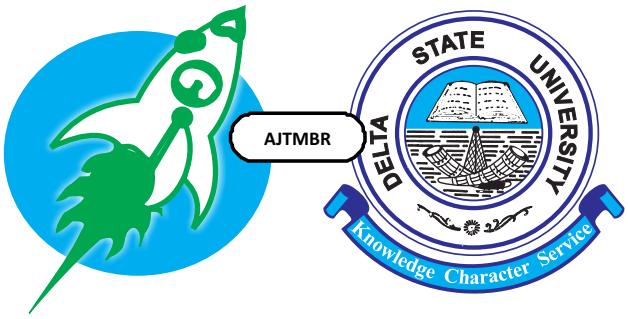
African Journal of Tropical Medicine and Biomedical Research (AJTMBR)



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Focus and Scope

The African Journal of Tropical Medicine and Biomedical Research is a multidisciplinary and international journal published by the College of Health Sciences, Delta State University of Abraka, Nigeria. It provides a forum for Authors working in Africa to share their research findings on all aspects of Tropical Medicine and Biomedical Sciences and to disseminate innovative, relevant and useful information on tropical medicine and biomedical sciences throughout the continent. The journal will publish original research articles, reviews, editorials, commentaries, short reports, case reports and letters to the editor. Articles are welcome in all branches of medicine and dentistry including basic sciences (Anatomy, Biochemistry, Physiology, Pharmacology, Psychology, Nursing etc) and clinical sciences (Internal Medicine, Surgery, Obstetrics and Gynaecology, Dental surgery, Child Health, Laboratory Sciences, Radiology, Community Medicine, etc). Articles are also welcome from social science researchers that document the intermediating and background social factors influencing health in countries of Africa. Priority will be given to publication of articles that describe the application of the principles of primary health care in the prevention and treatment of diseases.

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Articles submitted for publication should be typed double-spaced with 2.5cm margins with accompanying CD-ROM in Microsoft Word format for easy and quick peer review and typesetting. Each of the following sections should begin in a new page: title page, abstract, introduction, materials and methods, results, discussion, acknowledgment (s), references, tables, legends to figures and illustrations. The manuscript should include:

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The title page should include the following information: 1. the title and sub-title; 2. the name(s) of the author(s); 3. the affiliation(s) of the author(s); 4. name and address of the corresponding author and 5. three to six key words for indexing and retrieval purposes.

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Original Research- The journal welcomes articles reporting on original research, including both quantitative and qualitative studies. Full-length articles should generally not exceed 3000 words, excluding abstract, tables, figures, and references. The subject matter should be organised under appropriate headings and sub-headings as itemized above.

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Table of Contents

Review articles

The Pharmacological Profile, Therapeutic Importance and Limitations with the Use of Oxycodone: A Review

Umukoro, EK[1], Elijah OB[1], Igben VJO[1], Moke EG[2]

Abstract

Introduction: Pain is perhaps the commonest symptom for which patients seek medical care and represents a major socioeconomical burden on healthcare systems globally. Despite a great deal of research into pain and analgesic strategies, the effective management of pain remains challenging. Oxycodone is an old drug but still holds significant therapeutic utility today. Its use has however been fraught with challenges such as abuse. Furthermore, the precise mechanism of action/receptors through which it acts is still the subject of some controversy.

Materials and Methods: A literature search on PubMed and google scholar was performed using the terms 'opioid crisis' 'pain pathway', 'types of nociception', 'opioid receptors' 'peripheral and central sensitisation', 'descending modulation pathway', 'pain management'. Studies, review articles and editorials published in English from 1st Jan 2000 to 1st Dec 2023 were included in this study.

Results: The depth of the problem of the opioid crisis and the effects in different continents has prevented the global utilization of oxycodone; the pharmacological profile of oxycodone which is an old drug with current clinical relevance was also reviewed. Significantly, there exists a gap in existing knowledge of the mechanism of action and precise receptors through which oxycodone acts.

Conclusion: The pain pathway is a complex process with multiple interdependent processes and under modulations from neuronal, endocrine, and inflammatory systems. Oxycodone exploits the pain pathway in producing analgesia but presents a real and present danger of addiction and dependence.

Keywords: Oxycodone**;** pain pathway; opioid crisis; opioid receptors

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INTRODUCTION

Oxycodone, also known as "hillbilly heroin" is an opioid alkaloid that is one of the most commonly used opioid analgesics in the treatment of different forms of pain, especially acute post-operative pain and is comparable to morphine in terms of efficacy. The opioid crisis gave the drug more notoriety than fame; but being an old drug, the basic pharmacology of oxycodone is often overlooked in the field of research and as such, what is known about its mechanism of action is subject to some controversy. (Kalso, 2005) Drug discovery has developed in leaps and bounds since the discovery of oxycodone and contemporary techniques and facilities need to be applied to old drugs to confirm or discover their full pharmacological profile.

