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REVIEW ARTICLE

The Role of the Cannabinoid System in Opioid Analgesia and Tolerance

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Abstract: Opioid receptor agonist drugs, such as morphine, are very effective for treating chronic and severe pain; but, tolerance can develop with long-term use. Although there is a lot of information about the pathophysiological mechanisms of opioid tolerance, it is still not fully clarified. Suggested mechanisms for opioid tolerance include opioid receptor desensitisation, reduction of sensitivity G-proteins, activation of mitogen-activated protein kinase (MAPK), altered intracellular signaling pathway including nitric oxide, and activation of mammalian target of rapamycin (mTOR). One way to reduce opioid tolerance and increase the analgesic potential is to use low doses. Combination of cannabinoids with opioids has been shown to manifest the reduction of the opioid dose. Experimental studies revealed an interaction of the endocannabinoid system and opioid antinociception. Cannabinoid and opioid receptor systems use common pathways in the formation of analgesic effect and demonstrate their activity *via* G protein coupled receptors (GPCR). Cannabinoid drugs modulate opioid analgesic activity at a number of distinct levels within the cell, ranging from direct receptor associations to post-receptor interactions through shared signal transduction pathways. This review summarizes the data indicating that with combining cannabinoids and opioids drugs may be able to produce long-term analgesic effects, while preventing the opioid analgesic tolerance.

Keywords: Cannabinoids, cannabinoid receptors, cannabinoid analgesia, opioid analgesia, opioid tolerance.

1. INTRODUCTION

Morphine is one of the most commonly used opioid analgesic drugs in the treatment of severe and chronic pain. Besides the known unwanted side effects such as nausea, vomiting, respiratory depression, sedation, and cough suppression, its use for severe pain status is limited by the development of tolerance [1, 2]. Opioid analgesic tolerance is characterized by a reduced sensitivity to opioid agonists and is frequently obvious by the need to use increasing doses to obtain the desired analgesic effect [3]. Despite the existence of extensive information on this subject, the mechanisms of opioid tolerance are not yet fully understood.

There are many different studies on the mechanism of tolerance to the analgesic effects of opioids. There are different explanations for the development of opioid antinociceptive tolerance, including reduced receptor sensitivity, induction of nitric oxide-cGMP signaling pathway, mitogen-activated protein kinase (MAPK) and alfa-2 noradrenergic systems, and protein kinase-dependent changes in signal transduction cascades [4-6].

The analgesic effects of morphine are primarily mediated by the μ-opioid receptor (MOR). It has been demonstrated that prolonged exposure to opioid agonists reduces MOR-mediated G-protein activity suggesting that downregulation of MOR expression could be associated with tolerance to chronic opioid treatment [7]. One promising approach to improve the analgesic effect of morphine is a combination drug treatment in which low doses of distinct types of analgesics (such as cannabinoids) are administered. Synergistic interactions have been observed between opioid and cannabinoid (CB) analgesic drugs [8]. CBs are thought to predominantly exert their effects by binding to G-protein–coupled CB receptor type 1 and type 2. The study has indicated that coadministration of a low dose CB prevented antinociceptive tolerance to morphine in animal models of neuropathic pain [8]. Pretreatment with a non-analgesic dose of tetrahydrocannabinol (THC) has been shown to cause up to a 22-fold increase of the morphine analgesia [9] although the analgesic effects of cannabinoid products are relatively mild [10].

Although the role of CBs in opioid tolerance has been studied, the mechanism underlying these actions has not been exactly defined. Opioid and CB receptors both belong to the family of Gi/Go-protein–coupled receptors and are frequently coexpressed in the cells of the central nervous system [11]. Opioids and CBs may interact at multiple levels and have been associated with analgesic, psychotropic, and immunomodulatory effects. The interaction between opioid and CB receptors may be facilitated by similar intracellular

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signal pathways. The purpose of this paper is to review the role of cannabinoid system in morphine analgesia and tolerance.

