

OPIOID Pharmacology : A Review

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ABSTRACT

Pain is an unpleasant sensation that originates from ongoing or impending tissue damage. Management of different types of pain (acute, postoperative, inflammatory, neuropathic cancer) is challenging and yet the most frequent issue encountered by clinicians. Pharmacological therapy is the first line of approach for the treatment of pain and opioid drugs are prescribed for acute and chronic pain of moderate/severe intensity arising from malignant and non-malignant diseases. The opium poppy was cultivated as early as 3400BC in Mesopotamia. The term opium refers to a mixture of alkaloids from the poppy seed. Opiates are naturally occurring alkaloids such as morphine or codeine and opioid is the term used broadly to describe all compounds that work at the opioid receptors. The physiologic modulation of noxious stimuli involves a highly complex system that integrates the actions of multiple opioid receptors and endogenous opioid peptides. Opioids produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout the central nervous system (CNS) with high concentrations in the nuclei of tractus solitarius, peri-aqueductal grey area (PAG), cerebral cortex, thalamus and substantia gelatinosa (SG) of the spinal cord. They have also been found on peripheral afferent nerve terminals and many other organs. The efficacy of centrally applied opioids is well recognized, but when applied peripherally, for example in post-traumatic and inflammatory states, their actions are less reliable. Although they are associated with addiction, dependence, tolerance and abuse liability even then their place in pain management remains undebatable and unchallenged.

Keywords: Endorphins, Morphine, Opioids, Pain

I. INTRODUCTION

Pain transcends the boundaries of all medical specialties and impacts almost everyone at some stage of their life. Every second patient in most hospitals suffers from pain and every third patient complains of severe pain [1]. Since pain has a tremendous impact on the patient's physical and psychological well-being [2], inadequate pain therapy can greatly increase healthcare costs. The International Association for the Study of Pain has called unrelieved pain "a major global healthcare problem" [3].

Adequate pain therapy improves the patient's performance of daily activities, minimise sufferings, promote recovery and earlier discharge from hospital. Providing a rapid and effective pain relief without compromising the patient's general condition has remained a challenge for physicians till date. World

Health Organization (WHO) has designed a pain ladder (originally established for cancer pain) that has been used successfully in many diseases. According to this model, different classes of analgesic drugs are recommended based on the intensity of pain. At the first level, patients with mild pain (1-4 on a 10 point scale) are recommended to use non-opioids such as acetaminophen, non-steroidal anti-inflammatory agents or a cox-II inhibitor. At the second level, a weak opioid such as codeine and Tramadol (TRA) should be added for treatment of patients with moderate (5-6) pain. At the third level, the weak opioid is changed to a strong opioid such as morphine. This regimen clearly states that opioids are integral and indispensable part of pain management system. Severe inflammatory pain respond better to NSAIDs than an opioid while opioids are effective for nociceptive pain. Nociceptive pain commonly arise from tissue injury or inflammation, for example trauma, burns, infection, arthritis and ischemia.



Neuropathic pain is less responsive to opioids and requires the use of adjuvant medications like tricyclic antidepressants and anticonvulsants (gabapentin). Neuropathic pain occurs after damage to peripheral and central nervous system. Diabetic neuralgia, post-herpetic neuralgia and post-traumatic neuralgia are some examples.

The term opiate refers to compounds structurally related to products found in opium, a word derived from opos, the Greek word for "juice". Opiate is used to describe alkaloid molecules that include morphine and codeine. While the term opioid refers to compounds having functional properties like opiates; the opioid category includes not only the opiates but also semi-synthetic non-alkaloids and even endogenous peptides.