Oxycodone is also a common substance of abuse and as such is a controlled substance in most countries of the world. The opioid epidemic remains a significant pressing issue and will not resolve easily. Numerous factors, including the

inappropriate prescription of opioids, lack of understanding of the potential adverse effects of long-term therapy, opioid misuse, abuse, and dependence, have contributed to the current crisis. Alarmingly, the overwhelming majority of opioid abusers begin their addiction with prescription medications, primarily for chronic pain.

METHODOLOGY

We performed a literature search on PubMed and Google Scholar using the terms 'opioid crisis' 'pain pathway', 'types of nociception', 'opioid receptors' 'peripheral and central sensitisation', 'descending modulation pathway', 'pain management'. We included any studies, review articles and editorials published in English between 2000 to 2022. Due to the relatively large number of articles published on the subject, review articles that were published in well-established journals in the field were prioritised.

DISCUSSION

History

Oxycodone was synthesized from thebaine in 1916 and achieved clinical application in 1917. It was used in many parts of Europe mainly for acute pain, alone or in combination with acetaminophen and phenacetin (Kalso, 2005)

Oxycodone is also one of the most abused drugs worldwide. Since its release in 1917, it has proven to be a drug with significant risk of dependence and fatal toxicity if misused. In 2007, oxycontin (one of the brands of oxycodone) manufacturers, Purdue Frederic Company Inc., (an affiliate of Purdue Pharma), pled guilty to misleading regulators and prescribers about the risks of addiction abuse potential of this drug. The law suit arose due to the increase in incidence of oxycodone related deaths when there was an increase in prescription and supply of oxycodone and other related law suits have been filed since then. (Van Zee, 2009; Webster, 2012) There are presently more deaths due to prescription opioids than due to cocaine, heroin and psycho-stimulants combined and this appears to be aided by a high street demand for opioids, with street value for a single oxycodone tablet estimated to be about £25 (Pilgrim *et al.*, 2015) Most of the prescribers of oxycodone in the USA are located in Florida and there has been a steady increase in its prescription and supply in that region. Oxycodone related deaths in the region between 2007 and 2010 increased by 62.5% while during this same time frame, there was a decrease in deaths attributed to other painkillers such as methadone (1.1% decrease) and hydrocodone (30.7% decrease). These were the findings upon autopsy and toxicological screens to determine the cause of death in accidental deaths. Findings were compared to data from previous years and from other regions in the USA. (Ogle *et al.*, 2015) In 2015 alone, 52,000 people died of drug overdoses, with over 30,000 of those people dying from opioid drugs. A recent community forum led by the Cleveland Clinic contrasted this yearly death rate with the loss of 58,000 American lives in 4 years of the Vietnam War. (Vadivelu, 2018)

Non-medical prescription opioid use is particularly problematic in rural areas example of which are some American areas encompassing poverty stricken, educationally less developed and geographically mountainous Appalachian Kentucky, Virginia and West Virginia and this is where oxycodone derives its other name "hillbilly heroin". (Young *et al.*, 2010; Tunnell, 2016)

Classification of Opioids

Opiates are the non-peptide synthetic morphine-like drugs whilst the term opioid is more generic,

including all substances that have effects similar to morphine and can be classified into four:

- Endogenous opioid peptides (e.g. endorphin,dynorphin and enkephalin)
- Opioid alkaloids such as morphine purified from the poppy, *Papaver somniferum*
- Semi synthetic opioids such as heroin which have modifications to the basic morphine structure in this case, diacetylation.
- Synthetic derivatives with structure unrelated to morphine

  Examples are: The phenylpiperidine series e.g. Fentanyl
  The Methadone series e.g. Methadone
  The Benzomorphan series e.g. Pentazocine
  Semi-synthetic thebaine derivatives e.g. oxycodone. (Adapted from McDonald and Lambert, 2008)

Sources of Oxycodone

Phenantrenes and Benzyl-isoquinolines make up the two alkaloid chemical classes of Opium. Thebaine, a phenantrene alkaloid, is present in 90% of the opium derived from *Papaver bracteatum* which is morphine-free. It is also present to a lesser extent (0.2-0.8%) in *Papaver somniferum* which contains morphine. While thebaine is the precursor of oxycodone, it is very toxic and lacks analgesic properties. (McDonald and Lambert, 2008)

Structure of Oxycodone

The oxycodone molecule consists of four rings (two planar and two aliphatic). Its basic chemical formula is 6-deoxy-7, 8- dihydro- 14-3-O-methyl-6-oxomorphine and differs from morphine by a dehydroxylated 6th carbon atom. (Figure 1).

