Journal of Applied Pharmaceutical Science Vol. 5 (01), pp. 114-119, January, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.50120
ISSN 2231-3354 

Reviews on Calcium Mediated Secondary Messengers in Chronic Opioids Exposure/Addiction

Ibrahim H Sani[1], Maryam I Umar[1], Nasir Mohamad[2], U.S. Mahadeva Rao*[2], R. Mohd Adzim Khalili[2], Nor Hidayah Abu Bakar[2]

[1]Master's Degree students, Faculty of Medicine and Health Science, Universiti Sultan Zainal Abidin, Malaysia.
[2]Medical lecturers, Faculty of Medicine and Health Science, Universiti Sultan Zainal Abidin, Malaysia.

ARTICLE INFO

Article history:
Received on: 03/11/2014
Revised on: 22/11/2014
Accepted on: 09/12/2014
Available online: 30/01/2015

Key words:
Calcium;
Calmodulin;Opioid;
Oxidative stress; Neuronal cell.

ABSTRACT

Addiction and withdrawal are problems disturbing the health of the individual and also causes difficulties for society, raising the rates of divorce, unemployment and government spending on legal and medical systems. Opioids show an important pharmacological effect in the treatment of pain, with extremely addictive potential. Chronic opioid exposure is known to produce the complex behaviors of tolerance and dependence, a state exposed by opioid abstinence leading to withdrawal syndrome, as well as oxidative stress. Studies show that calcium mediated secondary messengers play a crucial role in the mechanism of addictive process and oxidative stress induced by chronic opioid usage. Calcium/calmodulin-dependent protein kinase II (CaMKII), is a major calcium regulated signal transducer that controls many neuronal systems and play important role in neuronal plasticity and can act as a key and direct promoting opioid tolerance and dependence and identifying such a direct mechanism may be useful for designing a pharmacology treatment for these conditions, recent studies, has been shown that calcium channels antagonist can be used in the treatment of withdrawal syndrome. Chronic opioid exposure associated with tolerance, dependence withdrawal syndrome and oxidative stress. Studies has shown that calcium mediated secondary messengers involved in the genesis of these conditions, better understanding of biological mechanisms underlie reduction in neuronal cell excitability could help in the identification of pharmacological targets for treatment.

INTRODUCTION

Opioids are highly effective for the treatment of pain (Williams *et al.*, 2001), Chronic exposure to opioids eventually leads to drug addiction, which is believed to involve maladaptive changes in brain function (Pu *et al*., 2002). Although compounds of extremely high potency have been produced, the problem of tolerance to and dependence on these agonists persists. the adaptive changes in cellular and synaptic function induced by chronic morphine treatment (Williams *et al*., 2001). Tolerance describes the need for an increasing dose of opioid to achieve the same effect; this term was based originally on the tolerance that develops to many of the acute behavioral actions of opioids (e.g., analgesia and autonomic inhibition). Dependence describes an altered physiological state caused by repeated opioid exposure such that cessation of drug administration leads to a withdrawal syndrome characterized by serious physiological disturbances, emotional or motivational symptoms. This latter form of dependence is perhaps the strongest determinant of opioid addiction (Nestler *et al*., 1996; Nestler, 2002). Which can be defined as loss of control over drug use, or the compulsive seeking and taking of drugs despite adverse consequences (Nestler, 2001). Globally opioid addiction and withdrawal are problems affecting the health of the individual and also causes problems for society, increasing the rates of divorce, unemployment and government expenditure on legal and medical systems (Saboory *et al*., 2012). In Mexico, according to the 2002 national addiction survey, opioids are among the drugs consumed without prescription, mainly in the urban zone by a large sector of the population, young and adult and are supply by physicians, friends, and stores with an increase in the use of these drugs with recreational purposes is currently in evidance, which produces resultant addictions (Guzman *et al*., 2006).

* *Corresponding Author*
Dr.U.S.Mahadeva Rao., MSc, PhD, PGDMLT, FICS.
Professor, Faculty of Medicine and Health Science, Universiti Sultan Zainal Abidin, Kampus Kota, 20400 Kuala Terengganu, Malaysia.
Phone: +60 09 6275680(Direct), Cell: + 60 11 16547654
Fax: +60 09 6275583; E-mail: raousm@gmail.com

Over time, chronic opioid exposure causes adaptation in the brain reward pathways (Nestler, 2002).