2. ENDOCANNABINOID SYSTEM

The endocannabinoid system is a lipid signaling system that is involved in a broad range of physiopathological processes such as energy metabolism, inflammation, and pain transmission [12]. The authors reported that cannabinoids are reliable for the management of severe and chronic pain [13]. The multiple endocannabinoids are generated from the hydrolysis of membrane polyunsaturated fatty acids. The endocannabinoids activate presynaptic neuron receptors. Therefore, one function of cannabinoids is being the retrograde messengers [14]. Endocannabinoids modulate synaptic plasticity by different mechanisms. These ligands acutely inhibit the synaptic transmission by way of hyperpolarization or repressing voltage-gated calcium channels. Persistent activation of cannabinoid receptors produces synaptic slow self-inhibition through K^+ conduction. Long-term synaptic inhibition occurs from phosphorylation of target receptors and the channels decreasing neurotransmitter release. The activity of synaptic transmission is blocked by cannabinoid intracellular translocation and catabolism [15].

N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) were firstly identified in intestine and brain (Fig. **1**). AEA was first explored in porcine brain and then discovered in other tissues from a variety of species: rat and bovine brain, human spleen and heart [16, 17]. AEA synthesis from *N*-arachidonoyl phosphatidylethanolamine (NAPE) occurs via various pathways and include enzymes such as phospholipase C and phospholipase A2 [18]. 2-AG was initially isolated from canine intestine and was later detected in rat brain, spleen and kidney. In most tissues, the amount of 2-AG is higher than anandamide [16, 19].

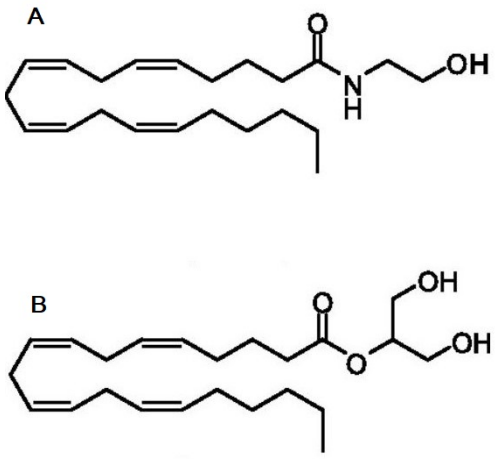

Fig. (1). (A) N-arachidonoylethanolamine (anandamide, AEA) and **(B)** 2-arachidonoylglycerol (2-AG).

Cannabis sativa flowers, which can stimulate the endocannabinoid system, contain more than 60 phytocannabinoids. Among these, THC and cannabidiol are known as the main components [20]. The cannabinoid-related compounds show inhibitory effects on obesity, digestion, pain, and vomiting due to chemotherapy in areas with CB receptor (CBR). Dronabinol, Nabilone, and Sativex are cannabinoid-based drugs that have been confirmed to treat pain, chemotherapy-induced nausea, appetite loss, and spasticity [21].

2.1. Cannabinoid Receptors

The endocannabinoid system is a complex system involving a number of lipid agonists and multiple receptors. Endocannabinoids regulate and/or modulate nociception, cardiovascular and gastrointestinal function, appetite, lipid metabolism, mood and motor function [22]. Endocannabinoid ligands are variable signal ligands, which may be agonists, antagonists or even inverse agonists depending on the dose, cannabinoid receptor, conformational state of the cannabinoid receptor, disease state as well as interactions with various ion channel [23].

Classical cannabinoid receptors (CB1R and CB2R) are 7 transmembrane G-protein couple receptors (GPCRs) negatively coupled to adenylyl cyclase (AC) and positively coupled to *mitogen-activated protein kinase* (MAPKs) such as extracellular signal-related kinases 1 and 2 (ERK1/2) through Gi/o proteins [24]. Orphan-related receptors (such as GPR55 and GPR18) are also 7 transmembrane GPCRs [25]. It was originally thought that calcium conductance increased with CB1R and not CB2R activation, even though it is now known that both receptors decrease calcium conductance. The CB1R and CB2R have a 44% amino acid identity [26]. CB1R is highly expressed in neurons within the hippocampus, cortex, basal ganglia, thalamus, cerebellum and periaqueductal gray but rarely expressed in the respiratory center of the brainstem, therefore the reason for lack of respiratory depression seen with cannabis toxicity [26]. CB2R is expressed on immunocytes including microglia and mast cells. CB2R is poorly expressed in the CNS but rapidly upregulated in neurons with neural inflammation [27].