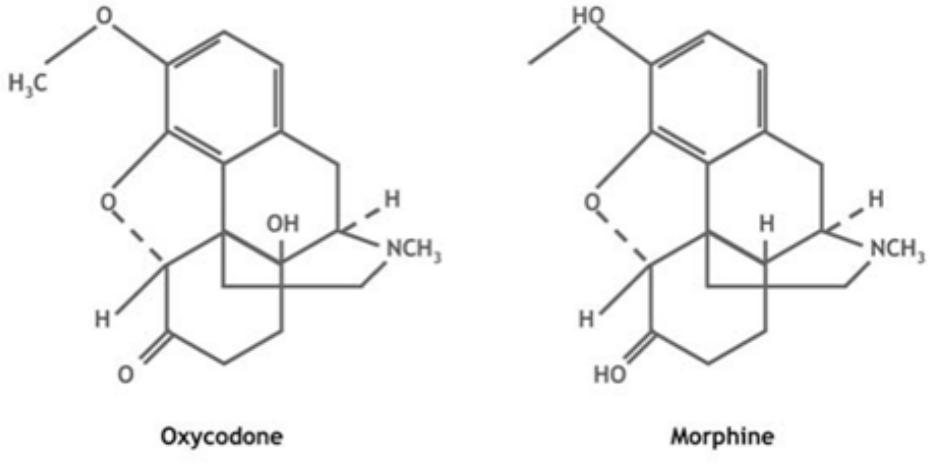

Figure 1: Chemical structural comparison of oxycodone and morphine (Ordonez *et al.,* 2007)

Pharmacokinetics of Oxycodone

Oxycodone is available in several different preparations for oral immediate, oral extended/ controlled release and intravenous use. Onset of action with pain relief is rapid, as the effect occurs as early as 15 minutes, and peaks at approximately one hour following oral administration. Peak Oxycodone plasma concentrations were noted at between 1.4 hours and 3 hours after administration depending on the type of preparation.

Oxycodone has an apparently higher bioavailability than morphine due to the 3-methoxy substituent that prevents significant first pass metabolism. This is reported at between 42% and 87 %. (Riley *et al.,* 2008)

Oxycodone is 45% protein bound, predominantly to albumin and is extensively distributed into tissues including skeletal muscle, liver, intestinal tract, lungs, spleen and brain. The apparent volume of distribution of oxycodone is 2.4 ± 0.8 L/Kg following intravenous administration. Oxycodone has relatively low lipid solubility and thus is not suitable for sublingual administration. (Lugo *et al.*, 2005)

The major metabolic pathway of oxycodone in man is by N-demethylation which leads to the formation of noroxycodone. Oxycodone and occasionally noroxycodone is further metabolized to noroxymorphone and oxymorphone most likely by O-demethylation. Oxymorphone and norxymorphone are active metabolites (), but as their plasma concentrations are significantly lower than that of the parent compound, oxycodone, they probably do not contribute markedly to the analgesic effects. Less than 10% of oxycodone also gets broken down to oxycodol via 6-keto reduction. (Lofddal *et al.*, 2013)

N-demethylation is carried out by CYP3A4/5 while O-demethylation is carried out by CYP2D6. The genetic polymorphisms of CYP2D6 causes inter individual and interethnic variability in the rate of metabolism giving rise to poor, intermediate, extensive and ultra-rapid metabolizers. (Kokki *et al.,* 2012)