Role of Calcium

McDonald and Lambert (2005); Smith *et al.* (2002) reported a reduced neuronal cell excitability resulting in reduce transmission of nerves impulses, inhibition of neurotransmitter release and pain stimulation following morphine administration. A recent study shows that calcium plays an important role in the genesis of morphine dependence and withdrawal (Seth *et al*., 2012).Calcium plays an important role in the transmission of pain signals in the central nervous system. At the presynaptic nerve terminal, voltage-gated calcium channels (VGCCs) open in response to action potentials to allow an influx of calcium ions. The influx is a graded process varying in a linear manner with the frequency of action potentials.

The influx, in turn, leads to release of various neurotransmitters that diffuse across the synaptic cleft to the postsynaptic membrane and binds to their specific receptors. Morphine is the drug of choice for treatment of chronic pain (McCarberg and Barkin, 2001).

It binds to m-opioid receptor (MOR) on the pre-and postsynaptic membranes. However, binding of morphine to MOR leads to inhibition of neurons concerned with transmission of pain. MOR does so by blocking VGCCs, opening inwardly rectifying potassium channels and inhibiting activity of adenylyl cyclase (North 1993). More recent observations have extended the actions of opioids to include the activation of protein kinase C (PKC), the release of calcium from extracellular stores, the activation of the mitogen-activated protein kinase (MAPK) cascade, and the realization that receptor trafficking plays an important role in receptor function (Belcheva *et al*., 2005).

Ca^{2+} Mediated Second Messenger

Calcium is a universal second messenger used to regulate a wide range of cellular processes. This role in signaling has to be conducted against the rigid homeostatic mechanisms that ensure that the resting level of Ca^{2+} is kept low (i.e. between 20 and 100 nmol l-1) in order to avoid the cytotoxic effects of a prolonged elevation of Ca^{2+}. Cells have evolved a sophisticated signaling system based on the generation of brief pulses of Ca^{2+} which enables this ion to be used as a messenger, thus avoiding its toxic effects (Berridge, 1997).

These second messengers can provide further pathways for opioid control of neuronal activity. Opioid effects on intracellular Ca^{2+} are of particular interest because of the widespread role of intracellular Ca^{2+} in a variety of cellular processes such as protein phosphorylation, membrane excitability, synaptic transmission, synaptic plasticity, genomic expression, cell growth and differentiation, and neurotoxicity (Siesjo, 1994; Ghosh and Greenberg, 1998). The chronic administration of morphine and related opioid drugs results in tolerance and dependence which limits the clinical utility of these agents. Neuronal plasticity is probably responsible in large part for tolerance and dependence.

Opioid and CaMKII activity

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) plays a crucial role in the neuroplastic events underlying memory formation and other phenomena (Liang *et al.*, 2004). CaMKII is an enzyme expressed in many tissues but is found in principally high abundance in the nervous system (Hanson and Schulman, 1992). CaMKII is a major calcium regulated signal transducer that regulates many neuronal systems including receptor-gated ion channels, calcium-dependent ion currents, and the synthesis and release of neurotransmitters (Schulman, 1993). Ca^{2+}regulation has further expanded the spectrum of opioid-induced biological effects on all three cloned opioid receptors (Piros *et al*., 1996). Many of Ca^{2+}mediated events occur when the released Ca^{2+} binds to and activates the regulatory protein calmodulin, which may activate calcium-calmodulin-dependent protein kinases, or may act directly on other effector proteins. Besides calmodulin, there are many other Ca^{2+}-binding proteins that mediate the biological effects of Ca^{2+}. In neurons, concominant increases in cytosolic and mitochondrial calcium are important for the synchronization of neuronal synaptic transmission with mitochondrial energy metabolism (Ivannikov *et al*., 2013). A study conducted by Przewlocki *et al* (1999) suggested that activation of opioid receptors can enhance several components of neuronal Ca^{2+} signaling pathways significantly and, as a consequence, enhance intracellular Ca^{2+} signals, the results provide evidence of a novel neuronal mechanism of opioid action on CNS neuronal networks that may contribute to both short and long-term effects of opioids. Learning and memory are proposed to be essentially involved in opioid addiction, it is interesting to hypothesize that selective inflection of those genes that play key roles in learning and memory processes could affect the development of opioid tolerance and dependence. Calcium/calmodulin-dependent protein kinase II (CaMKII) belongs to this group of genes, because it is expressed predominantly in cerebral cortex and hippocampus (Erondu and Kennedy, 1985) and is vital in certain types of learning and memory, inhibition or disruption of this kinase impairs spatial learning and memory tasks in rats (Fan et al., 1999). Interestingly, study has shown that morphine treatment increases the expression of CaMKII in rat hippocampus but not in other brain regions (Lou *et al*., 1999). A study conducted by Liang *et al* (2004) suggested that involving enhanced spinal expression of CaMKII after chronic exposure of mice to morphine would seem to fit well with an overall scheme in which CaMKII participates in the neuroplastic changes underlying tolerance to the analgesic effects of morphine. Studies has shown that CaMKII are essential for the development of opioid tolerance and dependence (Fan *et al.*, 1999; Lou *et al*., 1999), and suggested that CaMKII is important in neuronal development and formation of long-term potentiating (Bortolotto and Collingridge, 1998), so inhibition of this kinase prevents the neuronal changes induced by chronic opioid treatment and the subsequent tolerance and dependence (Fan *et al.*, 1999). However, intracellular Ca^{2+}, calmodulin, and CaMKII can all be regulated by opioids. Cytosolic free Ca^{2+} was increased after the treatment with opioids (Fields and Sarne, 1997;

