid receptor types are coupled to similar intracellular effectors via $G_{i/o}$-proteins, modulating cAMP levels, K^+ and Ca^{2+} channel activities, and MAP kinase phosphorylation (Bouaboula *et al*., 1995; Fukuda *et al*., 1996; Manzanares *et al*., 1999). Viganò *et al*. (2005) studied the mechanism of cross-modulation between cannabinoid and opioid systems for analgesia during acute and chronic exposure. The result showed that acute co-administration of ineffectual sub-analgesic doses of synthetic cannabinoid CP-55,940 and morphine resulted in significant antinociception whereas, in rats made tolerant to CP-55,940, morphine challenge did not produce any analgesic response. The result of Viganò *et al*. (2005) study also showed alterations in the cAMP system, which seem to mirror the behavioural responses, indicating that the two systems may interact at the post receptor level which might open-up new therapeutic opportunities for relief of chronic pain through cannabinoid-opioid co-administration.

CONCLUSION

Opioid receptors and their agonists have long been involved in the treatment of acute pain such as post-operative pain. They are generally prescribed and used due to their effective analgesic properties and when properly managed the medical use of opioid analgesic compounds is safe and do not cause addiction. They are found to be invaluable in palliative care to alleviate severe, chronic and disabling pain of terminal conditions such as cancer and AIDS. Opioid use has increased over time in the management of non-malignant chronic pain and clinical uses of opioids include for cough, diarrhoea, anxiety, heroin detoxification and maintenance programs during heroin replacement therapy. Opioids have been shown to be especially effective in the treatment of senile dementia, geriatric depression, and psychological distress due to chemo therapy or terminal diagnosis. Opioids receptors and their agonists are used to treat pain of moderate and greater severity, irrespective of the underlying pathophysiological mechanism.

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REFERENCES

Bailey, C.P. and M. Connor, 2005. Opioids: cellular mechanisms of tolerance and physical dependence. Curr. Opin. Pharmacol., 5(1): 60-68.

Berridge, M.J., 2006. Cell Signalling Biology. Portland Press Ltd., Retrieved from: www. cellsignallingbiology.org.

Bouaboula, M., C. Poinot Chazel, B. Bourrie, X. Canat, B. Calandra, M. Rinaldi-Carmona, G. Le Fur and P. Casellas, 1995. Activation of mitogen-activated protein kinases by stimulation of the central cannabinoid receptor CB1. Biochem. J., 312: 637-641.

Burford, N.T., D. Wang and W. Sadée, 2000. G-protein coupling of mu-opioid receptors (OP3): Elevated basal signalling activity. Biochem. J., 348(3): 531-537.

Carter, B.D. and F. Medzihradsky, 1993. G_o mediates the coupling of the mu opioid receptor to adenylyl cyclase in cloned neural cells and brain. Proc. Natl. Acad. Sci. USA, 90(9): 4062-4066.

Chakrabarti, S., P.L. Prather, L. Yu, P.Y. Law and H.H. Loh, 1995. Expression of the μ-opioid receptor in CHO cells - ability of μ-opioid ligands to promote a-azidoanilido [^{32}P]GTP labelling of multiple G-protein a subunits. J. Neurochem., 64: 2534-2543.

Chaturvedi, K., K.H. Christoffers, K. Singh and R.D. Howells, 2000. Structure and regulation of opioid receptors. Biopolymers, 55(4): 334-346.

Corbett, A.D., G. Henderson, A.T. McKnight and S.J. Paterson, 2006. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br. J. Pharmacol., 147: S153-S162.

Corchero, J., J.A. Fuentes and J. Manzanares, 1997. delta 9-Tetrahydrocannabinol increases proopiomelanocortin gene expression in the arcuate nucleus of the rat hypothalamus. Eur. J. Pharmacol., 323(2-3): 193-195.

Devi, L.A., 2001. Heterodimerization of G-protein-coupled receptors: Pharmacology, signaling and trafficking. Trend. Pharmacol. Sci., 22: 532-537.

Doyle, D., G. Hanks, I. Cherney and K. Calman, 2004. Oxford Textbook of Palliative Medicine. 3rd Edn., Oxford University Press, UK, pp: 367-727.

Eap, C.B., T. Buclin and P. Baumann, 2002. Interindividual variability of the clinical pharmacokinetics of methadone: Implications for the treatment of opioid dependence. Clin Pharmacokinet., 41(14): 1153-1193.

Eap, C.B., J.J. Deglon and P. Boumann, 1999. Pharmacokinetics and pharmacogenetics of methadone: Clinical relevance. Heroin addiction and related clinical problems. Official J. EUROPAD, 1(1): 19-34.

Fattore, L., G. Cossu, M.S. Spano, S. Deiana, P. Fadda, M. Scherma and W. Fratta, 2004. Cannabinoids and reward: Interactions with the opioid system. Crit. Rev Neurobiol., 16(1-2): 147-158.

