

Review

A brief history of opiates, opioid peptides, and opioid receptors

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“Presently she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow.”

The Odyssey, Homer
(Ninth century B.C.)

It is hard to decide when and where the opium poppy was first cultivated. It may have been grown for its seeds before people discovered how to prepare mekonion from the leaves and fruits of the plant or opium (from “opos,” the Greek word for juice) from the liquid that appears on the unripe seed capsule when it is notched.

The use of written records to decipher the early history of opium use and abuse is hard because descriptions of drugs by ancient authors are often ambiguous. The preparation described by Homer—given by Helen, the daughter of Zeus, to Telemachus and his friends to help them forget their grief over Odysseus’ absence—was attributed to Homer’s imagination by Theophrastus (300 B.C.) who was himself aware of the method used to produce opium. Other writers (e.g., Diskourides, A.D. 60) have argued that the drug alluded to by Homer contained henbane, the active ingredient of which is scopolamine. Most modern pharmacologists including Schmiedeberg (1) and Lewin (2) feel that Helen administered opium to the men. Indeed, Kritikos and Papadaki (3) have suggested that Telemachus may not have experienced any of the toxic effects of opium because he and his contemporaries used it habitually.

Despite difficulties in interpreting ancient writings and archeological data, a picture of opium use in antiquity does emerge from them. There is general agreement that the Sumerians, who inhabited what is today Iraq, cultivated poppies and isolated opium from their seed capsules at the end of the third millennium B.C. They called opium “gil,” the word for joy, and the poppy “hul gil,” plant of joy. It appears that opium spread from Sumeria to the remainder of the old world.

At first opium may have been employed as a euphoriant in religious rituals, taken by mouth or inhaled from heated vessels (4). Knowledge of its use may initially have been confined to priests representing gods who healed the

sick and gods of death as well. It was given along with hemlock to put people quickly and painlessly to death, and it came to be used medicinally. The *Ebers Papyrus* (ca. 1500 B.C.), for example, includes the following description of a “remedy to prevent excessive crying of children” (see ref. 2, p. 35): “Špenn, the grains of the špenn (poppy)-plant, with excretions of flies found on the wall, strained to a pulp, passed through a sieve and administered on four successive days. The crying will stop at once.” This remedy and others containing opium (such as *spongia somnifera*, sponges soaked in opium used to relieve pain during surgery) were dangerous because they varied in potency and rate of absorbance. Consequently, many physicians were wary of using them.

Most authors* agree that, as early as the eighth century A.D., Arab traders brought opium to India (6) and China (7) and that between the tenth and thirteenth centuries opium made its way from Asia Minor to all parts of Europe. With the drug came addiction. Starting in the sixteenth century, manuscripts can be found describing drug abuse and tolerance in Turkey, Egypt, Germany, and England. Nowhere was the problem of addiction greater than in China where the practice of smoking opium began in the mid-seventeenth century after tobacco smoking was banned. Efforts to suppress the sale and use of opium failed because the British, later joined by the French, forced the Chinese to permit opium trade and consumption.

In 1806, Sertürner (8, 9) isolated the active ingredient in opium and named it morphine after the god of dreams, Mor-

pheus. (Codeine was isolated from opium a few years later.) Pure morphine, a weak base or alkaloid, the structure of which is shown in Fig. 1, could be made in large amounts. After the invention of the hypodermic syringe and hollow needle in the 1850s, morphine began to be used for minor surgical procedures, for postoperative and chronic pain, and as an adjunct to general anesthetics. In fact, it was Claude Bernard who first investigated the use of morphine for premedicating experimental animals. He found that it reduced the amount of chloroform needed to produce anesthesia.

Unfortunately, morphine had just as much potential for abuse as opium and was not terribly safe to use either. Consequently, a great deal of energy was spent trying to develop a safer, more efficacious, nonaddicting opiate. In 1898, heroin was synthesized and pronounced to be more potent than morphine and free from abuse liability. This was the first of several such claims for novel opiates. To date, none has proven valid.

In 1939, the search for a synthetic substitute for atropine culminated serendipitously in the discovery of meperidine (10), the first opiate with a structure altogether different from that of morphine. This was followed in 1946 by the synthesis of methadone (11), another structurally unrelated compound with pharmacological properties similar to those of morphine. The abstinence syndrome seen when methadone consumption ceases is different from that of the natural alkaloid. Its onset is slower, it lasts longer, and it is less intense. Furthermore, it is orally active. Therefore, it is given to human addicts by clinicians as a substitute for morphine. Stable methadone addicts can lead reasonably normal lives, and the drug can gradually be withdrawn when they no longer desire to use it.