Quillan *et al.*, 2002). Likewise, chronic treatments with opioids have been found to increase calmodulin activity (Nehmad*et al*., 1982).

Tang *et al.* (2006) strongly supported the hypothesis that CaMKII can act as a key and direct factor in promoting opioid tolerance and dependence. Identifying such a direct mechanism may be useful for designing pharmacological treatments for these conditions. CaMKIIactivity was increased after the treatment with morphine; the effect exhibited a temporal correction with the development of opioid tolerance and dependence. In mice treated with morphine (100 mg/kg s.c.), morphine tolerance and dependence developed in 2 to 6 h. An acute supraspinal administration of KN93 [2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl)]amino-N-(4 chlorocinnamyl)-N methylbenzylamine)], a CaMKII inhibitor, was able to dose-dependently reverse the already-established antinociceptive tolerance to morphine ($p < 0.001$ for 15–30 nmol; not significant for 5 nmol). KN92 [2-[N-(4-methoxybenzenesulfonyl)] amino-N-(4-chlorocinnamyl)-N-methylbenzylamine] (30 nmol i.c.v.), a kinase-inactive analog of KN93, did not affect opioid tolerance, study conducted by Fan et al (1999) supported the above result. Previous study proposed that CREB play an important role in the development of opioid tolerance and dependence (Nestler, 2001), CaMKII affects a number of downstream effectors, a key CaMKII downstream effector, activation of CREB (pCREB) in mice that have been treated with morphine. As expected, chronic treatment with morphine increased the levels of pCREB (Tang *et al.*, 2006).Another study conducted by Bileckiet *al* (2005), has shown that chronic morphine treatment and withdrawal decrease the level of phosphorylation of extracellular signal-regulated kinase(ERK) due to participation of up-regulation of PKC and CaMKII pathways which seems to be engaged in the ERK inhibition, their results provide evidence that both opioid administration and opioid withdrawal, affecting similar intracellular pathways, can exert different effects on ERK activity. Study by Gray *et al* (1999), suggested that their data are consistent with a model in which systemic amphetamine, by reversing the dopamine transporter, increases dopamine release and activates dopamine receptors on ventral striatal output neurons, resulting in transsynaptic, calcium-dependent glutamate and dopamine release in vivo. It is the secondary, calcium-dependent release that appears to be regulated by k-opioid receptor inhibition. By decreasing calcium influx, stimulation of k-opioid receptors, residing on dopaminergic and glutamatergic terminals in the ventral striatum, would eliminate the calcium-dependent component of amphetamine-induced dopamine and glutamate release, contributing to inhibition of amphetamine stimulated behaviors. Pierce *et al.* (1998) suggested that that neuronal calcium, acting via calcium-dependent kinases, promotes the expression of behavioral sensitization to opioids.