Felder, C.C. and M. Glass, 1998. Cannabinoid receptors and their endogenous agonists. Ann. Rev. Pharmacol. Toxicol., 38: 179-200.

Fichna, J., K. Gach, M. Piestrzeniewicz, E. Burgeon, J. Poels, J.V. Broeck and A. Janecka, 2006. Functional characterization of opioid receptor ligands by aequorin luminescence-based calcium assay. J. Pharmacol. Exp. Ther., *317*(3): 1150-1154.

Freye, E. and J. Levy, 2005. Constitutive opioid receptor activation: A prerequisite mechanism involved in acute opioid withdrawal. Addict Biol., 10(2): 131-137.

Fukuda, K., S. Kato, H. Morikawa, T. Shoda and K. Mori, 1996. Functional coupling of the δ-, μ-, and κ-opioid receptors to mitogen-activated protein kinase and arachidonate release in Chinese hamster ovary cells. J. Neurochem., 67: 1309-1316.

Ghozland, S., H.W. Matthes, F. Simonin, D. Filliol, B.L. Kieffer and R. Maldonado, 2002. Motivational effects of cannabinoids are mediated by μ-opioid and κ-opioid receptors. J Neurosci., 22(3): 1146-1154.

Hasbi, A., S. Allouche, F. Sichel, L. Stanasila, D. Massotte, G. Landemore, J. Polastron and P. Jauzac, 2000. Internalization and recycling of delta-opioid receptor are dependent on a phosphorylation-dephosphorylation mechanism. J. Pharmacol. Exp. Ther., 293(1): 237-247.

Kieffer, B.L., 1995. Recent advances in molecular recognition and signal transduction of active peptides: Receptors for opioid peptides. Cell Mol. Neurobiol., 15(6): 615-635.

Koch, T. and V. Hollt, 2008. Role of receptor internalization in opioid tolerance and dependence. Pharmacol. Ther., 117(2): 199-206.

Laugwitz, K.L., S. Offermanns, K. Spicher and G. Schultz, 1993. μ and δ opioid receptors differentially couple to G protein subtypes in membranes of human neuroblastoma SH-SY5Y cells. Neuron, 10(2): 233-142.

Ledent, C., O. Valverde, G. Cossu, F. Petitet, J.F. Aubert, F. Beslot, G.A. Bohme, A. Imperato, T. Pedrazzini, B.P. Roques, G. Vassart, W. Fratta and M. Parmentier, 1999. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science, 283: 401-404.

Manzanares, J., J. Corchero, J. Romero, J.J. Fernández-Ruiz, J.A. Ramos and J.A. Fuentes, 1999. Pharmacological and biochemical interactions between opioids and cannabinoids. Trend. Pharmacol. Sci., 20(7): 287-294.

Manzanares, J., S. Ortiz, J.M. Oliva, S. Pérez-Rial and T. Palomo, 2005. Interactions between cannabinoid and opioid receptor systems in the mediation of ethanol effects. Alcohol, 40(1): 25-34.

Martin, M., C. Ledent, M. Parmentier, R. Maldonado and O. Valverde, 2000. Cocaine, but not morphine, induces conditioned place preference, sensitization to locomotor responses in CB1 knockout mice. Eur. J. Neurosci., 12: 4038-4046.

Massotte, D. and B.L. Kieffer, 1998. A molecular basis for opiate action. Essays Biochem., 33: 65-77.

Milligan, G., 2004. G protein-coupled receptor dimerization: function and ligand pharmacology. Mol. Pharmacol., 66: 1-7.

Milligan, G. and E. Kostenis, 2006. Heterotrimeric G-proteins: a short history. Br. J. Pharmacol., 147(Suppl 1): S46-S55.

Navarro, M., J. Chowen, A. Rocio, M. Carrera, I. del Arco, M.A. Villanua, Y. Martin, A.J. Roberts, G.F. Koob and F.R. de Fonseca, 1998. CB_1 cannabinoid receptor antagonist-induced opiate withdrawal in morphine-dependent rats. Neuro Report, 9: 3397-3402.

Piestrzeniewicz, M.K., J. Michna and A. Janecka, 2006. Opioid receptors and their selective ligands. Postepy Biochem., 52(3): 313-319.

Piiper, A. and S. Zeuzem, 2004. Receptor tyrosine kinases are signalling intermediates of G protein-coupled receptors. Curr. Pharm. Des., 10(28): 3539-3545.

Raynor, K., H. Kong, J. Hines, G. Kong, J. Benovic, K. Yasuda, G.I. Bell and T. Reisine, 1994. Molecular mechanisms of agonist-induced desensitization of the cloned mouse kappa opioid receptor. J. Pharmacol. Exp. Ther., 270(3): 1381-1386.

