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Chapter

Introductory Chapter: Opioid Analgesics - History, Uses and Risks

Pilar Almela

1. Introduction

Opiates have been used for various purposes throughout history [1, 2] (**Figure 1**). Interest in opium poppy plant (*Papaver somniferum*) arose more than 4500 years ago, due to the nutritional power of its seeds. Afterwards, around 1550 BC, opium was used in the Eastern Mediterranean and Egypt for religious and medicinal purposes. Greek medicine was the first to refer to opium as a narcotic, and it is at this time that a classification of the various preparations of this plant begins. In the seventeenth century, its use as a pain reliever in Sydenham's laudanum began to become general, until it was replaced by the currently used morphine hydrochloride.

In 1803, the German pharmacist, Friedrich Wilhelm Adam Sertürner, identified and isolated the major psychoactive agent in opium, at approximately 4–21% and named it "morphium," alluding to the Greek god of dreams Morpheus [3]. Sertürner and three young assistant experimented the narcotic effects of morphine by taking the raw material. From this moment on, morphine began to be used for the same cases in which opium was used through different routes of administration (oral, rectal, or transdermal). Twenty years after Sertürner's discovery, in 1820, a pharmacist named Heinrich Emmanuel Merck began to commercialize morphine. The medical use of morphine was widespread after the discovery of the hypodermic syringe in the mid-nineteenth century.

In 1973, three independent research groups headed by Solomon Snyder in Baltimore, Eric Simon in New York, and Lars Terenius in Sweden confirmed the existence of specific opioid receptors [4–6], and, 2 years later, Hughes discovered the presence of endogenous peptides able of activating the same receptors, although in a less intense way [7].

The endogenous opioid system plays a main role in multiple physiological functions of the organism. When people carry out certain daily activities (eating, exercising, sexual behavior and others), endogenous opioids are released, inducing a brain reward effect that increases the likelihood that these behaviors tend to repeat. It is the so-called behavioral reinforcing effect, which can lead to addictive behaviors.

Nowadays, morphine is widely used for chronic to severe pain relief in many conditions associated with heart attacks, serious injury, postoperative discomfort, and terminal illness such as cancer [8]. However, it is not possible to uncouple its beneficial analgesic effect from addiction, tolerance, and dependence. Being able to separate the potent analgesia from the addictive capacity would make pain relief to be a minor medical problem.

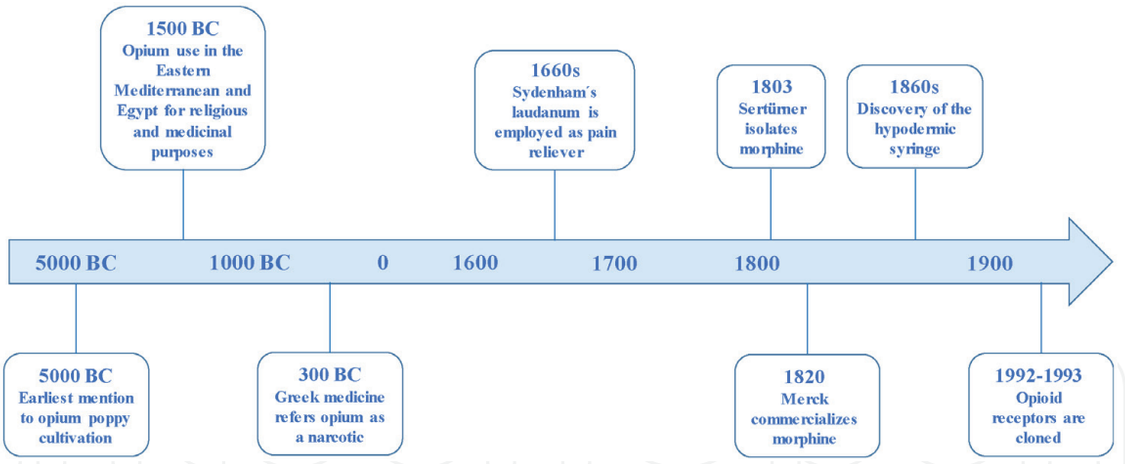

Figure 1.
Timeline of morphine history.

2. Opioid receptors

There are three main opioid receptor types that produce pharmacologic effects upon stimulation, mu (MOP), kappa (KOP), and delta (DOR), and morphine is a MOR-preferring agonist. The novel nociception/orphanin FQ receptor is considered to be a non-opioid branch of the opioid receptor family (**Figure 2**). However, substantial pharmacological evidence for additional opioid receptor phenotypes exists [9].

Opioid receptors are a group of G_i/G_o protein-coupled receptors, which consist of seven transmembrane domains, three extracellular, and three intracellular loops, extracellular amino acid N-terminus, and intracellular carboxyl C-terminus. They are activated both by endogenously opioid peptides and by exogenously administered natural, synthetic, or semisynthetic opiate compounds such as morphine and heroin.