Role of Ca^{2+} in Opioid Induced Oxidative Stress

The oxidative stress (OS) is defined as a state where oxidative forces exceed the antioxidant system due to loss of balance between them, it is not only causes hazardous events such as lipid peroxidation and oxidative DNA damage, but also physiologic adaptive phenomena and regulation of intracellular signal transduction (Yoshikawa and Naito, 2002). It is characterized by excessive formation of free radicals or reactive oxygen species (ROS) and reactive nitrogen species (RNS) that exceeds the capacity of antioxidant mechanisms to eliminate these radicals. ROS derived from oxygen include radical species such as superoxide (O_2^-) and hydroxyl radical (HO·), along with non-radical species such as hydrogen peroxide (H_2O_2) (Yung *et al*., 2006). The risks to health caused by addictive drugs in relation to oxidative stress and free radicals, since the processes of peroxidation of lipoperoxidation are severely damaged in these individuals due to a loss in the balance between oxidation and antioxidation (Zhou *et al*., 2001).However Morphine caused activation of NADPH oxidase and production of superoxide, which contribute to macrophage injury, are apparently mediated by activation of μ-opioid receptors and subsequent activation of the phospholipase D pathway and increase in intracellular Ca^{2+} concentration (Bhat *et al*., 2004). The increase of cytosolic content of calcium through a combination of effects on calcium pumps, exchangers, channels and binding proteins (Zima and Blatter, 2006), affects the multiple aspects of calcium homeostasis and calcium dependent signaling (Tang *et al*., 2013). Ca^{2+} is one of the most potent, specific and tightly controlled cellular regulators, and virtually every calcium control mechanism in the cell is both sensitive to oxidative stress and able to modulate it (Ermak and Davies, 2002; Bogeski*et al*., 2011). Reactive oxygen and nitrogen species can be used as messengers in normal cell functions. However, at oxidative stress levels they can disrupt normal physiological pathways and cause cell death. Such a switch is largely mediated through Ca^{2+} signaling. OS causes Ca^{2+} influx into the cytoplasm from the extracellular environment and from the endoplasmic reticulum or sarcoplasmic reticulum (ER/SR) through the cell membrane and the ER/SR channels, respectively. Rising Ca^{2+} concentration in the cytoplasm causes Ca^{2+} influx into mitochondria and nuclei. In mitochondria Ca^{2+}accelerates and disrupts normal metabolism leading to cell death. In nuclei Ca^{2+} modulates gene transcription and nucleases that control cell apoptosis (Ermak and Davies, 2002). However, Guzman *et al.* (2006) revealed that Glutathione (GSH) is the main regulator of the redox balance and contributes to the protection of tissues exposed to oxidizing agent, and shown decrease glutathione levels in both weaned and adult animals and suggested that opioids like morphine unprotected the brain from oxidative stress. Sumathi *et al*(2011) stated that the glutathione level in the brain was lowered in morphine treated rats than in the control animals. Heroin has been shown to elevate dopamine (DA) level, and It well known that increase in DA oxidative metabolism lead to increased ROS formation and thus, ROS have been frequently associated with neuronal cell death due to damage to carbohydrates, amino acids, phospholipids, and nucleic acids. Also decrease in antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in mice brain (Xu *et al.*, 2006). Zhou *et al* (2011) revealed that OS and apoptosis in the CNS,

mechanisms for morphine induced neurotoxicity, the study determined the activities of SOD, CAT and GPx in the C6 cells, and observed the decreased activities of SOD, CAT, and GPx in C6 cells after morphine treatment. Studies have been established that glutamate actions mediated through N-methyl-D-aspartate (NMDA) subtype glutamate receptors has been implicated in the development of tolerance and dependence (Bajo*et al.,* 2006; Murray *et al.*,2007), and glutamate actions mediated through NMDA receptors result from the subsequent activation of nitric oxide synthase (NOS) and formation of NO, which implicated in morphine tolerance and dependence, thus morphine-induced NO overproduction and oxidative stress (Abdel-Zaher *et al*., 2010). Similar studies has shown that chronic opioids abuse resulted in the decrease level of antioxidant and anti-oxidases status (Zhou *et al*., 2000; Sumathi *et al*., 2011), Furthermore, chronic morphine exposure can be connected with some pathological consequences including neurotoxicity and neuronal dysfunction, hepatotoxicity, kidney dysfunction, oxidative stress and apoptosis, However attention has been paid to morphine than other opioids in connection with oxidative stress. It was believed that there are two conceivable ways how this drug participate in the development of OS that can either promote formation of free radicals or reduced activity of different components of antioxidant systems in target cells (Skrabalova *et al.,* 2013). Samarghandian *et al* (2014), study the effect of long-term treatment of morphine on enzymes, oxidative stress indices and antioxidant status in male rat liver, Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and liver malondialdehyde (MDA) level as well as activities of superoxide dismutase (SOD), glutathione-s-transfrase (GST) and catalase (CAT) were measured. Serum levels of AST, ALT and LDH were significantly higher in the morphine group compared with the control group and the activities of SOD, GST and CAT were significantly lower in the morphine group compared with the control group ($P < 0.01$).. Similar study conducted by Zhang *et al* (2004) indicated that there was serious oxidative stress and damage, and the exogenous antioxidants were able to prevent oxidative damage of biomolecules and the hepatotoxicity in morphine-administered mice. Therefore, strategies of blocking oxidative stress may be useful in the development of therapy for chronic morphine exposure.

