AC

WRITING ASSIGNMENT # 2

Introduction

I have chosen to talk about morphine, because of my own experience with this powerful drug. Two years ago, I tore my knee ligaments, and I had to undergo a surgical operation to fix it. I stayed four days in the hospital after the operation, and during this time the pain was sometimes overwhelming; only a morphine injection could soothe the pain. During this period, I had about 2 injections per day. I still remember this strange feeling, frightening and wonderful at the same time, a strange sensation that all the parts of my body were falling asleep, vanishing, slowly but surely.In twenty seconds I could not feel my toes any more, then my legs, in one minute it reached the hands, I tried to fight the effect and to move my fingers but in vain. After 2 minutes I still retained consciousness but my body was asleep, and then, then I was just sleeping! I will always remember this sensation of feeling my own body falling asleep, aware, but unable to fight it. But I hope I will forget the horrible side-effect I had the day I left the hospital. I still don`t know if it was due to a kind of dependence, or just a side-effect due to my last injection during the night, but the nausea kept me in my bed during the whole day, I couldn`t get up.

So, that`s the reason why I have chosen to talk about this controversial drug. I am fascinated by this substance that symbolizes the narrow boundary between drug and medicine.

I – History

Morphine has been used in the form of **opium** for centuries. It is unknown exactly who, when, or where opium was first used or discovered, but the date can be narrowed to around 4000 BC. It was used to relieve anxiety and pain. It was also used to induce sleep and give a feeling of well being and peace. The first recorded use of opium for medical purposes was in 200 BC.

In the 16th century, a Swiss physician name Paracelcus experimented with the medical value of opium. He decided that its medical value was of such magnitude, that he called it Laudanum. Laudanum comes from the Latin word "laudare". Laudare means "to praise". He did not know of its addictive properties.

The first attempts to isolate the main active substance of opium were made by the French chemist Jean-François Derosne (1774-1855). In 1803 he managed to isolate a salt, the Derosne Salt, a **mix of narcotine and morphine**. In 1809 Dott found in a sample of opium that half the morphine was present as meconate and half as sulphate.

1817 can be seen as the true "birth date" or discovery date of Morphine. In 1817, Friedrich W.Serturner (1783-1841), a German pharmacist, identified and isolated the principal alkaloid and powerful active ingredient in opium. Serturner dissolved opium in acid and then neutralized it with ammonia. This resulted in the precipitation of morphine. This is similar to the method currently used for morphine extraction.

He called this alkaloid "Morphia" after Morpheus, the Greek God of Dreams. The name "Morphine" is now used instead of Morphia because of the standard that all alkaloids end in "-ine". This event was soon followed by the discovery of other alkaloids of opium: codeine in 1832 and papaverine in 1848. By the 1850s these pure alkaloids, rather than the earlier crude opium preparations, were being commonly prescribed for the relief of pain, cough, and diarrhea. This period also saw the invention and introduction of the hypodermic syringe.

His complex molecular structure was established only a century later in 1925 by the british chemist R. Robinson (1886-1975), a specialist in the chemistry of plants natural substances (pigments, alcaloids), ennobled in 1939, and winner of the chemistry Nobel Price in 1947.

Morphine was synthesized for the first time in 1952, but the synthesis method is not economically in position to compete with the extractive morphine as far as the costs of production are concerned.

Morphine was first used medicinally as a painkiller and, erroneously, as a cure for opium addiction. It quickly replaced opium as a cure-all recommended by doctors and as a recreational drug and was readily available from drugstores or through the mail. Substitution of morphine addiction for alcohol addiction was considered beneficial by some physicians because alcohol is more destructive to the body and is more likely to trigger antisocial behavior. Morphine was used during the American Civil War as a surgical anesthetic and was sent home with many wounded soldiers for relief of pain. At the end of the war, over 400,000 people had the "army disease," morphine addiction. The Franco-Prussian War in Europe had a similar effect. In the 1870s, chemists synthesized a supposedly non-addictive, substitute for morphine by acetylating morphine. In 1898 the Bayer pharmaceutical company of Germany was the first to make available this new drug, 3,6-diacetylmorphine, in large quantities under the trademarked brand name **Heroin**. 3,6-diacetylmorphine is two to three times more potent than morphine.