Opioid receptors are located in both the central and peripheral nervous system. Morphine analgesia is mainly due to its action on MOP receptors, although the activation of KOP and DOP receptors also participates in the analgesic effects of this drug. These receptors act synergistically in different places at CNS level, from the spinal cord to the cerebral cortex, inhibiting the nociceptive sensation whatever its location or intensity. Specifically, they act on the afferent system at the spinal level, where the activation of MOP receptors results in the inhibition of primary sensory fibers. Morphine also acts by regulating the transmission of the efferent system, inhibiting the nociceptive transmission sent from mesencephalic areas and the brainstem. Nevertheless, opiates not only diminish the painful sensation but also

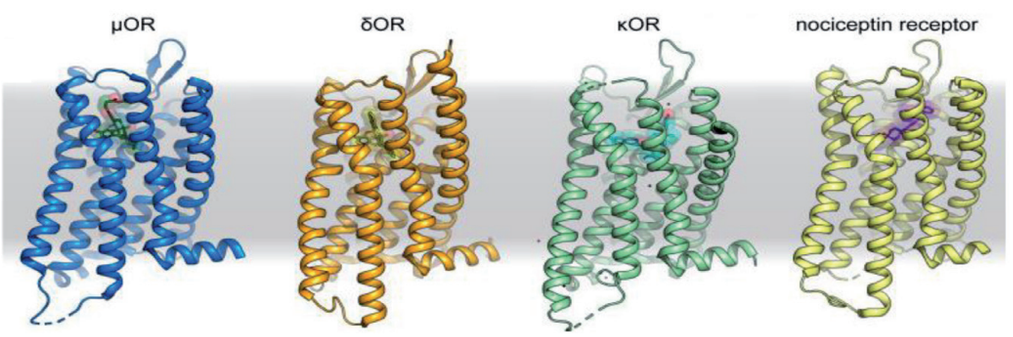

Figure 2.
Opioid receptor structures. Modified from [10].

block the unpleasant or distressing feelings that accompany pain through its action at the limbic and cortical level, areas involved in emotional physiological responses and where a large number of opioid receptors are expressed.

Some pharmacological properties of opioid agonists are routinely used in clinic practice. In addition to the aforementioned opioid analgesic power, these drugs have utility in other conditions as cough suppressant, antidiarrheal, emetic, and anesthetics, being also used in special situations as in the acute pulmonary edema or in respiratory rhythm regulation in patients undergoing artificial respiration.

3. Genetic polymorphisms modulating the pain response

Recent research in the field of pharmacogenomics has discovered important single-nucleotide polymorphisms that are thought to be linked to opioid dose variability. This could explain the genetic changes in the analgesic opioid dose. These polymorphisms appear in several areas involved in pain pathways, drug receptors, drug-metabolizing enzymes, and drug efflux molecules [11]. Among the genetic polymorphisms identified as possible modulators of the pain response, we can mention genes that code for voltage-gated sodium channels, the metabolic enzyme catechol-O-methyltransferase (COMT), the synthetic enzyme CTP cyclohydrolase, and the changes described in the OPRM1 gene [12].

A better knowledge of these polymorphisms can help clinicians to manage interindividual variability in opioid demands. These genetic markers could also help to design tools to precisely predict the analgesic opioid dose, increase efficacy, and reduce the incidence of drug dependence and addiction.

4. Opioid addiction: a severe substance use disorder

Today, morphine is a Schedule II narcotic, along with other drugs like fentanyl, hydromorphone, meperidine, methadone, or oxycodone, under the Controlled Substances Act (US Drug Enforcement Administration) [13], and is available only by a prescription due to its high potential for abuse. Morphine is also regulated because it is the precursor to heroin, a synthetic alkaloid that presents a different pharmacokinetics than morphine, resulting in more acute CNS effects, partly responsible for the tremendous addictive capacity of this molecule.

The first experiences with opioids are usually unpleasant, since the effects on the gastrointestinal tract (nausea and vomiting) predominate. However, when repeating the behavior, tolerance to the emetic action develops, then the feeling of euphoria prevails.

The addictive state is characterized by the compulsive consumption of the drug despite the serious negative consequences that it entails, such as diseases, neglecting social and family obligations, and the need to commit criminal acts to obtain the substance. For drug addicts, drugs become the main incentive within their scale of values, and, as a result, their lives are reduced to obtaining and consuming drugs.

In addition, drug addiction involves loss of control in limiting intake and emerging of a negative emotional state (e.g., dysphoria, anxiety and irritability), reflecting a motivational withdrawal syndrome when access to the drug is prevented [14].