Potential Role of Calcium Antagonist in the Treatment of Addiction

The voltage-dependent calcium channels have been the subjects of intensive research after chronic opioid exposure for the last few years (Little, 1995). A recent study has shown that calcium plays an important role in the genesis of morphine dependence and withdrawal, and suggests that calcium channel blockers could be useful in the management of opioid withdrawal (Seth *et al.,* 2012). Yamamoto *et al* (1978) reveal that a rise and fall of calcium level toward normal value in both chronic and acute morphone treatment during withdrawal syndrome, which suggest that different calcium related mechanism are involve in both types of dependence. The original classification showed the L-subtypes of channel to be selectively blocked by dihydropyridine calcium antagonists, which are used therapeutically as hypotensive and antiarrythmic agents (Tsien *et al;* 1988). Considerable evidence has been published indicating that dihydropyridine-sensitive calcium channels play a role in physical dependence on morphine and other addictive drugs (Little 1995; Verma *et al.,* 2001; Rabbani *et al*., 2003; Rabbani *et al.,* 2004). Antkiewicz (1999) revealed that number of dihydropyridine sensitive binding sites in the CNS represent voltage-sensitive calcium channels, which increase in rats showing signs of morphine withdrawal. Acute and chronic administration of L-type calcium channel blockers such as nimodipine, nifedipine and nicardipine were found to protect against naloxone-precipitated morphine withdrawal in mice and rats (Rabbani *et al*., 2003; and Rabbani *et al.,* 2004).

CONCLUSION

Derivatives from the opium plant have been described as analgesics and used for pain control since 3500 bc. It was not until 1806 that a pure opioid substance was isolated. This substance was called “morphine,” named after the Greek god Morpheus. Since that time the opium plant has yielded other derivatives, and synthetic analogues of morphine have been produced for medicinal use. The use of opioid medications has fluctuated because of a variety of factors, including but not limited to production, availability, governmental regulation, and physician and societal attitudes. Over the last 20 years the prescribing pattern of opioids has escalated significantly for a number of reasons. The increased trend in prescription writing has been accompanied by a concordant rise in the incidence of diversion and abuse, as well as an increase in the incidence of complications, including overdose and death. Over the past decade, evidence for a sustained benefit of opioids in alleviating chronic pain has remained weak and inadequate, although evidence of risk associated with use of the drugs has clearly escalated.

This change in which evidence of the efficacy of opioids has not changed whereas risk has increased should have a significant impact on treatment decisions based on risk-benefit analysis. Studies have shown that calcium mediated secondary messengers involved in the genesis of these conditions, better understanding of biological mechanisms underlie reduction in neuronal cell excitability could help in the identification of pharmacological targets for treatment.

REFERENCES

Abdel-Zaher AO, Abdel-Rahman MS, and Elwasei FM. Blockade of Nitric Oxide Overproduction and Oxidative Stress by Nigella sativa Oil Attenuates Morphine-Induced Tolerance and Dependence in Mice. Neurochem Res. 2010; 35:1557–1565.

Antkiewicz-Michaluk L. Voltage-operated calcium channels: characteristics and their role in the mechanism of action of psychotropic drugs. Pol. J. Pharmacol. 1999; 51: 179-86.

Bajo M, Crawford EF, Roberto M, Madamba SG, and Siggins GR. Chronic morphine treatment alters expression of N-methyl-D-

aspartate receptor sub-units in the extended amygdale. J Neurosci. Res. 2006; 83: 532–537.