Heroin was initially used with much success as a superior cough suppressant for patients with (then incurable) tuberculosis. Tuberculosis patients continued to die, but without the tortuous coughing and pain. A second use of heroin was to combat morphine addiction - just as morphine was originally used to combat opium addiction. Soon after its introduction, however, Heroin was recognized as having narcotic and addictive properties far exceeding those of morphine. But given intravenously, morphine is still considered the most effective drug for the relief of pain.

II – Origin

II.1 – The plant : *papaver somniferun*

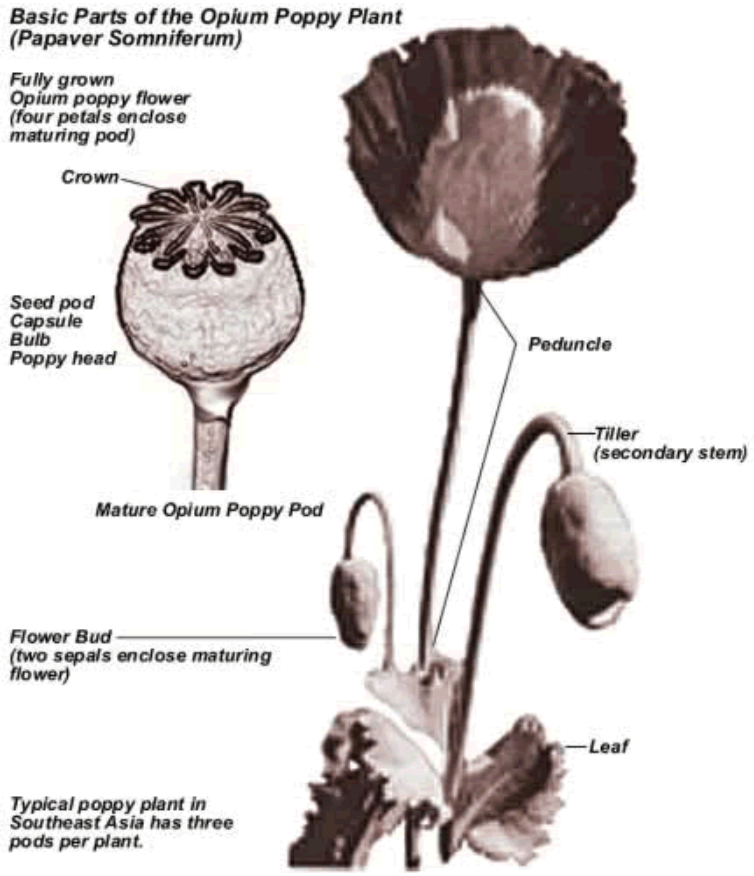
The opium poppy, *Papaver somniferum*, is an annual plant. From a very small round seed, it grows, flowers, and bears fruit (**seed pods**) only once. The entire growth cycle for most varieties of this plant takes about 120 days. The seeds of *P. somniferum* can be distinguished from other species by the appearance of a fine secondary fishnet reticulation within the spaces of the coarse reticulation found all over their surface. When compared with other *Papaver* species, *P. somniferum* plants will have their leaves arranged along the stem of the plant, rather than basal leaves, and the leaves and

stem will be 'glabrous' (hairless). The tiny seeds germinate quickly, given warmth and sufficient moisture. Sprouts appear in fourteen to twenty-one days. In less than six weeks the young plant has grown four large leaves and resembles a small cabbage in appearance. The lobed, dentate leaves are glaucous green with a dull gray or blue tint.

Within sixty days, the plant will grow from one to two feet in height, with one primary, long, smooth stem. The upper portion of this stem is without leaves and is the 'peduncle'. One or more secondary stems, called 'tillers', may grow from the main stem of the plant. Single poppy plants in Southeast Asia often have one or more tillers.