The addictive process consists of three stages (**Figure 3**): binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving). These stages interact with each other, becoming more intense and ultimately leading to the state known as addiction.

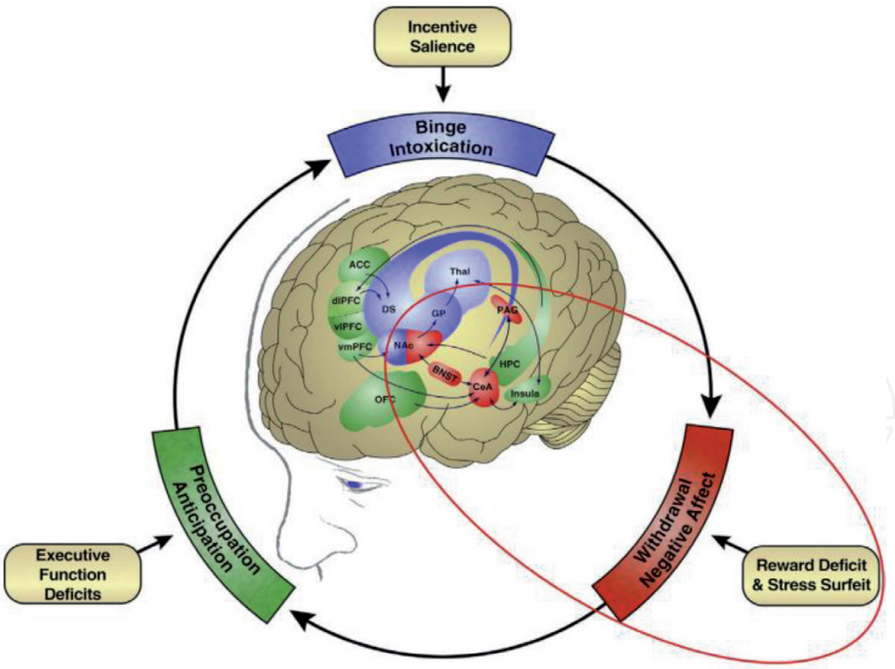

Figure 3.
Neurobiological bases of substance use disorders [14].

In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), addiction is synonymous with a severe substance use disorder, and opioid use disorder is included here [15]. Just like it happens with other substance use disorders, individuals can begin opioid misuse with recreational use of the drug and evolve to the withdrawal/negative affect stage as negative reinforcement appear.

Despite numerous treatment attempts and the serious risk to their lives, relapses to drug-seeking and drug-taking behaviors following months or years of abstinence are frequent when addicts find stimuli associated with the first contact with the drug [16]. This fact shows that we need more effective long-term treatments for drug dependence and emphasizes, on the other hand, the importance of better understanding the neurobiological mechanisms that underlie drug addiction and their persistence.

5. The opioid epidemic: challenges and opportunities

Over the past 20 years, there has been a significant increase in opioid prescription worldwide, but especially in the United States. This substantial increase in opioid prescribing patterns has been due, in part, to the influence of certain currents of opinion, which trivialized the potential drawbacks of opioid painkillers, along with the widely spread belief that any kind of pain could and should be treated with opioids. On the other hand, consuming higher doses than prescribed or by people who had not been prescribed, or switching to a more direct route of administration than the oral route, has contributed to the expansion of the abuse of these drugs among the population [17].

An opioid epidemic has been declared in 2017 in the United States [1, 18]. Europe and, particularly, low- and middle-income countries, appear to be less influenced by this problem. An estimated 10.3 million Americans aged 12 and older misused opioids in 2018, including 9.9 million prescription pain reliever (morphine, oxycodone, and hydrocodone) abusers and 808,000 heroin users. A report from the Centers for Disease Control and Prevention (CDC) indicated that opioid

sales multiplied by 14 from 1999 to 2010. Moreover, this center reported that, in 2017, the number of overdose deaths involving opioids (including prescription and illegal opioids) was six times higher than in 1999. Prescription opioid overdose, abuse, and dependence involve high economic costs for American society from around $78.5 billion.

Avoiding prescription of opioid pain relievers when its therapeutic indication is doubtful or unnecessary is always easier than proceeding later upon treatments for abuse, which will be even more difficult if the patient is not involved. Only in certain situations, opioid administration for pain relieve is essential; for all the others, a great diversity of interventions that can be as effective or more than the prescription of opioids are available, avoiding thus the potential risks of addiction and overdose that are associated with the consumption of opiates.

Different states have begun implementing prescription drug monitoring programs to control irregular prescribing practices by clinicians and the recreational use of opioids. In addition, current strategies include a greater involvement of healthcare professionals (such as psychiatrists) and approaches to address comorbidities [19]. These measures could be resulting in a decrease in opioid prescription, as shown in last reports from CDC, which indicate a reduction in these prescriptions from 2016 [20].

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