Isoforms of CB1R are derived from splice variance of the four exons, which constitute the CB1 gene. Endocannabinoids bind different receptor isoforms, which influence cellular signaling. Expression of various isoforms differs under different pathologic conditions, which potentially influences cannabinoids responses [28]. CB1R is localized on the inner surface of the plasma membrane and co-located with transient receptor potential vanilloid (TRPV-1) ion channels. Endocannabinoids can activate and/or desensitize vanilloid channels [29]. THC is a partial agonist for CB1R. Activated CB1R reduces excitatory neurotransmitter release and CB2R dampens microglia responses and neuroinflammation as basic mechanisms to antinociception [30]. CB2R is also largely found postsynaptically on neurons, particularly with neural injury and may dampen neuronal excitability [31]. CB2R may also form functional heterodimer with CB1R [32].

The orphan cannabinoid receptors GPR55 and GPR18 have low amino acid identity (14%) with classic opioid receptors. Both GPR55 and GPR18 are found in the CNS and modulate antinociceptive responses in animals [33, 34].

2.2. Signaling of Cannabinoid Receptors

CB1R and CB2R are members of the GPCR family and bind to Gi/o protein. CB1R couples to Gs but with low efficacy compared to Gi/o [35]. Activated Gi/o receptors inhibit AC and the formation of cyclic adenosine monophosphate (cAMP) (Fig. **2**). It has been reported that the CB1R (but not CB2R) activates other G proteins under certain circumstances [36]. The CB1R is able to stimulate typical AC isoforms via Gβγ protein subunits [37]. In addition, when the dopamine receptor 2 (D2R) is activated at the same time in striatal neurons, the CB1R stimulates cAMP via coupling to Gs. In transfected CHO-K1 cells, Gi is blocked by pertussis toxin (PTX), and in response to a relatively high level of synthetic cannabinoid WIN55,212-2 in rats [38]. However, this CB1R agonist enhances intracellular Ca^{2+} concentrations via Gq/11 protein in HEK-293 cells [39]. Furthermore, CB1R expressed in astrocytes of mice is coupled to Gq/11, increases intracellular Ca^{2+} concentrations and triggers astrocytic release of glutamate on pyramidal neurons [40]. In addition, the CB1R modulates the activity of several types of ion channels. The activation of CB1Rs inhibits synaptic transmission by modulating N-type Ca^{2+} channel in the presynaptic terminal of the granule cell to Purkinje cell synapse. [41]. It has been indicated that the cannabinoid CB1 receptor regulates Ca^{2+} influx to prohibit aminobutyric acid (GABA) release via modulation of the activity of presynaptic N-type Ca^{2+} channel [42]. However, P/Q-type of Ca^{2+} channels have been shown to be negatively regulated by CB1R in different neuronal systems [41, 43].

Several studies have suggested that stimulation of CB1 receptor leads to the activation of MAPK signaling pathways, including p38, extracellular signal-regulated kinase 1/2 (ERK1/2), and c-Jun N-terminal kinase (JNK). These signaling pathways are involved in the regulation of cell cycle, proliferation and cell death [36, 44]. β-arrestin is a fundamental molecule in suppressing G protein-associated signal transduction [44]. Following cannabinoid receptor phosphorylation by G protein coupled receptor kinase (GRK), β-arrestin binds to this receptor and initiates the internalization process [45].

2.3. Cannabinoid-Opioid Interactions

In the last decade, there has been increasing interest in the development of cannabis derivatives drugs to treat severe and chronic pain. Preclinical studies [46-48] suggest that both CB1R and CB2R agonists have analgesic action in various types of pain including inflammatory and neuropathic pain (Table **1**). In accordance, CB1R antagonist SR 141716A blocks cannabinoid-induced antinociception [49].

