

Opioid receptors to date*

Receptores opioides até o contexto atual

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SUMMARY

BACKGROUND AND OBJECTIVES: Due to the objective of the outpatient setting and to routinely used drugs, this study aimed at reviewing and updating the knowledge about opioid receptors and worked as a study complement after a lecture presented to team members.

CONTENTS: We have reviewed from historical aspects to most recent developments about opioid receptors, in addition to describing subtypes and action mechanisms. For such, Pubmed-indexed references were queried.

CONCLUSION: After reviewing current literature data, we have concluded that there is still a lot to be researched about the topic, aiming at safer drugs, and new biomolecular techniques are still needed.

Keywords: History of medicine, Morphine, Morphine receptors, Opioid antagonists, Opioid receptors, Opioids, Opium, Poppy.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Devido à finalidade do ambulatório e os fármacos utilizados rotineiramente, o objetivo deste estudo foi rever e atualizar os conhecimentos sobre os receptores opioides e como complemento de estudo após palestra apresentada aos integrantes da equipe.

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alizer os conhecimentos sobre os receptores opioides e como complemento de estudo após palestra apresentada aos integrantes da equipe.

CONTEÚDO: Foram revisados desde os aspectos históricos até os conhecimentos mais recentes sobre receptores opioides, descritos seus subtipos e mecanismos de ação. Para tal, foram consultadas referências indexadas pela Pubmed.

CONCLUSÃO: Com os dados presentes na literatura atual, concluiu-se que ainda existe muito a ser pesquisado sobre o tópico, visando medicações mais seguras e novas técnicas biomoleculares ainda são necessárias.

Descritores: Antagonistas opioides, História da medicina, Morfina, Opioides, Ópio, Papoula, Receptores de morfina, Receptores opioides.

INTRODUCTION

Since ancient times, opium has been used by different cultures, both as therapeutic formulae component and with recreational purposes. With the advances of biomolecular techniques and consequent discovery of opioid receptors, there has been further understanding of its effects and the possibility of synthesizing new derivatives with major impact on the population due to the possibility of treating pain in an unprecedented way. The laboratory identification of opioid receptors has contributed a lot for this evolution and is the current focus of several researches for the discovery of new receptors and their subtypes, in the hope to understand different therapeutic and side effects of this class of drugs, to allow the development of more specific and more tolerable drugs.

OPIOIDS: HISTORICAL ASPECTS

Opium is known since ancient times and has been used by humans probably before the written history.

There are archeological images suggesting its use by Sumerian cultures. In addition, several studies show that most ancient peoples already knew and used this substance including Assyrians, Arabs, Egyptians, Greeks, Romans, Chinese and Persians.

Since 3400 b.C., poppy seems to have been cultivated in Mesopotamia. Sumerians refer to it as *Hul Gil*, the “plant of joy” and they would soon teach Assyrians about the euphoric effects of this vegetal extract. This art would be transferred to Babylonians who, in turn, would transfer their knowledge to Egyptians¹⁻³.

In 1300 b.C., in the capital of Thebes, Egyptians started to grow opium *thebaicum*. Opium trade flourished during the reign of Tutmes IV, Akhenaten and Tutankhamun. Trade route would include Phoenicians, who would transport the item to the Mediterranean sea and Europe^{1,4}.

Hippocrates, in 460 b.C., rejected opium magic attributes, but agreed that it was useful as narcotic. In 330 b.C., Alexander, the Great, introduced opium to people of Persia and India. Religious Hindu hymns (Vedas) already mentioned opium powers. Several old medical texts, such as those described by Avicenna and Galen, revealed its use as potent analgesic¹⁻³.

Opium *thebaicum* is introduced for the first time in China by Arab merchants in 400 b.C. In the 12th century, old Indian medical treatises such as *Sarangdhar Samhita*, describe opium for diarrhea and sexual dysfunctions.

Around 1500, Portuguese start the habit of smoking opium. Effects were instantaneous. One century after, Persians and Indians start to eat and drink opium blends with recreational purposes.

In the early 16th century, opium is reintroduced in the European medical literature by Paracelsus as laudanum: an opium, citric juices and gold quintessence blend. Called black pills or “Immortality Pills”, they were made of *thebaicum*, being prescribed as analgesics^{1-3,5}.