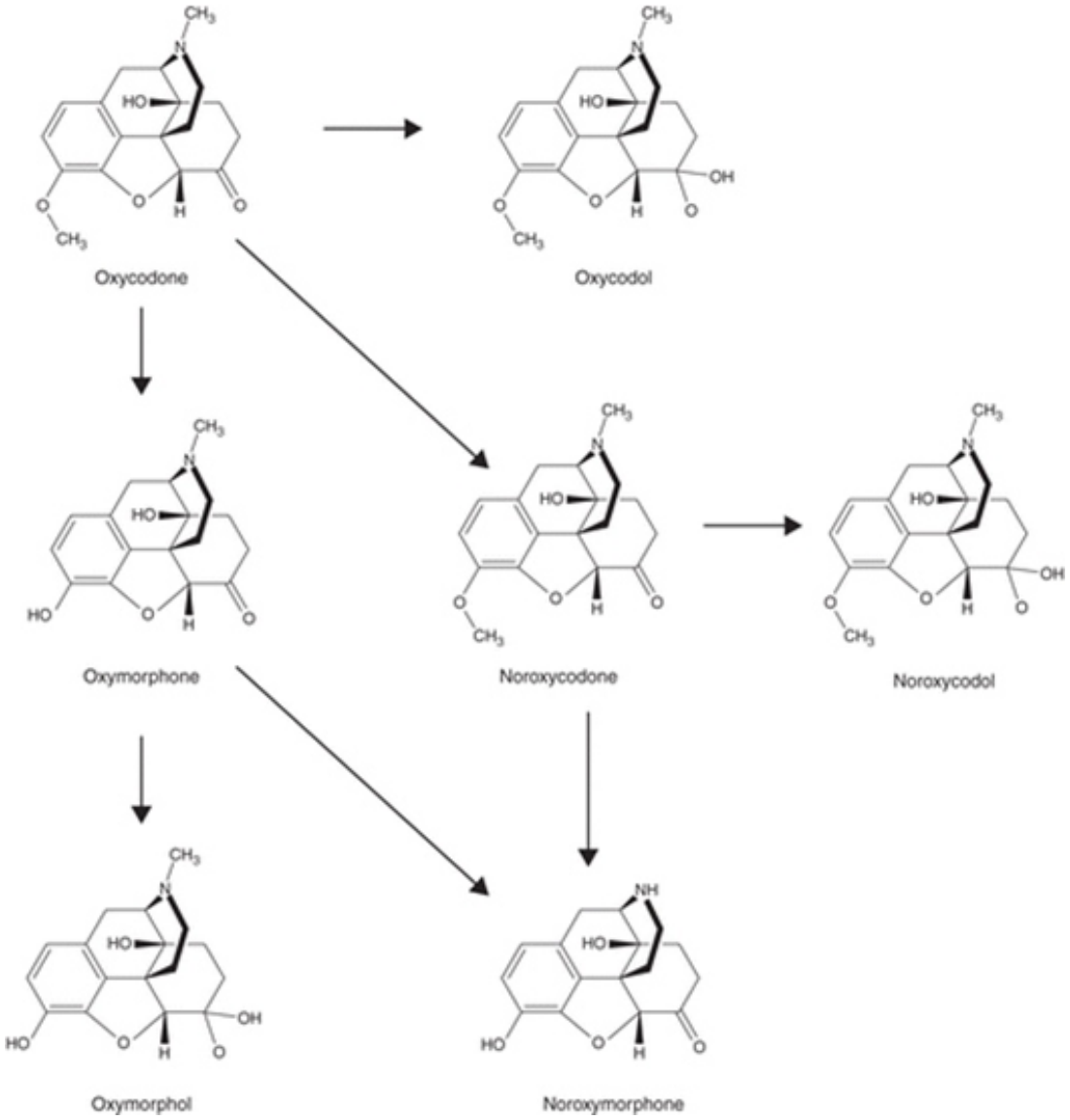

Figure 2: Metabolism of Oxycodone (Kokki et al., 2012)

Pharmacodynamics of Oxycodone

Although the major opioid receptors are G-protein coupled and as such similar in structure and function, binding affinity profiles and intrinsic efficacy exhibited with different ligands clearly distinguish them.

Types of opioid receptors

The opioid receptor family includes Mu opioid receptors (MOR), Delta opioid receptors (DOR),

Kappa opioid receptors (KOR) and ORL receptors. They are encoded by Oprm1, Oprd1, Oprk1 and pronociceptin/preproorphanin FQ genes respectively but all have approximately 60% amino acid sequence homology with each other. A number of subtypes are also known to exist such as MOR_1, MOR_2, $DOR_{1,}$ $DOR_{2,}$ $KOR_{1,}$ $KOR_{2,}$ and KOR_3 and were suggested on the basis of *invitro* and *invivo* pharmacological studies. Some techniques have been and are being employed to define the structure and mechanisms of the opioid receptors including agonist directed signalling at the different receptors and fluorescence recovery after photobleaching (FRAP). (Lomberk *et al.*, 2008)
The prototype agonist at MOR is morphine while that of KOR is ketocyclazocine. These agonists were used to define their respective receptors. The delta receptor was defined by comparing the activity of endogenous opioid peptides and opiate ligands across various systems while nociceptin/orphanin is the ligand at the ORL receptor. Their location and function appears to vary as do their ligands. In fact, ORL receptor plays a role in antinociception. (MacDonald and Lambert, 2011; Baiula *et al.*, 2015)