The first undisputed reference to "poppy juice" is found in the writings of Theophrastus in the third century B.C. Opium is obtained from the unripe seed capsules of the poppy plant, *Papaver somniferum*. The milky juice is dried and powdered to make powdered opium, which contains a number of alkaloids. Opioids can be categorized into three subgroups; 1) naturally occurring compounds (termed opiates) such as morphine and codeine) chemically modified natural compounds (semisynthetic) such as hydrocodone, buprenorphine and oxycodone) and completely artificial compounds (synthetic) such as fentanyl, tramadol and ketobemidone. Some opioids act as agonists to all kind of opioid receptors (morphine) and some act as both agonist and antagonist (buprenorphine). Morphine (the prototypical MOP-r agonist) is the main active alkaloid in opium, whereas the baine can be used as a starting point for production of semisynthetic MOP-r(mu opioid receptor) ligands

Opium has been used for thousands of years, and its clinical value cannot be overstated. Although mild to moderate pain is typically treated with acetaminophen or aspirin or other nonsteroidal anti-inflammatory drugs (NSAID), but the mainstay of pain management for severe pain remains the opiates. Their effects on pain are quite intriguing. Unlike local anesthetics that relieve pain by blocking all sensory transmission, opiates selectively modulate the perception of pain without interfering with basic sensations, such as light, touch, temperature, position sense and discrimination of sharp and dull. The opioids target the subjective component of

pain, an integrated sensation and it is common for a patient to remark after taking an opiate that "the pain is still there, but it does not hurt." [4]. The initial pharmacologic studies of opiates focused on the general effects of morphine in humans [5] which was isolated from opium in 1805 [6] and first sold by Merck in 1827, with its popularity increasing with the development of the hypodermic needle in 1857. Its synthesis was delayed by its complex ring structure until 1956 [7].

Opioids were first used for their actions on gastrointestinal motility, as they decrease propulsive peristaltic contractions, while increasing circular muscle tone and intraluminal pressure [8]. Morphine and its derivatives are used today for the treatment of acute and chronic pain. It is now understood that morphine and other opioid drugs act on an endogenous opioidergic system, which is not only involved in setting pain (nociceptive) threshold and controlling nociceptive processing but also participates in modulation of gastrointestinal, endocrine and autonomic function, as well as a possible role in cognition [9]. The modern era of opioid research came with the demonstration of opioid receptors in 1973 [10,11] using binding assays based upon stereo selectivity [12].

Although opioids are effective pain-relieving drugs, however they are associated with side effects and fortunately most of these are reversible. The most frequently appearing side effects are nausea, vomiting, pruritus and constipation; these also happen to be the most bothersome. Respiratory depression is uncommon at standard analgesic doses, but can however be life-threatening. Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. The pharmacology of the opioids is quite similar. They differ mainly in potency, duration of action and optimal route of administration.

II. METHODS AND MATERIAL

A. Opioid Receptors

The opioids were among the earliest neuropeptides identified in the nervous system [13]. Opioid receptors are most abundant in the CNS [14], but have also been localized in many peripheral tissues of the mammalian organism [15] Opioid receptors are a group of G protein-

coupled receptors (GPCR). Each receptor consists of an extracellular N-terminus, seven transmembrane helices, three extra- and intracellular loops, and an intracellular C-terminus characteristic of the GPCRs. The opioid receptor types are approximately 70% identical with differences located at N and C termini. The greatest diversity is found in their extracellular loops.

Three major type of opioid receptor have been identified, mu (μ), delta (δ) and kappa (κ). The G-protein coupled opiate receptor-like protein (ORL1 or NOP) was included to other members of the opioid receptor family, based on its structural homology (48-49% identity) to the other opioid receptors. μ -opioid receptor was identified in binding assays in 1973 and was cloned about 20 years later. Other opioid receptors have also been proposed, such as zeta (ζ) opioid receptor, which has been shown to be a cellular growth factor modulator and epsilon (ϵ) opioid receptor. However, efforts to locate a gene for ϵ -receptor have been unsuccessful and epsilon-mediated effects were absent in $\mu/\delta/\kappa$. It has been suggested that μ -, δ - and κ -receptors have several subtypes, μ 1-3, delta1-2 and κ -1-3. It has also been postulated that μ -1 receptors produce analgesia while μ -2 mediates respiratory depression. The function of the μ -3 receptor is unknown. The existence of opioid receptor subtypes has not been confirmed in either cloning studies or experiments with knock out animals.