Cannabinoid and opioid receptors are essential targets for many drugs of commonly used analgesics. The studies reported that these receptors mediate common signaling pathways central to clinical issues of dependence, addiction and antinociceptive tolerance [36, 59]. Both cannabinoid CB1 receptor and morphine receptor (MOR) agonist drugs have similar pharmacological profiles and have been shown to cause antinociception, sedation, hypotension, and drug reward/reinforcement [60, 61]. Cannabinoids modulate opioid function at many different levels in the cell with direct receptor relationships, post-receptor interactions via common signal transduction pathways, and changes in endogenous peptide release [63]. Evidence of these interactions can be

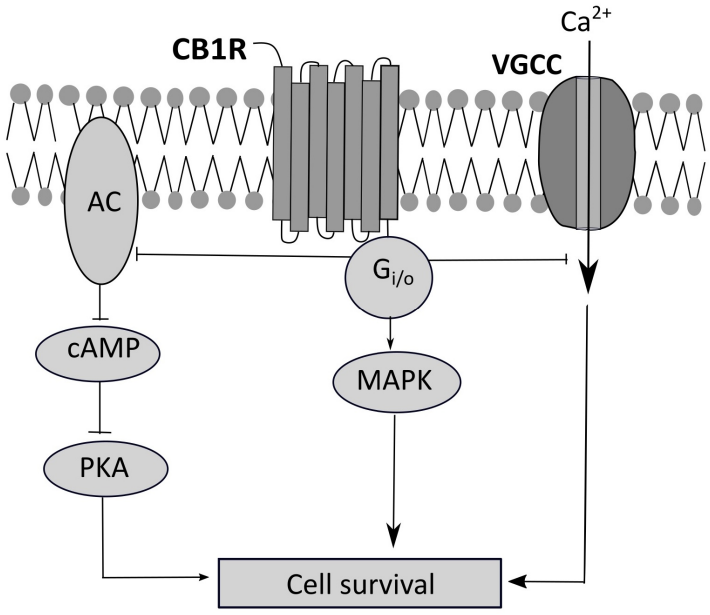

Fig. (2). CB1R-modulated primary signaling pathways. CB1R is coupled to Gi/o and inhibits the activity of adenylyl cyclase (AC), formation of cyclic adenosine monophosphate (cAMP), and the activity of protein kinase A (PKA). The CB1R is able to suppress calcium influx *via* voltage-gated calcium channel (VGCC). Mitogen-activated protein kinase (MAPK) is activated by the CB1R. The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway is activated by CB1R as well. Depending on the ligand and subcellular environment, the outcome of CB1R-mediated signaling could be promotion of cell survival. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 1. Analgesic actions of the cannabinoid receptor system.

Compound	Cannabinoid Receptors	Pain Test	Mode of action	Refs.
JWH-133	CB2R* agonist	von Frey anesthesiometer	Reduces inflammatory and neuropathic pain	[46]
WIN 55,212-2	CB1R agonist	Tail-flick and Formalin tests	Antinociceptive effect	[47]
GW405833	CB2R selective agonist	von Frey anesthesiometer	Antihyperalgesic effect	[48]
SR 141716A	CB1R antagonist	Tail-flick test	Blocks cannabinoid-induced antinociception	[49]
AM-1241	CB2R agonist	von Frey anesthesiometer	Chronic inflammatory pain inhibition	[50]
O-3223	CB2R selective agonist	Hot-plate and Formalin tests	Antinociceptive effect	[51]
WIN55,212-2	CB1R agonist	Tail-flick and Formalin tests	Antinociceptive effect	[52]
AM1710	CB2R agonist	von Frey anesthesiometer	Inhibition of the neuropathic pain	[53]
AM1241	CB2R agonist	Thermal withdrawal latency test	Antinociceptive effect	[54]
HU-210	CB1R agonist	Tail-flick test	Decreasing neuropathic pain	[55]
VD-hemopressin(β)	CB1R and CB2R agonist	Tail-flick test	Antinociceptive effect	[56]
JWH015	CB2R agonist	Tail withdrawal and Paw pressure tests	Antinociceptive effect	[57]
LY2828360	CB2R agonist	von Frey anesthesiometer	Suppression of the neuropathic pain	[58]
GW405833	CB2R agonist	Formalin test	Inflammatory pain inhibition	[27]

*CB2R, Cannabinoid 2 receptor.

observed *via* the different studies suggesting mutual potentiation and receptor cross-talk [62, 63]. Drugs targeting the cannabinoid system often appear to affect the opioid system at the same time. Individual modulation of CB1R or MOR has been shown to alter the noradrenergic activity indices. Distinctive modulation of CB1R or MOR has been shown to alter indices of noradrenergic activity [64]. Because of noradrenergic circuitry in the locus coeruleus (LC) are critical sites for opioid withdrawal and addiction, it is especially important to develop a comprehensive understanding of biochemical mechanisms. In this way, cannabinoid drugs may be used to effectively target the opioid system in this brain region [64].