Belcheva MM, Clerk AL, Haas PD, Serna JS, Hahn JW, Kiss A and Coscia CJ. μ and κ Opioid Receptors Activate ERK/MAPK via Different Protein Kinase C Isoforms and Secondary Messengers in Astrocytes.The Journal of biological chemistry. 2005; 280(30): 27662-9.

Berridge MJ. Elementary and Global aspects of calcium signalling. The Journal of Experimental Biol. 1997; 200: 315–319.

Bhat RS, Bhaskaran M, Mongia A, Hitosugi N, and Singhal PC. Morphine-induced macrophage apoptosis: oxidative stress and strategies for modulation. J. Leukoc. Biol. 2004; 75 (6): 1131-1138.

Bilecki W, Zapart G, Ligęza A, Wawrzczak-Bargiela A, Urbański MJ and Przewłocki R. Regulation of the extracellular signal-regulated kinases following acute and chronic opioid treatment. Cell. Mol. Life Sci. 2005; 62: 2369–2375.

Bogeski I, Kappl R, Kummerow C, Gulaboski R, Hoth M, Niemeyer BA: Redox regulation of calcium ion channels: chemical and physiological aspects. Cell Calcium. 2011; 50(5):407–423.

Bortolotto ZA and Collingridge GL. Involvement of calcium/ calmodulindependent protein kinases in the setting of a molecular switch involved in hippocampal LTP. Neuropharmacology. 1998; 37:535–544.

Ermak G, Davies KJ: Calcium and oxidative stress: from cell signaling to cell death. Molecular Immunology. 2002, 38(10):713–721.

Erondu NE and Kennedy MB. Regional distribution of type II Ca2+/calmodulin-dependent protein kinase in rat brain. J Neurosci. 1985; 5:3270–3277.

Fan GH, Wang LZ, Qiu HC, Ma L, and Pei G. Inhibition of calcium/calmodulindependent protein kinase II in rat hippocampus attenuates morphine tolerance and dependence. Mol Pharmacol. 1999; 56:39–45.

Fields A and Sarne Y. The stimulatory effect of opioids on cyclic AMP production in SK-N-SH cells is mediated by calcium ions. Life Sci. 1997; 61:595–602.

Ghosh A, Greenberg ME. Calcium signaling in neurons: molecular mechanisms and cellular consequences. Science. 1998; 268: 239 -247.

Gray AM, Rawls SM, Shippenberg TS, and McGinty JF. The k-Opioid Agonist, U-69593, Decreases Acute Amphetamine-Evoked Behaviors and Calcium-Dependent Dialysate Levels of Dopamine and Glutamate in the Ventral Striatum. J. Neurochem. 1999; 73: 1066–1074.

Guzman D, Va´zquez I, Brizuela N, Alvarez R, Mejı´a G, Garcı´a E, Santamarı´a D, de Apreza M, and Olguı´n H. Assessment of oxidative damage induced by acute doses of morphine sulfate in postnatal and adult rat brain. Neurochem Res. 2006; 31: 549–554.

Hanson PI and Schulman H. Neuronal Ca^{2+}/calmodulin-dependent protein kinases. Ann Rev Biochem. 1992; 61: 559-601.

Ivannikov MV and Macleod GT. "Mitochondrial Free Ca^{2+} Levels and Their Effects on Energy Metabolism in Drosophila Motor Nerve Terminals". J Biophys. 2013; 104 (11): 2353–2361.

Liang D, Li X, and Clark JD. Increased expression of Ca^{2+}/calmodulindependent protein kinase II alpha during chronic morphine exposure. Neuroscience. 2004; 123:769–775.

Little HJ. The role of calcium channels in drug dependence. Drug Alcohol Depend. 1995; 38: 173-94.

Lou LG, Zhou TH, Wang P and Pei G. Modulation of Ca2+/calmodulindependent protein kinase II activity by acute and chronic morphine administration in rat hippocampus: Differential regulation of a and b isoforms. Mol Pharmacol. 1999; 55:557–563.

McDonald J. And Lambert D. Opioid receptors. Continuing Education in Anaesthesia, Critical care and Pain 2005; 5(1): 22-25.

McCarberg BH and Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance complaince, quality of life, and analgesia; Am. J. Therapeutics. 2001; 8: 181–186.

Murray F, Harrison NJ, Grimwood S, Bristow LJ, Hutson PH. Nucleous accumben NMDA receptor subunit expression and function is enhanced in morphine-dependent rats. Eur J Pharmacol. 2007; 21: 191–197.