In 1942, Weijlard and Erikson (12) produced nalorphine (*N*-allylnormorphine), the first opiate antagonist (13). This compound could reverse the respiratory depression produced by morphine and precipitate the abstinence syndrome in addicts. In spite of the fact that nalorphine counters the actions of morphine, it is effective as an analgesic agent. This is because it is a mixed agonist–antagonist. Its utility as a pain killer is limited since

*The Arabian system of medicine, including the use of opium, was introduced into India by Muslims in the ninth century A.D. The Greeks, however, were using Indian drugs by the third century B.C., and conversely, opium seems to have been employed in Indian folk remedies in the same period. As for China, opium was mentioned in the medical book *K'ai-pao-pên-tsão* in A.D. 973. The recent discovery of silk in the hair of a tenth century B.C. Egyptian mummy (5) indicates that there may have been regular traffic on the “Silk Road” in ancient times. One might infer from the above that opium was known, if not widely used, on both the Indian subcontinent and in Asia well before the eighth century A.D.

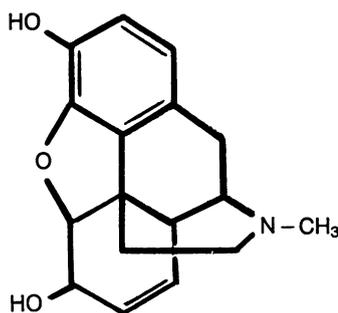


FIG. 1. Morphine ($pK_b = 6.13$). Heroin, diacetylmorphine, is more lipid soluble than morphine and enters the brain more readily. Heroin is converted to 6-monoacetylmorphine and morphine, which are responsible for its actions on central peripheral targets.

it often produces anxiety and dysphoria, but its discovery led to the development of additional compounds, such as naloxone, that are relatively pure opiate antagonists.

By the mid-1960s, it was becoming clear that the actions of opiate agonists, antagonists, and mixed agonist-antagonists could best be explained by actions on multiple opiate receptors. Goldstein *et al.* (14) suggested that radiolabeled drugs might be used to demonstrate the existence of these receptors and to characterize them. Their efforts to do this failed, however, because they could not obtain radioligands with high specific activities. In 1973, Pert and Snyder (15), Simon *et al.* (16), and Terenius (17) succeeded almost simultaneously in showing that there are stereospecific opiate binding sites in the central nervous system and, soon afterwards, these receptors were found to have a nonuniform distribution there (38, 39). People reasoned that the opiate receptors might be the targets of neurotransmitters—endogenous opiates. This argument was strengthened when Akil *et al.* (18) found that footshock stress induced analgesia, which was partially reversed by naloxone. They inferred that stress must cause the release of opiate-like compounds.

In 1975, Kosterlitz and Waterfield (19) observed that brain extracts contain a factor that inhibits acetylcholine release from nerves innervating the guinea pig ileum. This inhibition was blocked by naloxone. The factors responsible for these effects proved to be pentapeptides (20): Tyr-Gly-Gly-Phe-Met (Met-enkephalin) and Tyr-Gly-Gly-Phe-Leu (Leu-enkephalin). It soon became obvious that the Met-enkephalin sequence was present on the N terminus of another molecule, β -endorphin (21), a fragment of β -lipotropin that had been isolated several years earlier from pituitary extracts. Like the enkephalins, β -endorphin proved to have a high affinity for brain opioid receptors.

Another group of peptides structurally related to the enkephalins were identified in 1981 (22). The first of these was named dynorphin. Finally, a fourth family of opioid peptides was shown to be present in the skin of the frog *Phyllomedusa bicolor* (23). These peptides, now known collectively as deltorphins, are quite unusual; they contain D-amino acids. The first such species characterized had the sequence Tyr-D-Met-Phe-His-Leu-Met-Asp-NH₂.

Not unexpectedly, each of the opioid peptides is made as part of a larger precursor protein. In mammals there are three such precursors—proenkephalin (24), prodynorphin (25), and proopioidmelanocortin (26). Proenkephalin gives rise to four Met-enkephalins, one Leu-enkephalin, one Met-enkephalin-Arg⁶-Phe⁷, and one Met-enkephalin-Arg⁶-Gly⁷-Leu⁸. Additional larger fragments of proenkephalin have been isolated from tissues. These may be incompletely processed or, possibly, opioid ligands in their own right.

Prodynorphin also gives rise to several biologically active peptides all of which contain the Leu-enkephalin sequence. These include dynorphin A, dynorphin B, α -neoendorphin, and β -neoendorphin. Proopioidmelanocortin is the precursor for corticotropin and α -melanotropin along with β -endorphin. In total the three precursors described above give rise to more than 20 candidate opioid ligands. In addition, there is evidence that proteolysis of milk proteins generates opioid peptides (casorphins) *in vitro* (27) and that morphine-like compounds may occur naturally in mammals (28). That there were many potential ligands gave credence to the suggestion, mentioned earlier, that there might be more than one opioid receptor.