All receptors appear to have a high affinity for the opioid receptor antagonist, Naloxone. Further studies have also suggested MOR_1 subtype antagonist, naloxonazine. (Chaijale, *et al.*,

Opioid receptor signalling and behaviour
All four opioid receptors are coupled to heterotrimeric (Gαβ) inhibitory G proteins $G_i/G_{(0)}$ as seen in . Following ligand binding, the G protein dissociates into subunits and initiates a cascade of events ending in interaction with inward rectifying potassium channels (kir3) and inhibition of adenylyl cyclase activity with a decrease in cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) while there is an increase in mitogen activated protein kinase (MAPK) phosphorylation. There is also a reduction in voltage activated opening of calcium ion channels. Interaction with these ion channels causes cellular hyperpolarization and inhibition of tonic neural activity. (Costantino *et al.,* 2012; Al Hasani and Bruchas, 2011) Studies have shown that all opioid receptor subtypes may come together to form homomeric or heteromeric complexes. () These complexes appear to show a unique pharmacological profile distinct from that of individual receptors. There is also evidence that complexes may also be formed between some opiate receptors and cannabinoid or α2 adrenergic receptors or even proteins such as β arrestin 2 at the level of desensitization. (Costantino *et al.,* 2012)

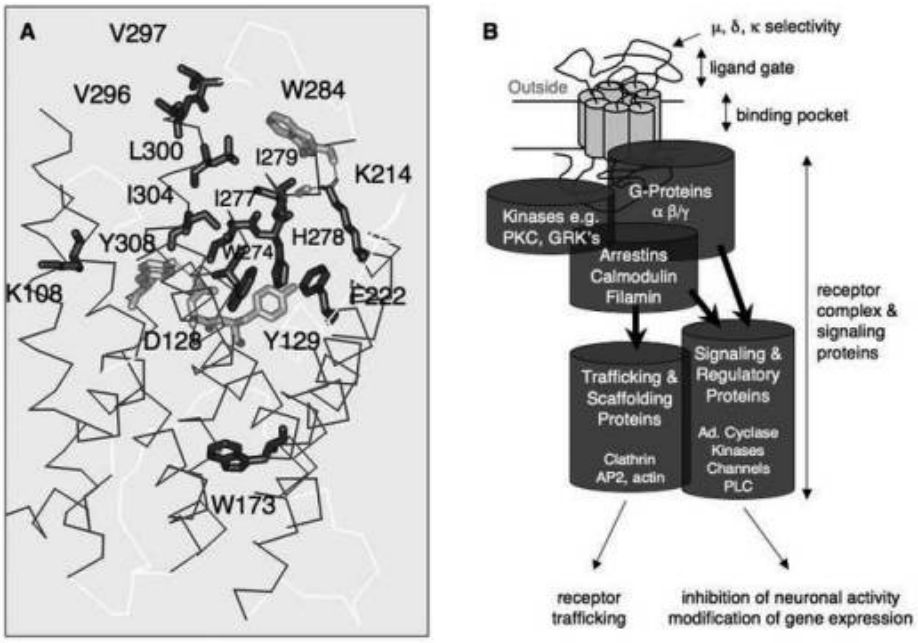

Figure 3: Prototype structure and signalling pattern of opioid receptors (Kieffer and Evans, 2010)

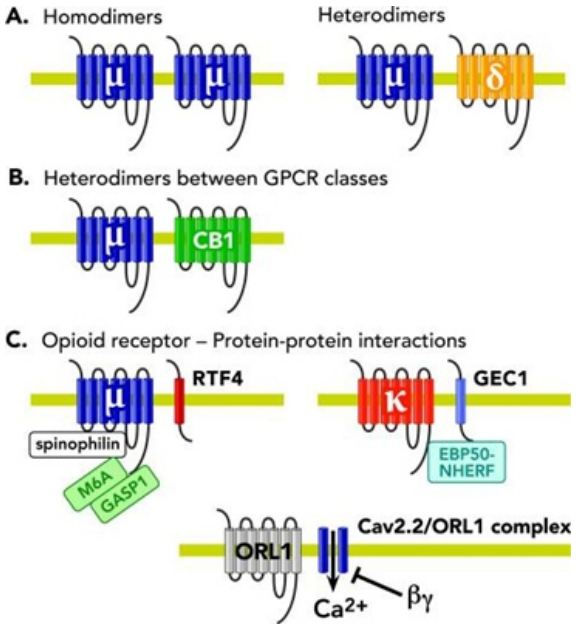

Figure 4: Opioid receptor dimerization/ complex formation (Al Hasani and Bruchas, 2011)