Physiological roles for each of the opioid receptors have not been clearly defined. Pain relief effects are mediated by all three receptor types, but in different degree. μ -Receptor mediates the most potent nociceptive effects, accompanied however by the development of dependence. δ -Receptor has lower efficacy in mediating pain relief but also a reduced addictive potential. κ -Receptor mediates analgesic effects in peripheral tissues [15]. The nociceptinopioid receptor (NOP receptor), is phylogenetically related to δ receptor, μ receptor, and κ receptor, it does not bind the same ligands [16].

μ Receptor: The receptor is characterized by its high affinity for Morphine. It is the major receptor mediating action of morphine and its congeners. Endogenous ligands for μ receptor are Endomorphins-1 and Endomorphin-2, found in mammalian brain, produce biological effects ascribed to this receptor. Other opioid peptides like β -endorphins, Enkephalins and Dynorphins

bind to μ receptor with lower affinity [17]. Two subtypes of μ receptors have been proposed:

μ 1 : Has higher affinity for morphine, mediates supraspinal analgesia and is selectively blocked by naloxone.

μ 2 : Has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action [18].

Mu (μ) (agonist morphine) Mu receptors are found primarily in the brainstem and medial thalamus. Mu receptors are responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility and physical dependence. Mu1 is related to analgesia, euphoria, and serenity, while Mu2 is related to respiratory depression, pruritus, prolactin release, dependence, anorexia, and sedation. These are also called OP3 or MOR (morphine opioid receptors) [19].

Activation of the mu opioid receptor (mu is named for morphine) results in: inhibition of adenylyl cyclase, closure of voltage-gated calcium channels, opening of potassium channels and membrane hyperpolarisation (Ben Snyder, 2014). These cellular events can inhibit neuronal firing and neurotransmitter release. All of the opioid analgesics act as agonists at the μ receptor. Mu activation inhibits the ascending pain pathway, which includes neurons passing through the dorsal horn of the spinal cord, brainstem, thalamus and cortex. Mu agonists also activate the inhibitory descending pain pathway, which involves sites in the brainstem. Peripheral mu receptors located at the site of tissue injury and inflammation may also mediate analgesia (Inturissi CE2002). Mu receptor agonism is responsible for the euphoria associated with opioids. This effect is distinct from the pain pathways and depends on the mesolimbic dopaminergic system [20].

Kappa (κ) Receptor: is defined by its high affinity for ketocyclazocine and Dynorphin A. Norbinaltorphimine is a selective κ -antagonist. Two subtypes of receptors K1 and K3 are functionally important. Analgesia caused by agonist is primarily spinal (K1) or supraspinal (K3) [17]. Kappa receptors are found in the limbic and other diencephalic areas, brain stem, and spinal cord, and are responsible for spinal analgesia, sedation, dyspnea,

dependence, dysphoria, and respiratory depression. These are also known as OP2 or KOR (kappa opioid receptors).

Delta (d) (agonist delta-alanine-delta-leucine-enkephalin) Delta receptors are located largely in the brain and their effects are not well studied. They may be responsible for psychomimetic and dysphoric effects. They are also called OP1 and DOR (delta opioid receptors).

Sigma (s) (agonist N-allylnormetazocine) Sigma receptors are responsible for psychomimetic effects, dysphoria, and stress-induced depression. They are no longer considered opioid receptors, but rather the target sites for phencyclidine (PCP) and its analogs [19].