The first conclusive evidence for this was provided by Martin *et al.* (29). They performed a detailed analysis of the neurophysiological and behavioral proper-

ties of several opiate compounds and looked for "cross tolerance" among the opiates as well (i.e., the ability of a drug to prevent withdrawal symptoms after removal of a second drug from an animal tolerant to it). The results of these experiments suggested the existence of three types of receptors named after the drugs used in the studies: μ (morphine), κ (ketocyclazocine), and σ (SKF 10,047 or N-allylnormetazocine). The σ receptor is now generally thought not to be an opioid receptor.

After they discovered the enkephalins, Kosterlitz and his colleagues (30) wanted to know which receptor(s) they act on. They found that morphine was more effective than the enkephalins in inhibiting electrically induced contractions of the guinea pig ileum. Surprisingly, the peptides were more active than morphine in inhibiting contraction of the mouse vas deferens. Furthermore, the action of enkephalins on the vas deferens was comparatively insensitive to naloxone. Based on these observations, Kosterlitz and his colleagues (30) proposed that a fourth type of opioid receptor, the δ receptor, must be present in the vas deferens.

Unlike the enkephalins, the dynorphin-related peptides appear to bind principally to κ receptors. β -endorphin interacts with both μ and δ sites as does Met-enkephalin-Arg⁶-Gly⁷-Leu⁸. Interestingly, the deltorphins, as their name implies, are highly selective δ receptor agonists. In fact, iodinated and tritiated deltorphins are considered prototypic δ ligands.

Additional prototypic ligands have been developed for each of the opioid receptors (Table 1). These ligands and others like them are bound with high affinity and specificity, and they have been used for receptor binding as well as anatomical, physiological, and pharmacological studies. The results of these studies have suggested that there are subtypes of μ , κ , and δ receptors (see ref.

Table 1. Opioid receptor ligands

Receptor	Agonist	Antagonist	Agonist effect(s)
μ	Morphiceptin DAGO Normorphine Sufentanyl	Naloxone	Analgesia Respiratory depression Miosis Reduced gastrointestinal motility Nausea Vomiting Euphoria
δ	Deltorphin DPDPE DADLE	ICI 154,126 ICI 174,864	Supraspinal analgesia
κ	U 50,488 Trifluadom	MR2266	Analgesia (spinal level) Miosis (weak) Respiratory depression (weak) Dysphoria

DAGO, Tyr-D-Ala-Gly-MePhe-Gly-ol; DPDPE, [D-Pen²,D-Pen⁵]enkephalin; Pen, penicillamine; DADLE, [D-Ala²,D-Leu⁵]enkephalin; deltorphin II, Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH₂; morphiceptin, β -casomorphin-(1-4)-amide or Tyr-Pro-Phe-Pro-NH₂.

31). All of these receptors have high affinity for compounds with one common structural feature: a protonated amine juxtaposed to an aromatic ring (see Fig. 1).

The opioid receptors are all acknowledged to be guanine nucleotide binding (G)-protein-coupled. Both μ and δ receptors mediate the inhibition of adenylate cyclase (32) and the activation of inwardly rectifying potassium channels (33). κ and δ receptors have also been shown to inhibit the opening of voltage-dependent calcium channels (34).

Attempts to purify opioid receptors to homogeneity were thwarted by their paucity in most tissues and their lability after detergent solubilization (35). Until this year, the structure of opioid receptors remained a mystery. Now two groups of investigators have published descriptions of the expression cloning of cDNAs encoding the δ receptor on the neuroblastoma-glioma (NG108-15) cells (36, 37). This receptor proved to be a member of the rhodopsin receptor superfamily. As expected, it is coupled to the inhibitory G protein G_i and inhibits activation of adenylate cyclase. It binds [D-Pen², D-Pen⁵]enkephalin (DPDPE), [D-Ala², D-Leu⁵]enkephalin (DADLE), and other δ -specific ligands with high affinity. It has considerably lower affinity for U 50,488 and dynorphin, and very low affinity for morphiceptin and Tyr-D-Ala-Gly-Me-Phe-Gly-ol (DAGO). It is stereospecific and has a marked preference for (-)-naloxone and levorphanol vs. (+)-naloxone and levorphanol. Thus, unlike receptor candidates cloned earlier, it behaves just as one might have expected it to.

The description of a δ receptor marked the beginning of the race for additional members of the opioid receptor family, and a κ -1 receptor with high affinity for U 50,488 has been cloned (40). Surely a new chapter in the annals of opiate research is about to be written.

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