As the plant grows tall, the main stem and each tiller terminates in a flower bud. During the development of the bud, the peduncle portion of the stem elongates and forms a distinctive 'hook' which causes the bud to be turned upside down. As the flower develops, the peduncle straightens and the buds point upward. A day or two after the buds first point upward, the two outer segments of the bud, called 'sepals,' fall away, exposing the flower petals.

Figure 1: Basic parts of Papaver Somniferum



Opium poppies generally flower after about ninety days of growth and continue to flower for two to three weeks. The exposed flower blossom is at first crushed and crinkled, but the petals soon expand and become smooth in the sun. Opium poppy flowers have four petals. The petals may be single or double and may be white, pink, reddish purple, crimson red, or variegated. The petals last for two to four days and then drop to reveal a small, round, green fruit which continues to develop. These fruits or pods (also called 'seedpods', 'capsules,' 'bulbs,' or 'poppy heads') are either oblate, elongated, or globular and mature to about the size of a chicken egg.

Figure 2: Flower and fruit of opium poppy

The main stem of a fully-matured *P. somniferum* plant can range between two to five feet in height. The green leaves are oblong, toothed and lobed and are between four to fifteen inches in diameter at maturity. The mature leaves have no commercial value except for use as animal fodder.

Fig 3: Poppy seedling

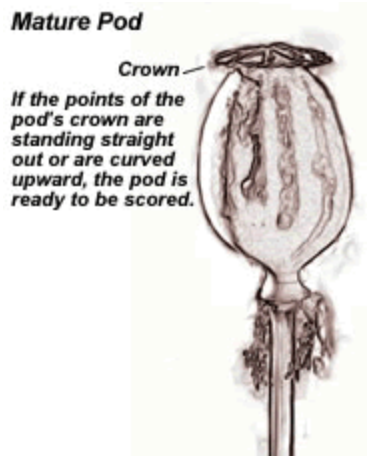
Fig 4: Poppy Flower

Fig 5: Seedpods

II.2 – Opium extraction

Only the pod portion of the plant can produce opium alkaloids. The skin of the poppy pod encloses the wall of the pod ovary. The ovary wall consists of an outer, middle, and inner layer. The plant's latex (opium) is produced within the ovary wall and drains into the middle layer through a system of vessels and tubes within the pod. The cells of the middle layer secrete more than 95 percent of the opium when the pod is scored and harvested.

Fig 6: Poppy pod



If the points of the pod`s crown are standing straight out or are curved upward, the pod is ready to be scored.

Cultivators in Mainland Southeast Asia tap the opium from each pod while it remains on the plant. After the opium is scraped, the pods are cut from the stem and allowed to dry. Once dry, the pods are cut open and the seeds are removed and dried in the sun before storing for the following year's planting.

Fig 7: Mature pod

Opium is extracted as follows:

1) When the flowers go to seed, the seed pod sare scraped with a pin, all around the pod.

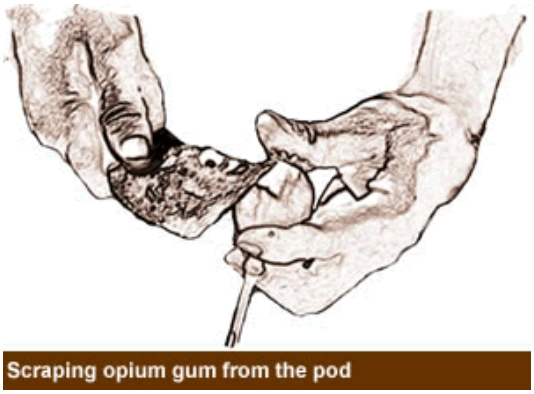


Fig 8: scraping opium from the pod

Fig 9: scraped pod

Fig 10: location of scrapes

2) Little blobs of white are coming out. The wounds are left to seep for a few hours.

Fig 11: white blobs

3) A couple of hours later, opium can be harvested. The white blobs have turned into black tar that can be scraped off and collected on an old, blunt dinner knife or some such.