B. Transduction Pathways

The signaling pathways of opioid receptors well understood and characterized now. The conformation changes of receptor occur when ligand binds to the receptor that replaces GDP bound to G α -subunit by GTP. The activated G α dissociates from trimeric G-protein complex and inhibits the adenylyl cyclase and thereby inhibits the formation of cAMP, which subsequently activates the ion channels in the membrane. Ion channels can also be regulated by direct interaction with G $\beta\gamma$ subunits. Activation of Ca²⁺ channel, suppresses Ca²⁺ influx, and thereby attenuates the excitability of neurons and/or reduces neurotransmitter release such as substance P and calcitonin gene-related peptide (CGRP) (pro-nociceptive and pro-inflammatory neuropeptides). At the postsynaptic membrane, opioid receptors mediate hyperpolarization by opening G protein-coupled K⁺ channels thereby preventing neuronal excitation.

Opioid receptors located on the presynaptic terminals of the nociceptive C-fibers and A delta fibers, when activated by an opioid agonist, will indirectly inhibit these voltage dependent calcium channels, decreasing cAMP levels and blocking the release of pain neurotransmitters such as glutamate, substance P and calcitonin gene-related peptide from the nociceptive fibers, resulting in analgesia [19].

Opioids also modulate protein kinases. The MAP kinases signaling system comprises a series of hierarchical kinases that transduce signals through successive

phosphorylation. The MAP-kinase pathways were initially discovered to be driven by growth factors but were also found to be involved in cross-talk between GPCR and growth factor signaling [21]. ERKs (extracellular signal-regulated kinases) one of the major MAPKs, plays a central role in regulation of cellular processes as proliferation, differentiation and cell-cell communication [22].

Opioids also modulate pain perception by acting through AKT or protein kinase B (PKB) signaling pathway. The best known effect of activated AKT is inhibition of apoptosis, programmed cell death and activation of protein syntheses. AKT is activated via a protein kinase called PI3-kinase (PI3K) that in turn is activated by the G $\beta\gamma$ subunits of GPCR [23,24]. PI3K can also activate ERK. Opioid receptor signaling has been associated with both cell proliferation and cell death in various cells expressing opioid receptors [25].

It has been suggested that binding of opioid ligands triggers the same signaling pathways as in neuronal cells, in other words modulation of cAMP, Ca²⁺ channels and kinases. Stimulation of opioid receptors on leucocytes modulates proliferation, chemotaxis and cytotoxicity of leucocytes [26,27].

Within the central nervous system, activation of MOP receptors in the midbrain is thought to be a major mechanism of opioid-induced analgesia. Here, MOP agonists act by indirectly stimulating descending inhibitory pathways which act upon the periaqueductal grey (PAG) and nucleus reticularis paragigantocellularis (NRPG) with the net effect of an activation of descending inhibitory neurons. This leads to greater neuronal traffic through the nucleus raphe magnus (NRM), increasing stimulation of 5-hydroxytryptamine and enkephalin-containing neurons which connect directly with the substantia gelatinosa of the dorsal horn. This in turn results in a reduction of nociceptive transmission from the periphery to the thalamus. Exogenous and endogenous opioids can also exert a direct inhibitory effect upon the substantia gelatinosa (in the dorsal horn) and peripheral nociceptive afferent neurones, reducing nociceptive transmission from the periphery. This series of cellular events and mechanisms produces much of the analgesic effect commonly seen following the administration of MOP agonists [28].

C. Endogenous Neurotransmitters

Morphine and its alkaloid derivatives are used extensively in the treatment of pain [29]. These compounds are the most potent class of analgesics used clinically. The high potency and specificity of morphine suggest that it may bind to specific receptors in the nervous system to induce its biological effects. In the early 1970s, several groups of researchers identified specific opioid receptors in brain and peripheral tissues [30]. While these receptors were highly sensitive to morphine, morphine is not endogenously expressed in the body and therefore could not be the endogenous ligand for these receptors. This led to the search for the endogenous neurotransmitters at the opiate receptors.