Effects of Oxycodone and the Controversy Surrounding its Mechanism of Action

The beneficial and adverse effects of oxycodone in part, contribute to the controversy surrounding its mechanism of action. Some authors suggest that based on the mechanism of its effects, oxycodone is primarily a KOR agonist with only a little affinity for the MOR, (Ordonez *et al., 2007)* while others join the school of thought that oxycodone is an MOR agonist primarily.

Pain

The most vital effect of the opioid family is on pain control and as such they are the mainstay of treatment for moderate to severe postoperative pain as well as other types of pain. Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage. (Terman and Bonica, 2003) Pain may also be classified as physiological or pathological. Physiological pain occurs in the absence of actual tissue or nerve damage, serving as a warning sign for impending injury. Examples include muscle cramp and abdominal colic. In pathological pain, tissue or nerve damage occurs. (Liu and Kelliher, 2022)

Pain can be acute or persistent and it is in the latter that opioids find the most significance. Persistent pain is classified into nociceptive pain (such as post-operative or chronic inflammatory pain) or neuropathic pain which is a dysfunction of the nervous system causing pain perception in the absence of tissue injury (such as phantom limb pain and post-stroke pain). While nociceptive pain readily responds to opioids, neuropathic pain does not. Nociceptors are pain receptors that are located in the dorsal root ganglia and trigeminal ganglia. They receive sensory information from the peripheral tissues and transmit these signals to the higher centres via the peripheral and central branches respectively. The source of sensory information is usually from release of neurotransmitters following tissue damage. There are two types of nociceptors: peptidergic nociceptors which express neuropeptides and terminate in the most superficial laminae of the dorsal horn targeting lamina I projection neurons and interneurons of outer lamina II; and non peptidergic nociceptors which target interneurons of inner lamina II. These are important in nociception and complex interactions between excitatory and inhibitory parts of the pain pathway occur. (Zhang et al., 2013) Tissue injury evoked hyperalgesia evolves in two distinctive forms. First is primary hyperalgesia which is characterised by enhanced nociceptor excitability within the damaged zone and caused by accumulation of pro inflammatory mediators. Secondary hyperalgesia develops more slowly around the zone of injury and is due to central sensitization which is neuronal sensitization at the spinal cord level. Secondary hyperalgesia gives rise to referred pain in visceral inflammation. (Treede and Mageri, 2003) Both these forms of hyperalgesia involve ascending and descending tracts. () The ascending tracts contain second order neurons which ascend to higher centres via the contralateral spinothalamic and spinoreticular tracts, which are located in the anterolateral white matter of the spinal cord and terminate in the primary and secondary somatosensory cortices, the insula and the anterior cingulate cortex and the prefrontal cortex. Information travelling along this tract gets processed in the thalamus. (Liu and Kelliher, 2022) The descending pathways are responsible for modulating pain and are inhibitory. They involve the peri aqueductal gray (PAG) which receives input from the thalamus, hypothalamus and cortex and also collaterals from the spinothalamic tract. MOR is found mainly pre-synaptically in the periaqueductal gray and in the superficial dorsal horn of the spinal cord. They are also located in external plexiform layer of the olfactory bulb, the nucleus accumbens in several

layers of the cerebral cortex and in some of the nuclei of the amygdala as well as the nucleus of the solitary tract. (Liu and Kelliher, 2022; McDonald and Lambert, 2005) The PAG neurons excite cells in the Nucleus Raphe Magnus (NRM) that in turn projects down to the spinal cord to inhibit pain transmission by the dorsal horn cells. NRM cell bodies synapse on cells in lamina II and III and stimulation of this region produces a powerful analgesia by activation of inhibitory interneurons. (Steeds, 2009) KOR localizes to the limbic and other diencephalic areas, brain stem and spinal cord and has been implicated in spinal, supra-spinal and peripheral analgesia. The DOR are found primarily in the brain and participate in supra-spinal and spinal analgesia. (Lomberk *et al.,* 2008)

Under physiological conditions, opioid receptors are transported from primary afferent neuronal cell bodies to central/spinal terminals. Cell bodies of the DRG neurons express mRNA and proteins of opioid receptors which are also subsequently transported to the small medium and large diameter peripheral nerve terminals. Tissue injury induces this process even more so. These opioid receptors mediate anti-hyperalgesia by opioid agonist binding. (Stein and Lang, 2009)