Raynor, K., H. Kong, S. Law, J. Heerding, M. Tallent, F. Livingston, J. Hines and T. Reisine 1996. Molecular biology of opioid receptors. NIDA Res. Monogr., 61: 83-103.

Reche, I., J.A. Fuentes and M. Ruiz-Gayo, 1996. Potentiation of 9-tetrahydro cannabinol-induced analgesia by morphine in mice: involvement of μ- and κ-opioid receptors. Eur. J. Pharmacol., 318: 11-16.

Reisine, T. and G.I. Bell, 1993. Molecular biology of opioid receptors. Trend. Neurosci., 16(12): 506-510.

Reisine, T. and M.J. Brownstein, 1994. Opioid and cannabinoid receptors. Curr. Opin. Neurobiol., 4(3): 406-412.

Rhim, H. and R.J. Miller, 1994. Opioid receptors modulate diverse types of calcium channels in the nucleus tractus solitarius of the rat. J. Neurosci., 14(12): 7608-7615.

Rodríguez de Fonseca, F., P. Rubio, F. Menzaghi, E. Merlo-Pich, J. Rivier, G.F. Koob, and M. Navarro, 1996. Corticotropin-Releasing Factor (CRF) antagonist [D-Phe12, Nle21,38,C alpha MeLeu37]CRF attenuates the acute actions of the highly potent cannabinoid receptor agonist HU-210 on defensive-withdrawal behaviour in rats. J. Pharmacol. Exp. Ther., *276*(1): 56-64.

Saidak, Z., K. Blake-Palmer, D.L. Hay, J.K. Northup and M. Glass, 2006. Differential activation of G-proteins by mu-opioid receptor agonists. Br. J. Pharmacol., 147(6): 671-680.

Smart, R.G. and A.C. Ogborne, 2000. Drug use and drinking among students in 36 countries. Addict. Behav., 25: 455-460.

Samways, D.S. and G. Henderson, 2006. Opioid elevation of intracellular free calcium:possible mechanisms and physiological relevance. Cell Signal, 18(2): 151-161.

Smith, F.L., D. Cichewicz, Z.L. Martin and S.P. Welch, 1998. The enhancement of morphine antinociception in mice by delta9-tetrahydrocannabinol. Pharmacol. Biochem. Behav., 60(2): 559-566.

Smith, P.B., S.P. Welch and B.R. Martin, 1994. Interactions between ^{9}-tetrahydro cannabinol and κ-opioids in mice. J. Pharmacol. Exp. Ther., 268: 1381-1387.

Tanda, G., F.E. Pontieri and G. Di Chiara, 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science, 276(5321): 2048-2050.

Thorat, S.N. and H.N. Bhargava, 1994. Evidence for a bi-directional cross-tolerance between morphine and ^{9}-tetrahydrocannabinol in mice. Eur. J. Pharmacol., 260: 5-13.

Tso, P.H. and Y.H. Wong, 2000. G(z) can mediate the acute actions of mu- and kappa -opioids but is not involved in opioid-induced adenylyl cyclase supersensitization. J. Pharmacol. Exp. Ther., 295(1): 168-176.

Valverde, O., R. Maldonado, E. Valjent, A.M. Zimmer and A. Zimmer, 2000. Cannabinoid withdrawal syndrome is reduced in pre-proenkephalin knock-out mice. J. Neurosci., 20: 9284-9289.

Valverde, O., F. Noble, F. Beslot, V. Dauge, M.C. Fournie-Zaluski and B.P. Roques, 2001. ^{9}-tetrahydrocannabinol releases, facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect. Eur. J. Neurosci., 13: 1816-1824.

Vela, G., M. Ruiz-Gayo and J.A. Fuentes, 1995. Anandamide decreases naloxone-precipitated withdrawal signs in mice chronically treated with morphine. Neuro Pharmacol., 34: 665-668.

Viganò, D., T. Rubino and D. Parolaro, 2005. Molecular and cellular basis of cannabinoid and opioid interactions. Pharmacol. Biochem. Behav., 81(2): 360-368.

Wang, J., Q. Gao, J. Shen, T.M. Ye and Q. Xia, 2007. Kappa-opioid receptor mediates the cardioprotective effect of ischemic postconditioning. Zhejiang Da Xue Xue Bao Yi Xue Ban, 36(1): 41-47.

Williams, J.T., M.J. Christie and O. Manzoni, 2001. Cellular and synaptic adaptations mediating opioid dependence. Physiol. Rev., 81: 299-343.

Xiong, L.Z., J. Yang, Q. Wang and Z.H. Lu, 2007. Involvement of delta-and mu-opioid receptors in the delayed cerebral ischemic tolerance induced by repeated electroacupuncture preconditioning in rats. Chin. Med. J. (Engl), 120(5): 394-399.