The endogenous ligands for the opioid receptors are the enkephalins, endorphins and dynorphins, encoded by separate genes. These pentapeptides vary in their affinity for the opioid receptor, but none binds exclusively to one type. A new class of highly selective μ selective endogenous peptide the endomorphines has recently been described. Endomorphin-1 and endomorphin-2 are tetrapeptides structurally unrelated to the other endogenous opioid peptides. Their distribution in the central nervous system mirrors that of the μ -opioid receptors and they display extremely high affinity and selectivity for the μ receptor. Their affinity for receptor binding sites is more than 1000-fold greater than for delta or kappa receptors and they are thought to be the endogenous ligands for the μ receptor [31,32]. Both the enkephalins and dynorphins are neurotransmitters in the brain involved in pain perception, cognitive functions, affective behaviors and locomotion, and they are involved in the central control of certain endocrine functions such as water balance [33]. Both peptides are widely distributed in the central nervous system (CNS) but localized to discrete neuronal pathways [34]. Beta-endorphin is expressed at much lower levels in the brain and only synthesized in a few neuronal pathways in the CNS, in particular in those originating from hypothalamic nuclei. As a result, the enkephalins and dynorphins are considered the predominant central opioid peptide transmitters.

Endorphins: Endorphins are endogenous opioid polypeptide compounds. They are produced by the pituitary gland and the hypothalamus in vertebrates during strenuous exercise [Partin1983], excitement, pain

and orgasm and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. Endorphins work as "natural pain relievers." They can be found in more than twenty different parts in the body, such as the pituitary glands as well as in many parts of the brain and nervous system [35, 36].

The term "endorphin" implies a pharmacological activity as opposed to a specific chemical formulation. The term endorphin is a general name for many opioid-like proteins. (It consists of two parts: endo and orphin; these are short forms of the words endogenous met-enkephalin which means "a morphine-like substance which is produced by the human body") [37].

Types of Endorphins: Four types of endorphins are created in the human body. They are named alpha, beta, gamma and sigma endorphins [38]. The four types have different numbers and types of amino acids in their molecules; they have between 16 and 31 amino acids in each molecule. More endorphins are released in the pituitary gland during times of pain or stress. Exercise increases the endorphin release too. For the same reason, exercise results in a better mood. Endorphins are the most powerful endogenous opioid peptide neurotransmitters and are found in the neurons of both the central and peripheral nervous system. They are present abundantly in the hypothalamus and pituitary gland. They are released when the body encounters any sort of stress or pain. During severe pain the endorphins in our body cause an analgesic effect to occur, to lessen the pain that is inflicting our body. But during stress, endorphins act differently. They are released in the limbic system which reduces the extent of anxiety that our body is feeling. Not only does the opiate cause the pain to decrease it also causes the feelings of euphoria to occur as well as the release of many sex hormones [Koltyn2000]. Endorphins act through opiate receptors. Endorphins have the highest affinity for the μ 1-opioid receptor, slightly lower affinity for the μ 2 and δ -opioid receptors and low affinity for the κ 1 opioid receptors.

Enkephalins: Enkephalins are pentapeptides involved in regulating nociception in the body. Discovered in 1975, two forms of enkephalin were revealed, one containing leucine ("leu") and the other containing methionine ("met"). Both are products of the proenkephalin gene [39].

Dynorphins

Dynorphins are produced in many different parts of the brain, including hypothalamus, hippocampus, midbrain, medulla, pons and the spinal cord and has many different physiological actions, depending upon their site of production. For example, dynorphins that are made in magnocellular vasopressin neurons of the supraoptic nucleus are important in the patterning of electrical activity. Dynorphins produced in magnocellular oxytocin neurons cause negative feedback inhibition of oxytocin secretion. Dynorphin produced in the arcuate nucleus and in orexin neurons of the lateral hypothalamus affects the control of appetite. Dynorphins are stored in large (80-120 nm diameter) dense-core vesicles that are considerably larger than vesicles storing neurotransmitters. These large dense-core vesicles differ from small synaptic vesicles in that a more intense and prolonged stimulus is needed to cause the large vesicles to release their contents into the synaptic cleft. Dense-core vesicle storage is characteristic of opioid peptides storage [40].