Nehmad R, Nadler H, and Simantov R. Effects of acute and chronic morphine treatment of calmodulin activity of rat brain. Mol Pharmacol. 1982; 22:389–394.

Nestler EJ. Under Siege: The Brain on Opiates. Neuron. 1996; 16: 897–900.

Nestler EJ. From neurobiology to treatment: Progress against addiction, nature neurosci. Supplement. 2002; 5: 1076-79.

Nestler EJ. Molecular basis of long term plasticity underlying addiction. Nature reviews/neuroscience. 2001; 2: 119-128.

North R A. Opioid actions on membrane ion channels. Hand book of Exp. Pharmacol. 1993; 104: 773–797.

Pierce RC, Quick EA, Reeder DC, Morgan ZR and Kalivas PW. Calcium-Mediated Second Messengers Modulate the Expression of Behavioral Sensitization to Cocaine. The journal of pharmacology and experimental therapeutics. 1998; 286: 1171–1176.

Piros ET, Hales TG, and Evans CJ. Functional analysis of cloned opioid receptors in transfected cell lines. Neurochem. Res. 1996; 21 (11): 1277-1285.

Przewlocki R, Parsons KL, Sweeney D, Trotter C, Netzeband JG, Siggins GR, and Gruol DL. Opioid Enhancement of Calcium Oscillations and Burst Events Involving NMDA Receptors and L-Type Calcium Channels in Cultured Hippocampal Neurons. The Journal of Neurosci. 1999; 19(22): 9705–9715.

Pu L, Bao G, Xu N, Ma L and Pei G. Hippocampal Long-Term Potentiation Is Reduced by Chronic Opiate Treatment and Can Be Restored by Re-Exposure to Opiates. The Journal of Neuroscience. 2002; 22 (5): 1914–1921.

Quillan JM, Carlson KW, Song C, Wang D, and Sadee W. Differential effects of mu-opioid receptor ligands on Ca2+ signaling. J Pharmacol Exp Ther. 2002; 302:1002–1012.

Rabbani M, Jafarian A and Sobhanian MH. Comparison of acute and chronic effects of nifedipine on naloxone precipitated morphine withdrawal in mice. J. Islamic Rep. Iran. 2003; 17 (3): 251-257.

Rabbani M, Jafarian A and Ahmadi A. Acute and Chronic effect of nitrendipine on naloxone precipitated morphine withdrawal in mice. Iranian Journal of Pharmaceutical Research. 2004; 2: 109-114.

Saboory E, Ghazizadeh V, Heshmatian B and Khademansari MH. Desmopressin accelerates the rate of urinary morphine excretion and attenuates withdrawal symptoms in rats.Psychiatry and Clinical Neurosciences.2012; 66: 594–601.

Samarghandian S, Afshari R and Farkhonden T. Effect of long-term treatment of morphine on enzymes oxidative stress indices and anti-oxidant status in male rats liver. Int J Clin Exp Med. 2013; 7(4): 1449-53.

Schulman H. The multifunctional Ca^{2+}/calmodulin-dependent protein kinases. Curr Opin Cell Biol. 1993; 5:247–253.

Seth V, Upadyaya P, Moghe V and Ahmad M. Role of calcium in morphine dependence and naloxone-precipitated withdrawal in mice. Journal of Experimental Pharmacology. 2011; 3: 7–12.

Siesjo BK. Calcium-mediated processes in neuronal degeneration. Ann NY Acad Sci. 1994; 747:140 –161.

Skrabalova J, Drastichova Z and Novotny J. Morphine as a Potential Oxidative Stress-Causing Agent. Mini-Reviews in Organic Chemistry. 2013; 10: 367-372.

Smith M T, Cabot P J, Ross F B, Robertson A D and Lewis R J. The novel N-type calcium channel blocker, AM336, produces potent dose-dependent antinociception after intrathecal dosing in rats and inhibits substance P release in rat spinal cord slices; Pain. 2002; 96: 119–127.

Sumathi T, Nathiya VC, and Sakthikumar M. Protective effect of bacoside-A against morphine-induced oxidative stress in rats. Indian J Pharm Sci. 2011; 73: 409-15.

Tang L, Shukla PK, Wang LX and Wang ZJ. Reversal of Morphine Antinociceptive Tolerance and Dependence by the Acute Supraspinal Inhibition of Ca2+/Calmodulin-Dependent Protein Kinase II. J Pharmacol Exp Ther. 2006; 317 : 901-909.