The different techniques used to differentiate the distribution and endogenous ligands of opioid and cannabinoids receptors assured precious information on the interactions between this system. The anatomical and immunohistochemical data have displayed potential systems and sites where cannabinoid agonists may be used to target the opioid system. Morphological substrates for cannabinoid-opioid interactions have been shown by cannabinoid CB1 receptor and MOR co-localization in various brain areas. It has been reported that these receptors co-localize in the dorsal horn of spinal cord [65]. CB1R and MOR are both localized in the nucleus accumbens (NAc), a region critical to the reward circuitry, and synaptically-linked pairs of cells [11]. In addition, a molecular study on the caudate nucleus and putamen suggested MOR and CB1R labeling targeted to special patches of post-synaptic neurons with nearly 50% of all CB1R-positive dendrites containing the MOR [66]. Pharmacological data provide additional evidence of local cannabinoid effects, following local infusions of cannabinoids to opioidergic LC regions [67]. Cannabinoid CB1 receptor is expressed in the terminals of noradrenergic projections from the opioid-sensitive LC to the frontal cortex [68]. CB1R may be modulate the norepinephrine release that occurs as a result of opioid withdrawal and dependence. Furthermore, it is not possible to rule out the mechanisms by which GABA interneurons are indirectly involved [69]. There is also a lot of data of MOR and CB1R co-localization in shared postsynaptic neurons that give rise to these projections [70].

The studies have displayed a synergistic effects combination of cannabinoid and opioid such as cannabinoid agonist CP55,940 and morphine in mice, and Δ9-THC and morphine in an arthritis model [71, 72]. Additionally, combined sub-analgesic doses of Δ9-THC and morphine had synergistic analgesic properties while preventing the development of tolerance to morphine [8]. At same time, cannabinoid systems have been shown to exert cross-antagonism within the opioid system [73]. Similarly, the studies have implicated the cannabinoid system in opioid dependence, as inhibition of cannabinoid signaling with the selective CB1R antagonist SR141716A decreased opioid withdrawal effects [74]. It has also been demonstrated that cross-sensitization has occurred against the antinociceptive effects of cannabinoids and opioid [75].

3. MECHANISMS OF OPIOID ANALGESIC TOLERANCE

The opioid tolerance, defined by the reduction of the analgesic efficacy of opioid analgesics after prolonged use, is an important clinical problem [76]. There are two different

theories related to the mechanisms of opioid antinociceptive tolerance. The first theory is associated with a decrease in opioid receptor activation. Several studies demonstrate that the down-regulation of opioid receptor is partly responsible for the development of opioid analgesic tolerance. Desensitization of opioid receptor is defined as a progressive decrease of signal transduction that occurs less or more rapidly after MOR receptor activation by the agonist. The more rapidly desensitisation is mostly observed on the regulation of ion channel conductance in a few seconds while a sustained desensitisation is slightly observed on the management of enzymes after several minutes [77]. Several data indicate that the opioid receptor desensitisation is a cellular tolerance mechanism.

The study suggests a reduction of morphine receptor activity on the outward potassium current compared to control group rats, when the rats are prolonged exposed to morphine [78]. In contrast to this, desensitisation may be defined as a reduction of signal transduction from opioid receptor after acute activation by agonists that recovers when cells are placed in non-agonists [79]. The second mechanism of opioid analgesic tolerance is performed through internalisation of the opioid receptor from the cell membrane. The number of opioid receptor is regulated by endocytosis and export of synthesised receptors. When agonists stimulate receptor internalisation, one could expect a reduction in signal transduction. The opioid receptor cannot perform long-term activity after entering the nerve cells and is down-regulated after a while. It prevented the development of opioid analgesic tolerance in β-arrestin2 (a down-regulators) deficient rats and continued to have sustained opioid analgesia [80]. The essential tools are opioid receptor phosphorylation by protein kinases C (PKC), and other protein kinases like calcium-calmodulin kinase and phospholipase [1].