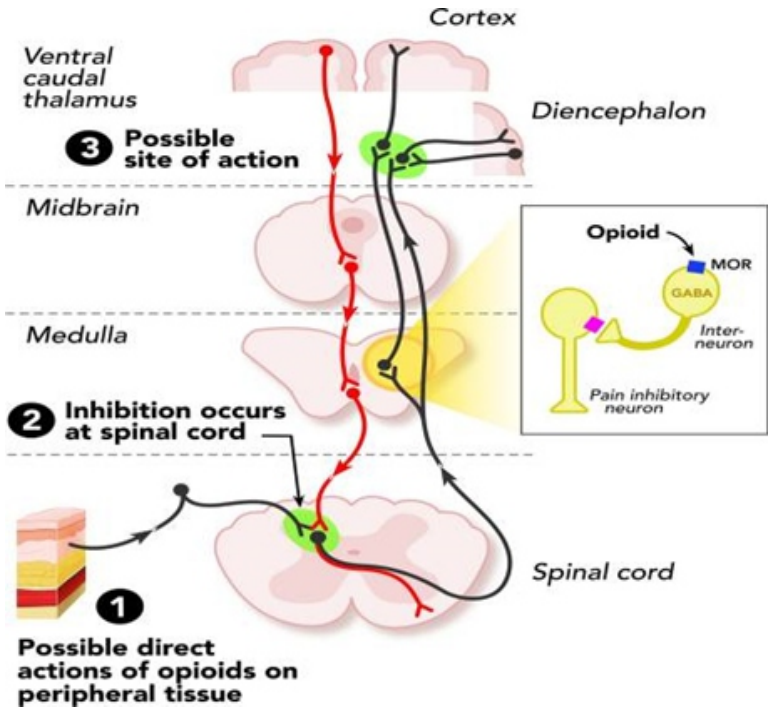

Figure 5: **The pain pathway and the role of opioids (Al Hasani and Bruchas, 2011)**

Mechanism of action

The mechanism of action of oxycodone in analgesia is still controversial. In one study, experimental rats with chronic constriction injury of the sciatic nerve and streptozotocin induced diabetes were given either morphine or oxycodone intravenously or subcutaneously. Behavioural studies confirmed analgesic effects

of oxycodone and morphine on test animals. The effects of oxycodone however, were abolished by the selective KOR antagonist nor-binaltorphimine (norBNI), while those of morphine were not. This was also supported by radioligand binding which found preferential binding of oxycodone to KOR specifically $KOR_{2\beta}$ over MOR in the CNS. (Riley *et al*., 2007) Similar study by Nielson et al., in 2007 appear to confirm this. Following chronic constriction injury (CCI) of the sciatic nerve in rats, the antinociceptive effects of intrathecal (i.t.) oxycodone, but not intrathecal morphine, were abolished by nor-BNI. They therefore concluded that oxycodone is active at KOR in contrast to morphine. KOR has also been implicated in aetiology of visceral pain in animal models as mice lacking KOR are found to be more susceptible to visceral inflammation and hence visceral pain. Furthermore following abdominal inflammation, KOR signalling, mRNA and protein expression are up regulated suggesting that agonists with significant enough activity at KOR can cause sufficient analgesia in pathologic conditions but not in health. (Hughes *et al.,* 2013) The effect of oxycodone and morphine on visceral pain was studied in human subjects who received multimodal pain stimulation to the oesophagus in order to elicit pain. It was observed that oxycodone was superior to morphine in improving pain threshold, though this could not be categorically attributed to KOR. (Riley *et al.,* 2007) A further study on efficacy of oxycodone and morphine in chronic pancreatitis concluded that oxycodone was a more effective mode of pain management than morphine. (Staahl *et al*., 2007) Together, these studies provide presumably sufficient evidence that oxycodone is a KOR agonist at the very least.

If the data that oxycodone acts by stimulating KOR primarily appears compelling, the evidence that it is a MOR agonist is even more so. In fact, most of the effects of oxycodone have been suggested as being caused by MOR stimulation. However, Kokki *et al.,* (2012) opines that oxycodone is a MOR agonist but with comparatively significant lower binding affinity than morphine. It also has affinity for the KOR and DOR but comparatively lower than that for the MOR. Nozaki and Kamei (2007) agreed with this suggestion at least in part by experiments on normal mice and mice with streptozocin induced diabetes mellitus. Different groups of both sets of mice were pre-treated with norBNI (KOR selective antagonist), β-funaltrexamine and naloxonazine (selective MOR antagonist); then administered oxycodone. Behavioural analyses were then carried out to assess the effects of all the drugs on pain threshold. It was found that the analgesic effects of oxycodone were abolished completely by naloxonazine, attenuated to a lesser extent by β-funaltrexamine and partially but significantly by norBNI. It was therefore concluded that oxycodone produces its antinociceptive effects primarily through MOR_1, and to a lesser extent through KOR and other MOR subtypes.