Tang T, Chang C, Wang H, Erickson JD, Reichard RA, Martin AG, Shannon EK, Martin AL, Huang Y and Aronstam RS. Oxidative stress disruption of receptor-mediated calcium signaling mechanisms. J Biomedical Science. 2013; 20:48.

Tsien RW, Lipscombe D, Madison DV, Bley KR and Fox AP. Multiple types of neuronal calcium channels and their selective modulation. Trends Neurosci. 1988; 11: 431-8.

Williams JT, Christie MJ and Manzoni O. Cellular and synaptic adaptations mediating opioid dependence. Physiol Rev. 2001; 81: 299-343.

Verma V, Mediratta PK and Sharma KK. Potentiation of analgesic and reversal of tolerance to morphine by calcium channel blockers. Indian Journal of Experimental Biology. 2001; 39: 636-642.

Xu B, Wang Z, Li G, Li B, Lin H, Zheng R and Zheng Q. Heroin Administered Mice Involved in Oxidative Stress and Exogenous Antioxidant-Alleviated Withdrawal Syndrome. Basic & Clinical Pharmacology & Toxicol. 2006;99: 153–161.

Yamamoto H, Harris RA, Loh HH, Way EL. Effects of acute and chronic morphine treatments on calcium localization and binding in brain. J Pharmacol Exp Ther. 1978;205:255–264.

Yoshikawa T and Naito Y. What Is Oxidative Stress. JMAJ. 2002; 45 (7): 271–276.

Yung LM, Leung FP, Yao X, Chen ZY, and Huang Y. Reactive oxygen species in vascular wall. Cardiovasc. Hematol. Disord. Drug Targets. 2006; 6 (1): 1-19.

Zhang Y, Zheng Q, Pan J and Zheng R. Oxidative Damage of Biomolecules in Mouse Liver Induced by Morphine and Protected by Antioxidants. Basic & Clinical Pharmacol. Toxicol. 2004; 95: 53–58.

Zima AV, Blatter LA: Redox regulation of cardiac calcium channels and transporters. Cardiovascular Research 2006, 71(2):310–321.

Zhou J, Li Y, Yan G, Bu Q, Lv L, Yang Y, Zhao J, Shao X, Deng Y, Zhu R, Zhao Y, and Cen X. Protective role of taurine against morphine-induced neurotoxicity in C6 cells via inhibition of oxidative stress. Neurotox. Res. 2011; 20: 334–342.

Zhou JF, Yan XF, Ruan ZR, Peng FY, Cai D, Yuan H, et al. Heroin abuse and nitric oxide, oxidation, peroxidation, lipid peroxidation. Biomed Environ Sci 2000;13: 131-9.

How to cite this article:

Ibrahim H Sani, Maryam I Umar, Nasir Mohamad, Mahadeva Rao US., Mohd Adzim Khalili R, Nor Hidayah Abu Bakar. Reviews on Calcium Mediated Secondary Messengers in Chronic Opioids Exposure / Addiction. J App Pharm Sci, 2015; 5 (01): 114-119.

Opioid addiction, a chronic relapsing disorder, continues to impose great health and economic burden on our society. Americaâ€™s opioid crisis has become an epidemic due in part to the lack of effective treatments for the negative physical and emotional states suffered by the individuals during withdrawal from chronic opioid use.Â Opioid-MOR signaling mediates a variety of intracellular functions through the Gi/o protein. One such function is the modulation of specific adenylate cyclase (AC) isoforms.Â However, upon repeated opioid exposure, the LC becomes increasingly excitable through allostatic adaptations. This results in increased NA signaling, causing many of the observed withdrawal symptoms associated with opioid abstinence [7,72]. Chronic opioid use may render vulnerable individuals at risk for developing opioid misuse and OUD due to neuropsychopharmacological effects of opioids on reward processing and hedonic regulation in the brain (2).Â Consequently, addiction involves a process of hedonic dysregulation, in which the motivation to obtain natural rewards is reorganized around seeking drug-associated reward and the desire to alleviate aversive states (e.g., stress and pain) (5). During the process of hedonic dysregulation, chronic use of drugs of abuse, including opioids, produces neurobiological alterations that increase the incentive salience of drug-related cues (6.Â However, a mindfulness-based intervention for prescription opioid misuse that