Dynorphins primarily exert their effects through the μ -opioid receptor and act as modulators of pain response, maintain homeostasis through appetite control and circadian rhythm, weight control and regulation of body temperature [18].

Beta-endorphin and the enkephalins have relatively high affinity at μ and δ receptors and much lower at κ . The dynorphins, by contrast, have relative selectivity for κ receptors over the μ and δ . These receptors mediate a complex, partially overlapping array of physiologic and neurobio-logic functions [41].

Beta-endorphin is a product of proopiomelanocortin in which is produced primarily in the anterior pituitary of humans. It is also produced in the central nervous system and in the periphery. The μ receptors mediate both the analgesic and rewarding effects of opioid compounds (be they heroin or prescription opioids) as well as their effects on many systems in the body, such as in the hypothalamic-pituitary-adrenal (HPA) axis, immune, gas-trointestinal (GI), and pulmonary function.

D. OPIOID Receptor Ligands

Two types of ligands at opioid receptors can be differentiated in view of their chemical structure: alkaloids and peptides.

1. Alkaloids

The original opiates, morphine and codeine were isolated from opium. Their structures provided the scaffolds upon which many of the current μ opiates are based. Thebaine, another major component of opium, is a valuable precursor in the synthesis of many of these derivatives.

Agonists. The first known opiate alkaloid was morphine, isolated from the poppy seeds in 1803 by Seturner. The structure of morphine was elucidated 120 years later [42], and its full systematic name is: 7, 8 - didehydro -4, 5 - epoxy - 17 - methyl - (5 α , 6 α) - morphinan - 3, 6 - diol. Morphine and other opiates are widely used in clinical practice for blockade of most severe pain syndromes or for anesthetic purposes.

Morphine is primarily an agonist ligand for the μ receptor. Its affinities for δ and κ receptors are sufficiently low that it is used as a selective μ receptor ligand in pharmacological studies [43]. Antagonists. Opioid antagonists most frequently used by pharmacologists are synthetic alkaloids such as naloxone and naltrexone [44]. Naloxone, which was the first pharmacologically pure antagonist identified, is considered to be a "universal", non-selective opioid antagonist. The action of an agonist is characterized as opioid only if its effects are "naloxone-reversible" [45]. Although naloxone and its analog naltrexone bind to all three opioid receptors, they have the highest affinity for the μ receptor [46].

2. Peptides

Kosterlitz and Hughes were the first to sequence the pentapeptide enkephalins [13] which soon expanded into the following three families of peptides, each with its own precursor peptide: preproenkephalin, prodynorphin, and b-lipotropin [47].

The "typical" opioid peptides, including enkephalins, dynorphins and β -endorphin are derived from three precursor molecules; pro-enkephalin, pro-dynorphin and

pro- opiomelanocortin, all of which are expressed in the CNS, but their presence in peripheral tissues has also been confirmed [48].

The “atypical” opioid peptides originate from the variety of precursor proteins and carry various amino acid sequences at their N-terminal regions, only the N-terminal Tyr residue is conserved [49]. The N-terminal tetrapeptide of most atypical opioid peptides represents the minimum sequence for full opioid activity.

The first group of “atypical” opioid peptides, identified by Brantl et al. [50] in 1979 were milk protein derived β -casomorphins (β -CM), which are obtained by proteolytic fragmentation of β -casein. Aside from butorphanol and nalbuphine, all clinically available opioids are mu -opioid receptor preferring agents. The k -opioid agonists, butorphanol and nalbuphine, are limited by partial agonist activity as well as central side effects, primarily dysphoria, sedation, and hallucinations, and are little used in the treatment of chronic pain. Oxycodone has only recently been suggested to be a K -opioid preferring agonist [51] and has not been systematically examined in the treatment of chronic pain. Thus, although there is strong preclinical evidence for efficacy of k-opioid agonists in chronic pain treatment, current agents are inadequate, and novel agents are under experimental study in humans [52].

