

Opioid Receptors in Pain Management: Past, Present and Future

Opioids play a unique role in society. They are widely feared compounds, which are associated with abuse, addiction and the dire consequences of diversion; they are also essential medications, the most effective drugs for the relief of pain and suffering. Opium, which is derived from the unripe seed capsules of the opium poppy, *Papaver somniferum*, has a long history; in fact, opioids have been used and abused by humans for longer than any drug aside from alcohol.^{1,2} The Sumerians in Mesopotamia were among the first people identified to have cultivated the poppy plant around 3400 BC. They named it Hul Gil, the 'joy plant'. Later, the Greeks and Romans—fully aware of the analgesic and euphoric properties of opium—used the drug for pain relief and recreation. Hippocrates and Galen used opium to treat a broad range of conditions, including asthma, coughing, headache, and melancholy. The opium poppy is also prominently described in what could be considered the first textbook of pharmacology, *De Materia Medica*, by the Roman physician Dioscorides. In 1804, the active ingredient of opium was isolated by Friedrich Wilhelm Adam Sertürner; named morphine, after Morpheus, the Greek God of sleep. Later, Dr Charles Wood invented the hypodermic needle, which was first used to inject morphine to relieve pain from neuralgia. Opioid abuse subsequently became common; in fact, it was seen so often in veterans of the Civil War that it became known as the 'soldier's disease.' The 1970's brought a revolution in our understanding of the physiological mechanisms underlying both the efficacy and the addictive effects of these agents. In particular, Pert et al³ reported the autoradiographic localization of the opiate receptor in the rat brain and identification of opiate receptor binding in intact animals.⁴

In 1975, Hughes et al⁵ discovered the first of the endogenous opioids—specifically, the enkephalins—which subsequently became the focus of intensive research. However, it was not until 2012 that the full three dimensional structure of all of the known receptors for opioids was fully elucidated.^{6,7} It is now clear that endogenous opioid peptides produced by the body are the natural ligands for the opioid receptors and in this way act as neuromodulators that modify the excitability of neurons and the actions of other neurotransmitters in the central nervous system. In the 1970s, the opioid receptors

were identified by radioligand binding techniques, and the endorphin, enkephalin and dynorphin peptides were identified as prominent endogenous ligands.⁸ In 1997, highly selective m-peptides, termed endomorphins, were added to the roster of endogenous ligands.⁹⁻¹¹

Opioid receptors belong to the family of metabotropic membrane receptors that couple via the Gi/Go subtypes of G proteins to cellular transduction processes. The opioid receptors are widely distributed throughout the body; those involved in pain modulation are found in the central nervous system and the peripheral nervous system; opioid receptors are also found on cells of the immune system,¹²⁻¹⁴ throughout the enteric nervous system of the gastrointestinal tract¹⁵ and elsewhere. Opioid receptors do not necessarily function independently, and can exist as dimers and heterodimers which modulates their pharmacology, and presents new opportunities for drug development. High affinity interactions are possible between each opioid peptide and each receptor, although there are differences in affinity that drive selectivity.¹⁶ Therapeutically used agonists, such as morphine, fentanyl, oxycodone, and methadone bind preferentially to μ -opioid receptors, whereas the semisynthetic opioid nalbuphine binds to the κ -opioid receptor. Even within a class of opioid receptor, differences in affinity and function can be distinguished. This diversity in receptor properties is related to the ability of opioid receptors to homooligomerize and heterooligomerize in various combinations, resulting in the generation of novel 'opioid receptors' with unique agonist and/or antagonist affinities.¹⁷ Homooligomerization may lead to signal amplification; heterooligomerization modulates the ligand binding profile of both receptors. For example, a heterooligomer formed from the μ -opioid receptor and the δ -opioid receptor has increased affinity for endomorphin 1 and leu-enkephalin. In addition to their interactions with opioid receptors, recent evidence suggests that opioids also interact with the innate immune pattern recognition receptor, Toll-like receptor 4, and that this action may impair the analgesic action of opioids but also modify drug tolerance and dependence.¹⁸ The complex heterooligomeric composition of opioid receptors offers novel opportunities to separate the wanted effects of opioids (analgesia) from some of their unwanted effects, such as tolerance, constipation, and