In 1680, British botanic Thomas Sydenham, after studying poppy varieties, introduced *Laudanum Sydenham*, a compound of opium, cherry wine and herbs, recommending it as powerful analgesic and antidiarrheal, and states: “from all drugs that powerful God has given to men to relief suffering, none is so universal and effective as opium”^{1,2,5}.

In mid 18th century, Linnaeus, disciple of Paracelsus, was the first to classify poppy, *Papaver somniferum* – “sleep inducer”. Its extraction is through its latex, removed from small scarifications on its still green

flowers, from which a milky liquid flows. Most traditional varieties have in this juice up to 10% of medicinal alkaloids, especially morphine in addition to other substances such as thebaine, codeine, papaverine and noscapine, identified years later^{1,2,6}.

In 1803, Friedrich Sertürner, in Germany, discovered the opium active ingredient, dissolving it in acid and then neutralizing it with ammonia. The result: an alkaloid – *principium somniferum*, or morphine. Some years later, in 1827, Merck & Co. company in Germany started the commercial production of morphine. In 1843, Alexander Wood, from Edinburgh, Scotland, discovered a new way to administer morphine using a syringe. Its effects were instantaneous and three times more potent^{1,2}.

Charles Romley A. Wright, British researcher was the first to synthesize heroin, or diacetylmorphine in 1874, by boiling morphine. In the early 19th century, in several medical journals, physicians discussed the side effects of heroin and its withdrawal symptoms^{1,2}. Currently, Australia, Turkey and India are the largest opium producers for medicinal purposes.

RECEPTORS

Since mid 20th century there was the concept of the possible existence of cell structures which would recognize different molecules, thus allowing their activation. These structures, called receptors, showed a high level of specificity for each substance. However, only with the development of modern molecular biology techniques it would be possible to recognize their details.

The first opioid antagonists appeared in the 1940s: naloxone and afterward naltrexone. The first synthetic opioid, meperidine, was also developed during this period^{3,7}.

The interest in this area increased even more with the liberal investment of the American government, especially during the Nixon era, who declared War against Heroin, encouraging the creation of opioid research centers⁷.

In the mid 1960s, Paul Janssen synthesized for the first time fentanyl in his lab, and in the 1970s, the first endogen polypeptides (encephalins and β -endorphins) were isolated and purified⁸.

A pioneer study by Candace Pert and Solomon Snyder, published in March 1973, has shown the existence of specific naloxone receptors in the brain of mammals and in the bowels of guinea-pigs^{7,9}.

One year after this discovery, in May 1974, several researchers from different centers met in Boston, in the Neuroscience Research Program. Many subjects were discussed, such as details about the binding of opioid receptors and the first publications about endogenous opioids⁷.

Pharmacological nalorphine studies in humans have shown an interesting result. In low doses it would antagonize morphine analgesic effects. However, the analgesic effect would return with higher doses. With this finding, it was apparent the existence of more than one receptor to explain this dualism¹⁰.

Opioids are very important for analgesia and the image of the opium poppy appears in traditional symbols of medical entities such as the Royal College of Anaesthetists.

By convention, opiates are all substances of natural origin present in the poppy opium, while opioids would be all natural or synthetic molecules acting on their specific receptors¹¹.

Other poppies, especially *Papaver bracteatum* and *Papaver orientale* are rich in thebaine and are used to produce hydromorphone, hydrocodone and other synthetic opioids.

Through research with rodent ileum preparations it was possible to identify three opioid receptors which were named with Greek letters according to the corresponding first letter of each specific substance used to stimulate them¹². So, morphine-activated receptor was called μ (mu); ketocyclazocine responsive was called κ (kappa) and the one activated by substance SKF10047 was called σ (sigma). Described psychomimetic effects related to sigma receptors were later reanalyzed and the conclusion was that they were in fact caused by NMDA-type glutamatergic receptors blockade. Similarly, subsequent studies have failed to show the existence of the sigma-type receptor^{3,9}.

Another endogenous polypeptides group was identified during the 1980s and was called dynorphins. These peptides derive from major precursors which, in mammals, are: proenkephalin A, prodynorphin and proopiomelanocortin³.

Later, Kosterlitz et al.¹³ using *vas deferens* rats, has determined a new receptor type and, following the same naming rule, has called it δ (delta), again totaling three opioid receptors^{3,9}.