Pharmacokinetics of OPIOIDS Absorption

The majority of opioids i.e. morphine, oxycodone, hydro-morphone, methadone, ketobemidone, tramadol, tapentadol, fentanyl, sufentanil, buprenorphine and codeine all show a high gastrointestinal permeability, and thus they are readily and completely absorbed from the gastrointestinal tract following oral administration. However, the bioavailability of fentanyl, sufentanil and buprenorphine is very low and highly variable since these opioids are subjected to high hepatic first pass metabolism [53-55]. As a consequence they are not available in pharmaceutical formulations intended for oral administration. Recent research has revealed that low and variable bioavailability seen after oral administration may partly be explained by the substances being substrates for transporters present in the intestinal epithelium [56]. Drug transporters are present all over the body in the gastrointestinal tract, in the kidneys, in hepatocytes and at the blood–brain

barrier. The two main families of drug transporters of relevance to opioid pharmacokinetics are (i) the ATP binding cassette (ABC) efflux transporters [e.g. P-glycoprotein (P-gp)], which restrict the passage and (ii) the solute carrier (SLC) influx transporters which facilitate the passage [57,58].

Distribution

After being absorbed the opioids distribute throughout the body tissue i.e. the site of main action within the central nervous system (CNS). To reach the CNS opioids have to cross the blood–brain barrier. Fentanyl, morphine and methadone have been shown to be substrates for the P-gp efflux transporters [59,60]. The clinical aspects of fentanyl have been confirmed in a single human study, where an increased respiratory depression was seen in patients with a decreased P-gp expression. Oxycodone is not a substrate for the P-gp efflux transporters, but it is substrate for the SCL influx transporters thus being actively transported into the brain. Most of the research elucidating the transport of opioids across the blood–brain barrier has been done in rodents and thus caution should be taken when extrapolating the findings to humans. However, as for the absorption, this may play a role in treatment heterogeneity [58].

Metabolism

After absorption most opioids undergo first pass metabolism in the liver and here there are major differences between classes of drugs as well as individual differences in responses to the same opioid. The chemical class phenylpiperidines are metabolized by CYP3A4. This enzyme has many genetic polymorphisms but until recently none has been shown to be of major clinical relevance. Within the class 4,5-epoxymorphinans (which additionally are alkyl esters at the 3-phenolic hydroxyl group i.e. codeine, hydrocodone and oxycodone) drugs are subject to O-dealkylation, catalyzed by CYP2D6 enzymes. Opioids of the 4,5-epoxymorphinan class are also subject to N-dealkylation. This results in nor-derivatives, which bind to the m receptors, but show lower affinities than the parent compounds. The N-dealkylation is mainly catalyzed by CYP3A4 [58].

Excretion

The vast majority of opioids are excreted as metabolites through the kidneys. Thus for substances transformed to pharmacologically active metabolites, decreased kidney function may influence the overall clinical effect due to accumulation of the metabolites and this may explain differences in effects and side effects between opioids. The best described examples of clinically relevant active metabolites are morphine-6-glucuronide and morphine-3-glucuronide. As stated above the 6-glucuronide is thought to be an active analgesic like the parent compound, morphine. Although the potency ratio to morphine still remains to be established it is plausible that in steady-state conditions and in patients with impaired kidney function it contributes more to analgesia. Results from some studies have suggested the 3-glucuronide possess anti-analgesic and excitatory effects. However results from other studies have failed to prove that. Thus clinical relevance of accumulation of this metabolite in patients with impaired kidney function still remains controversial [61].

III. RESULT AND DISCUSSION

PHARMACOLOGICAL ACTIONS OF OPIOID AGONISTS

Central Nervous System

Analgesia: Most effective in relieving dull, continuous and poorly localised pain arising from deeper structures, for example the gut. Less effective against superficial and sharp pain. Neuropathic pain can be very resistant, but patients may report that pain is still present, but the intensity is decreased and it no longer bothers them as much.