Fig 12: black tar

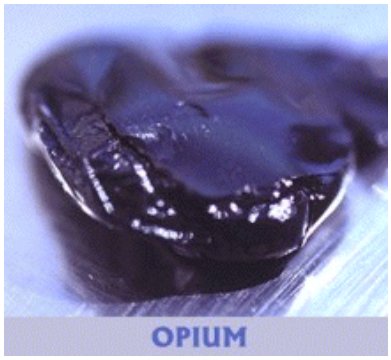


Fig 13: crude opium

Opium is then gathered in blocks of 500 grams to 1 kilogram, and then is solidified during evaporation. The more dry the less malleable it becomes. Each pod can provide 0.2 to 2 grams of brut opium. The principal psychoactive alkaloid in opium is morphine, which represents about 10% of the dry weight, but opium also contains tens of other alkaloids more or less psychoactives.

II.3 – Morphin extraction

The process

The process of extracting morphine from opium involves dissolving opium in hot water, and adding lime (calcium hydroxide) to precipitate the non-morphine alkaloids. The lime converts the

water insoluble morphine into the water soluble calcium morphenate. The other opium alkaloids do not react with the lime to form soluble calcium salts. Ammonium chloride is added to the heated calcium morphenate solution to adjust the alkalinity to a pH of 8 to 9, and the solution is then allowed to cool. Within one or two hours, the morphine base and the unextracted codeine base precipitate out of the solution and settle to the bottom of the cooking pot. The solution is then poured off through cloth filters. Any solid morphine base chunks in the solution will remain on the cloth. The morphine base is removed from both the cooking pot and from the filter cloths, wrapped and squeezed in cloth, and then dried in the sun. When dry, the crude morphine base is a coffee-colored powder. This 'crude' morphine base may be further purified by dissolving it in hydrochloric acid, adding activated charcoal, re-heating and re-filtering. The solution is filtered several more times, and the morphine (morphine hydrochloride) is then dried in the sun.

The resulting precipitates are formed via a manipulation of pH which causes one substance to be soluble while the other is not and vice versa.

The structure

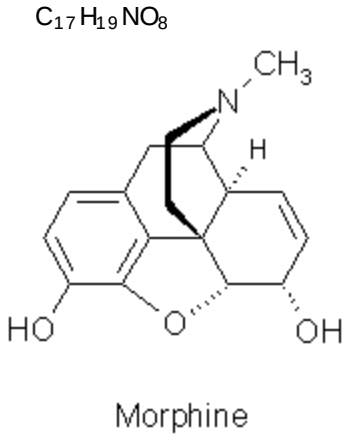


Fig 14: morphine stucture

The Morphine Rule

The following structural features are found in most opioid analgesic analogues, and are collectively referred to as the "Morphine Rule".

- 1. A tertiary nitrogen with a small alkyl substituent.
- 2. A quaternary carbon.
- 3. A phenyl group or its isosteric equivalent directly attached to the quaternary carbon.
- 4. A 2 carbon spacer between the quaternary carbon and the tertiary nitrogen.

Physical properties

Morphine is obtained as monohydrate as small rhombic prisms often resembling needles on crystallization from aqueous methanol and as anhydrous prisms from anisole. The base is sparingly soluble in most organic solvents but readily soluble in benzyl alcohol. Morphine, being a phenol, is

soluble in alkali hydroxide solutions. It can be purified by sublimation and as a result of sublimation the alkaloid is present in the smoke from burning opium.

The quantitative determination of the morphine content of opium

Many different methods have been used to discover a very accurate micromethod for the quantitative determination of the morphine content of opium, using paper chromatography (Svendsen 1951, Svendsen Aarnes & Paulsen 1955). For a very accurate micromethod the following conditions must be fulfilled:

1. The morphine must be completely extracted from the opium;
2. The morphine must be completely separated from other substances likely to affect the quantitative determination, and
3. A colour reaction or the like so far as possible specifically to morphine must be available for the quantitative determination of morphine

Originally the main methods to characterize morphine have been paper chromatography and paper electrophoresis. Today liquid chromatography is widely used.