NMDA is an important excitatory neurotransmitter in central nervous systems. The authors indicate that NMDA has a crucial role in development of morphine tolerance [81, 82]. NMDA inhibitors such as ketamine and MK-801 attenuate hyperalgesia and development of opioid tolerance [82, 83]. GABA is an inhibitory neurotransmitter in nervous systems that could be affected by morphine analgesia [84, 85]. It has been suggested that microinjection of baclofen ($GABA_B$ agonist) in locus coereleus could attenuate naloxone withdrawal syndrome in morphine tolerant rats [86]. Dopamine, another neurotransmitter, is involved in opioid analgesia and tolerance [80]. The studies indicated that activation of opioid receptors on dopaminergic neurons in the brain plays an important role in morphine tolerance [87, 88]. Studies also show that bromocriptine, a D2-receptor agonist, attenuates morphine tolerance [89]. The serotonergic system as one of the neurotransmitters of a monoaminergic system that involved in descending inhibitory pathway which modulate pain in spinal level. It is well established that part of the analgesic effects of morphine caused by the serotonergic system [90]. In addition, co-administration of fenfluramine (selective 5-HT uptake inhibitor) with morphine inhibits the development of morphine antinociceptive tolerance [91].

Animal studies indicated that activation of hypothalamic-pituitary-adrenal axis modulates the analgesic effect of morphine and has an important role in the development of morphine tolerance [92]. ACTH directly acts on the adrenal medulla and increases the activity of tyrosine hydroxylase. ACTH has an inhibitory effect on the development of morphine tolerance [93].

3.1. Cannabinoid Systems and Opioid Tolerance

Cannabinoid and opioid receptors share a similar antinociceptive profile. The activity of cannabinoid and opioid indicates potential interaction between these two different analgesic drugs. It is well known that the antinociceptive effects of opioids and cannabinoids are related to central effects [94, 95]. Cannabinoids co-administered with opioids have been shown to decrease the dose of opioid needed for analgesic effects [96, 97]. Ongoing experimental studies are determining whether cannabinoids increase other clinically side effects of opioids besides their analgesic effects. However, the initial findings of the studies on monkeys showed that cannabinoids did not increase the side effects of opioid drugs [97, 98]. Co-administration of cannabinoids with morphine results in a reduced dose of morphine for analgesic effect, thereby maintaining the therapeutic efficacy of the opioids. If the negative effects of opioids are increased by cannabinoids, this approach will be less useful. Some effects of opioids are not altered or attenuated by cannabinoids, including distinctive stimulants, dependence and withdrawal as well as reinforcing effects [97].

A number of studies demonstrate that cannabinoids have a significant role in opioid analgesia and tolerance (Table **2**). It has been indicated that the inactivation of either cannabinoid CB1 or CB2 receptors reduces the antinociceptive effects of morphine when assessed with the formalin test in mice [112]. In addition, co-administration of morphine with AM-251 (CB1-receptor antagonist) inhibited the development of both acute and chronic analgesic tolerance and reduce the activity of CGRP in the dorsal root ganglion (DRG) and spinal cord neurons [102]. Administration of Δ^9-tetrahydrocannabinol and low dose morphine attenuates antinociceptive tolerance and reduces desensitization of receptors [103]. In contrast to this, another study indicates that when combined treatment with morphine and Δ9-tetrahydrocannabinol (1 mg/kg) antinociceptive tolerance was greater in the tail-withdrawal test [109]. Moreover, CB_1 receptor agonist (CP-55940) and NMDA receptor antagonist (LY235959) attenuate the development of morphine antinociceptive tolerance [105].

A recent study has shown that cannabinoid receptor antagonist SR141716 attenuates morphine analgesic tolerance [107]. Co-injection of selective CB1 antagonist (AM251) and CB2 antagonist (JTE907) with morphine decrease the morphine analgesia and attenuate development of tolerance to morphine [97]. Experimental study suggests that administration of a nonanalgesic dose of a CB2 receptor agonist (AM1241) enhances analgesia effect and reduces tolerance to morphine in tumor-bearing rats, presumably by increasing MOR expression in the spinal cord and DRG [108]. Administration of selective CB2 receptor agonist (JWH-133) with morphine moderate attenuates morphine tolerance. These study results indicate that JWH-133 and morphine have an additive effect on antinociception [111].