Sedation: Drowsiness, feeling of heaviness and difficulty in concentrating are common. Sleep may occur with relief of pain, although they are not true hypnotics.

Euphoria and dysphoria: Morphine and other opioids cause a sense of contentment and well-being (euphoria). If there is no pain, morphine may cause restlessness and agitation (dysphoria).

Hallucination: These are more common with KOP agonists, but morphine and other MOP agonists may also cause hallucinations.

Tolerance and Dependence: Tolerance is the decrease in effect seen despite maintaining a given concentration of a drug. The mechanism is not fully understood but could involve down regulation of opioid receptors or decreased production of endogenous opioids. Dependence exists when the sudden withdrawal of an opioid, after repeated use over a prolonged period, results in various physical and psychological signs. These include; restlessness, irritability, increased salivation, lacrimation and sweating, muscle cramps, vomiting and diarrhoea.

Cardiovascular System: Mild bradycardia is common as a result of decreased sympathetic drive and a direct effect on the sino-atrial (SA) node. Peripheral vasodilatation caused by histamine release and reduced sympathetic drive may result in a slight fall in blood pressure that may be significant in hypovolaemic patients.

Respiratory System: Respiratory depression is mediated via MOP receptors at the respiratory centres in the brainstem. Respiratory rate falls more than the tidal volume and the sensitivity of the brain stem to carbon dioxide is reduced. Its response to hypoxia is less affected but if hypoxic stimulus is removed by supplemental oxygen then respiratory depression may be augmented. Concurrent use of other CNS depressants, for example benzodiazepines or halogenated anaesthetic, may cause marked respiratory depression. Opioids suppress cough. Codeine suppresses cough to a degree similar to morphine but has lesser analgesic activity. Morphine and diamorphine are used in paroxysmal nocturnal dyspnoea, as they produce sedation, reduce preload and depresses abnormal respiratory drive.

Gastrointestinal System : Stimulation of the chemoreceptor trigger zone causes nausea and vomiting. Smooth muscle tone is increased but motility is decreased resulting in delayed absorption, increased pressure in the biliary system (spasm of sphincter of Oddi) and constipation.

Endocrine System: The release of ACTH, prolactin and gonadotrophic hormone is inhibited. Secretion of ADH is increased.

Ocular effects: MOP and KOP receptors in Edinger-Westphal nucleus of oculomotor nerve are stimulated

by opioids resulting in constriction of the pupils (meiosis). Histamine release and itching Some opioids cause histamine release from mast cells resulting in urticaria, itching, bronchospasm and hypotension. Itching occurs most often after intrathecal opioids Muscle rigidity Large doses of opioids may occasionally produce generalised muscle rigidity especially of thoracic wall and interfere with ventilation.

Immunity: The immune system is depressed after long-term opioid abuse Effects on Pregnancy and Neonates All opioids cross the placenta and if given during labour, can cause neonatal respiratory depression. Chronic use by the mother may cause physical dependence in utero and lead to a withdrawal reaction in the neonate at birth that can be life threatening. There are no known teratogenic effects [62].

IV. CONCLUSION

Opioid agonists inhibit adenylyl cyclase (decreasing cyclic AMP production), close N-type voltage-operated calcium channels, and open calcium-dependent inwardly rectifying potassium channels. This results in hyperpolarization and a reduction in neuronal excitability. Changes in intracellular Ca^{2+} influence the release of neuro-transmitters and modulate the activity of protein ki-nases. Opiates are one of the most valuable drugs in medicine. Their ability to alleviate pain and suffering led Thomas Sydenham, an English doctor in the nineteenth century to call them ‘God’s own medicine’. Their use to alleviate pain dates back thousands of years. Despite their medical effectiveness they are in news for wrong reasons too that include use of these drugs on the street and the potential for addiction that has led to an ‘opiophobia’ in clinical medicine. Thus their place although is prerequisite, and undebatable yet their precautionary use is highly recommended.

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