The δ receptor was the first to be cloned in laboratory. It has as major agonist agents enkephalin (deltorphin) with low selectivity by high affinity, and also SIOM, derived from naltrexone, more selective and potent.

Naltrindol, also derived from naltrexone, antagonizes such substance and is the first to be synthesized in laboratory¹³.

In κ receptors, the first identified agonist was ketocyclazocine and the antagonist is nor-binaltorfemin with potent action. Finally, μ receptors had as first identified antagonist morphine and as antagonist naltrexone¹⁴.

According to receptors subtype and their location in the nervous system, some actions are well defined. δ receptors are primarily responsible for analgesia, but also for modulating cognitive and physical dependence functions. They are located in pontine angles, tonsils, olfactory bulb, deep cerebral cortex and peripheral sensory neurons¹⁵.

κ receptors have nociception, thermoregulation, diuresis control and neuroendocrine secretion functions. They are located in the hypothalamus, periaqueductal gray matter, spinal cord gelatinous matter, in addition to peripheral sensory neurons¹⁵.

As to μ receptors, they regulate functions such as nociception, respiratory cycle and intestinal transit, being located in cerebral cortex laminae III and V, in the thalamus, in the periaqueductal gray matter, in the gelatinous matter and in the gastrointestinal tract¹⁵.

In humans, genes codifying these receptors transcription are located as follows: in chromosome 1 for δ receptors, in the long arm of chromosome 8 for κ receptors and μ receptors are codified by chromosome 3¹⁵.

These receptors are coupled to G protein in the cell membrane. When stimulated by an opioid, there is inhibition of the enzyme adenylate cyclase decreasing the intracellular level of cyclic adenosyl. This closes voltage-dependent calcium channels in pre-synaptic terminations decreasing neurotransmitters release and receptors activation, however not K^+ channels in the postsynaptic membrane. This leads to a hyperpolarization of this neuron, partially blocking pain stimulation transmission¹⁶.

There is a proposal advocated by molecular biologists to change the name of δ , κ and μ receptors, which were defined by pharmacologists. According to this proposal, they would become DOR, KOR and MOR (delta, kappa and mu, respectively). However, such naming is still highly controversial. Finally, the International Union of Pharmacologists (IUPHAR) has defined new names according to the historical sequence of receptors cloning. Receptors would be called OP, followed by a subscript number referred to the chronological cloning order and, when necessary, by a letter related

to subtypes. So, DOD receptors would become OP_1 , KOP would become OP_2 and so on^{9,15}.

Studies of activity with radioligands have determined the presence of two μ receptor subtypes. μ_1 receptor has a binding site sensitive to naloxone and μ_2 receptors are selective for morphine¹⁷.

Two δ antagonists were compared, naltrindol and encephalin. The δ_1 subtype was considered the site where naltrindol has blocked deltanorphine effects and δ_2 the site where one encephalin (DALCE) has selectively blocked the action of another encephalin (DPDPE)¹⁸.

The presence of two κ receptor subtypes was shown using radiomarked ketocyclazocine. Subtype κ_1 is the site sensitive to substance U50, 488H, while κ_2 ended up being considered a κ_1 receptor dimmer. Among κ_1 receptors there is another subdivision categorized according to receptor's affinity with dynorphins. κ_{1a} was considered with the lowest affinity and κ_{1b} with the highest affinity. Subtype κ_3 came from studies with a solution containing agonist and antagonist (naloxone benzoyl-hydrazone), determining the site where it would antagonize morphine¹⁹.

New receptor subtypes have been studied, determining that ϵ (epsilon) receptors are located in lymphocytes and have high affinity with β -endorphin²⁰. Another subtype called ζ (zeta) is present in skin, cornea and brain cells, being selective for met-enkephalin. They are related to the growth of some tumor cells²¹. Other receptor subtypes are described as ι (iota), the enkephalin of which has high affinity being present in the ileum of rabbits, and λ (lambda), with affinity to epoxymorphine, being found in fresh preparations with cell membranes of rats²².

CONCLUSION

In the future, further molecular biology technique advances and complementary DNA isolation shall probably bring new knowledge and better understanding and identification of opioid receptors, including their actions.

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