addiction. This development is exemplified by drug candidates that activate μ -opioid receptors but inhibit δ -opioid receptors, such as UMB 425 and eluxadoline.^{19,20} UMB 425 exhibits sustained analgesic activity that is not attenuated by the development of tolerance. Eluxadoline has been found to be beneficial in patients with irritable bowel syndrome with diarrhea in whom pain and diarrhea are attenuated at a low incidence of constipation.²⁰ A new drug candidate, MMG22, which stimulates the μ -opioid receptor but inhibits the metabotropic glutamate receptor 5, was found to have powerful analgesic properties with little, if any, liability for tolerance.²¹

In the field of analgesia, the cloning of the opioid receptor family produced some major problems in classification as single genes for the classical m (MOP), d (DOP), and k (KOP) have been described; however, the anesthetic literature is peppered with reference to m1–3, d1–2, and k1–3.1. Despite the relatively rapid advances in molecular pharmacology of one of our most important receptor classes, clinical development, as described by Power, has been slow. However, the advent of significant new molecules, such as tapentadol and the reuse of old drugs in combination (e.g. morphine/oxycodone and oxycodone/naloxone) are already in the clinic.

The expression of opioid receptors and their enhanced transport to sensory nerve terminals becomes prominent especially in the presence of inflammation. Immune cells are then recruited to the damaged tissue and secrete opioid peptides which bind to peripheral opioid receptors reducing pain. This endogenous pain-relief mechanism became an inspiration for the exogenous administration of endogenous, synthetic opioid peptides and novel peptidomimetics in the hope to conquer pain. The development of novel peptidomimetics characterized by increased plasma stability, lower toxicity, and high affinity for opioid receptors is a milestone for researchers aiming for satisfactory long-lasting pain relief in patients. Morphiceptin [Tyr-Pro-Phe-Pro-NH₂] is an example of opioid peptide showing high opioid receptor affinity and peripheral activity in visceral pain. Biphalin [(Tyr-D-Ala-Gly-PheNH)-2], dimeric peptide analog of enkephalin, is another example of an opioid peptide that has limited permeability of an intact BBB (Silbert et al 1991). Biphalin expresses synergic activities with current drugs used in AIDS therapy. Therefore, biphalin has been proposed to be applied as a component of antiviral HIV multidrug therapies in combination with chronic pain treatment in AIDS patients as a primary therapeutic target (Tang et al 2008).

The future of opioid analgesics seems to be linked to the study of the Kappa receptor. The kappa receptor induces analgesia without the dangerous and unwanted

side effects that the mu and delta receptors are associated with. However, there are not any selectively strong agonists to this receptor as of now. Another area of research important to the future of opioid analgesics is the study of the endogenous opioid peptides. Because these peptides are endogenous, on metabolic degradation (unlike opiates) they break down to amino acids. Hence, the metabolites are nontoxic and do not cause kidney and liver damage. Also, because they are made from amino acid residues, 'a large number of analogs can be synthesized from a few basic building blocks and simple modifications may be attempted to develop analogs with a desired biological effect.' The further study of the endogenous opioid peptides seems to be integral to development of new safer drugs. In the recent outbreak, the scientists melded the light sensing protein rhodopsin to key parts of opioid receptors to activate receptor pathways using light. The eventual hope is to develop ways to use light to relieve pain, a line of discovery that also could lead to better pain killing drugs with fewer side effects.

Opioids have been used to alleviate since ancient times and with the greater understanding at molecular level showing role of receptors specific drugs have been developed to conquer pain. Still iceberg has to be elucidated and advancement in our knowledge about opioid receptors will open new doors for a pain-free life.

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