Constipation, a common side effect of oxycodone characterised by inhibition of propulsion in the GIT, appears to be a direct consequence of MOR activation. Ahmedzai *et al.,* (2012) clinically proved this by carrying out a study on patients with moderate to severe cancer pain. Patients were switched from other opioids to either oxycodone alone or a combination of oxycodone and naloxone. The patients switched to the combination therapy experienced clinically relevant and statistically significant improvement in constipation compared to those on oxycodone alone. Furthermore, Delgado-Aros *et al*., (2003) compared the effects of selective KOR agonist Asimadoline and a placebo on visceral sensation and gastrointestinal motor functions in humans

and concluded that it did not cause inhibition of gastrointestinal reflexes thus reducing the possibility that effects noted by Ahmedzai *et al.,* (2012) could have been caused by naloxone antagonism at KOR. *Invitro* pharmacological techniques have also been used to compare the mechanism of inhibition in circular muscle and longitudinal muscle. Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP), naltrindole, norBNI, DAMGO [Tyr-D-Ala-Gly-(*N*–Me)Phe-Gly-ol] and DADLE [d-Ala^2, d-Leu^5]-enkephalin acetate amongst others, which are all antagonists and agonists at MOR, DOR or KOR were used to define the mechanism of inhibition and the conclusion was that MOR and not KOR mediated the inhibition of contraction in longitudinal muscle. (Gray *et al.,* 2005*)*

The role of MOR in onset of physical dependence was studied using knockout mice with MOR gene deletions and strengthens the case for MOR stimulation as the mechanism of action of oxycodone. They displayed no expression of naloxone induced withdrawal symptoms. (Narita, 2001) Stimulation of the reward pathway results in craving which is the psychological component of dependence and this is mediated by MOR located in the mesocorticolimbic pathway originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens, amygdala and prefrontal cortex. Oxycodone appears to induce dopamine release indirectly by decreasing GABA-inhibition via MOR located in the VTa which releases dopamine. This release of dopamine causes euphoria and reinforcement of drug-seeking behaviours. Stimulation of KOR however, appears to inhibit striatal dopamine release. (Narita, 2001; Ballantyne and La Forge, 2007) Euphoria, nausea, vomiting, pupillary constriction and respiratory depression which are long known to be caused by stimulation of MOR are more commonly associated with Oxycodone use. (Eldalal et al., 2020)

All together, these studies suggest a preponderance of evidence for oxycodone as a MOR agonist; however, when contrasted with evidence for oxycodone as a KOR agonist which appears compelling by itself, it highlights the controversy on the subject and justifies the need for further research in the area. Oxycodone remains a drug poorly or incompletely studied, universally abused yet clinically relevant and as such extensive research of its mechanism of action is necessary to better improve its benefit profile.

Oxycodone as a substance of abuse

Oxycodone is approved by the US Food and Drug Administration (FDA) as a schedule II narcotic analgesic though it is not commonly prescribed in Nigeria. Consequently, the opioid crisis in Nigeria was more centred around codeine and tramadol. (Dumbili, 2023) Each year however, prescription opioid abuse and misuse results in approximately 13,800 deaths and 250,000 emergency department visits as reported in. Over 85,000 admissions to addiction treatment facilities for prescription opioid abuse occur annually. Prescription opioid abusers incur more healthcare costs than non abusers, and fraud associated with prescription opioids is estimated to cost public and private payers

about $75 billion per year. It is estimated that nearly a third of people who abuse drugs started with prescription opioid medicines. This has severely limited the use of oxycodone in healthcare. (Vadivelu et al., 2018)

CONCLUSION

In conclusion, oxycodone is a potent analgesic that works primarily by stimulating opioid receptors. The particular receptors stimulated is still of some dispute as modern technology is yet to be applied to research the mechanism of action of the drug. Furthermore, the use of these drugs has over time been severely limited by the high abuse potential as oxycodone played a major role in the opioid crises. It will also be beneficial to research the specific receptors oxycodone stimulates in bringing about its effects as well as the relative abundance of different opioid receptors in different tissue.

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