Table 2. The role of cannabinoid system in opioid analgesia and tolerance.

Compound	Cannabinoid Receptors	Pain Test	Opioid Analgesia / Tolerance	Refs.
Anandamide and CP55,940	CB1R/CB2R and CB1R agonist	Tail-flick test	↑ / -	[99]
WIN 55, 212	CB1R and CB2R agonist	Tail-flick test	↑ / -	[100]
Δ9-THC	CB1R and CB2R agonist	Visual analog scale	↑ / -	[62]
CP-55940	CB1R agonist	Tail-flick and Hot-plate test	↑ / -	[101]
AM-251	selective CB1R antagonist	Tail-flick test and Paw-pressure test	↑ / ↓	[102]
Δ9-THC	CB1R and CB2R agonist	Paw withdrawal test	↑ / ↓	[103]
HU-210	CB1R and CB2R agonist	Hot-plate test	↑ / -	[104]
CP-55940	CB1R agonist	Hot-plate test	- / ↓	[105]
CP-55940	CB1R agonist	Warm-water tail withdrawal test	↑ / -	[106]
SR141716	CB1R inverse agonist	Tail-flick and Hot-plate test	↑ / ↓	[107]
JWH-015	Selective CB2R agonist	Tail-flick and Hot-plate test	↑ / ↓	[95]
AM1241	Selective CB2R receptor agonist	von Frey anesthesiometer and Hot-plate test	↑ / ↓	[108]
WIN 55,212	CB1R and CB2R agonist	Warm-water tail withdrawal test	- / ↓	[109]
JWH-015	CB2R agonist	Tail-flick test	↑ / -	[110]
JWH-133	CB2R agonist	Formalin test	↑ / ↓	[111]
LY2828360	CB1R agonist	von Frey anesthesiometer	↑ / ↓	[58]

Slowly signaling G protein–biased CB2 cannabinoid receptor agonist LY2828360 suppresses neuropathic pain with sustained efficacy and attenuates morphine tolerance and dependence in mice [58]. There is co-localization of TRPV1 and CB2 receptor in human and dorsal root ganglia in rats. Co-administration of a CB2 receptor agonist AM1241 and morphine decrease morphine analgesic tolerance through regulation of TRPV1 protein expression in the dorsal root ganglion in severe cancer pain [113].

CONCLUSION

Opioids, such as morphine, are commonly used analgesic drugs that are very efficient for treating acute and chronic pain conditions. However, long-term opioid treatment may have undesirable effects and may cause a significant reduction in analgesic effect due to the development of tolerance. Combined drugs are being tried to reduce the development of tolerance to opioids and for an effective analgesic effect. One of the combined drugs is the cannabinonoid receptor agonist. Several studies have reported interactions between cannabinoid and opioid receptor systems. Although the mechanisms underlying such an interaction between the two systems are not known, cannabinoids have been shown to induce the release of endogenous opioids. Several studies suggest that co-administration of cannabinoid receptor agonists and opioids lead to opioid peptide release, proving that there are synergistic interactions between the two receptor systems. Numerous evidence has shown that cannabinoid receptor agonists reduce opioid tolerance and increase analgesic efficacy. A detailed understanding of the molecular and cellular events occurring in the development of tolerance will lead to the development of newly designed effective drugs. Finally, co-administration cannabinoid receptor agonists with opioids may be an alternative way to prevent the side effects of opioid drugs.

LISTS OF ABBREVIATIONS

AEA = Anandamide, N-arachidonoylethanolamine

cAMP = Cyclic Adenosine Monophosphate

CB = Cannabinoid

CB1R = Cannabinoid Receptors

ERK1/2 = Extracellular Signal-Related Kinases 1 and 2

GPCR = G protein Coupled Receptors

GRK = G protein Coupled Receptor Kinase

JNK = c-Jun N-Terminal Kinase

MAPK = Mitogen-Activated Protein Kinase

MOR = μ-Opioid Receptor

mTOR = Mammalian Target of Rapamycin

NAPE = *N*-arachidonoylphosphatidylethanolamine

PTX = Pertussis Toxin

THC = Tetrahydrocannabinol

TRPV-1 = Transient Receptor Potential Vanilloid

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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