III – Forms and Effects

III.1 – Forms

Morphine is a drug that can be produced in many different forms and can be administered using many different methods. Addicts most commonly use the injected (intravenous) form of the drug.

Forms of Morphine

- oral solutions (Roxanol)
- sustained-release tablets (MSIR and MS-Contin)
- suppositories
- injectable preparations

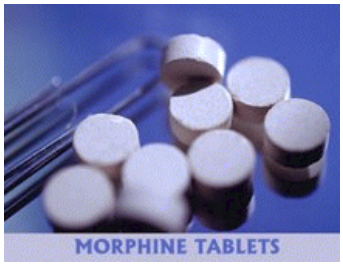


Fig 15: morphine tablets

Consumption Methods

- **orally**: the bio-disponibility is weak (20 to 30%), so the doses have to be quite high to provide a good efficiency. The elimination half-life is relatively long (4 to 5h).
- **rectally**: the kinetic is similar to the oral consumption. This method is mostly used in case of oesophagus cancer, or emetic chemotherapies.
- **subcutaneously and intramusculary**: used in case of sharp pain, during a few days. After this short period the oral consumption is preferable.
- **intravenously :** used in intensive care unit
- **epidurally:** used to administer routinely to chronically ill people who can`t be soothed by other methods.

III.2 – Uses

Today morphine is used medicinally for severe pain, cough suppression, and sometimes before surgery. It is seldom used illicitly except by doctors and other medical personnel who have access to the drug.

▪ When consumed, injected, etc. morphine is a very effective pain killer. This is the drug's primary intended use. Because of morphine's pain relieving properties, it is the standard that new analgesics are measured against.

▪ Morphine is most often given to hospital patients with various physical conditions that would cause them to have extreme, constant pain. The drug is most commonly given to patients such as these, and it is most commonly administered to these patients in the form of controlled release tablets.

III.3 – Side effects

- Respiratory depression is the most common, most significant hazard of morphine when it is being used for medical purposes. Respiratory depression most commonly occurs in the elderly and/or debilitated.
- Injected morphine contains sodium bisulfite. Sodium bisulfite can cause allergic-type reactions in certain susceptible people. Asthmatic episodes are a common form of these allergic-type reactions. Sulfite sensitivity is most commonly seen in people with asthma.

- Morphine can have adverse effects on the central nervous system. The central nervous system includes the spinal cord and the brain.
- It is possible that a person with some form of gastrointestinal obstruction can have adverse consequences when taking controlled release tablets of morphine. Specifically, it is possible that the morphine may not release for quite some time, sitting idly in the stomach. The morphine may eventually be released at a later date, when the substance is no longer needed.

III.5 – Tolerance and dependence

Morphine is highly addictive. Clinical and recreational opioid use is limited by the development of tolerance and dependence which develop quickly, and are induced by chronic exposure to morphine and other opioids more than any other group of drugs.

Tolerance can be defined as the decreased potency of a drug, such that progressively larger doses must be used to achieve the same effect. Tolerance is mainly due to receptor desensitisation induced by functional uncoupling of opioid receptors from G-proteins, thus uncoupling the receptors from their effector systems. However, the mechanism of this desensitisation is still not fully understood.

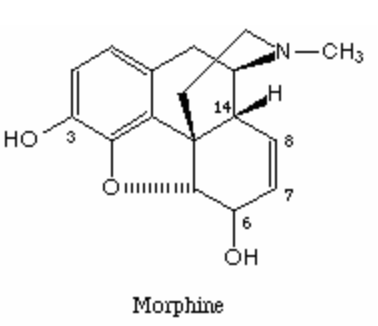
Dependence, which is closely associated with tolerance, involves a continued need for opioid administration in order to prevent withdrawal symptoms. These symptoms include nausea, gastrointestinal disturbances, chills, and a general flu-like state in humans, and ptosis (drooping eyelid), teeth chattering, jumping, irritability, wet dog shakes, and diarrhea in animals. Lesion studies indicate that no single brain structure is responsible for the withdrawal symptoms.

Although dependence usually accompanies tolerance, they are **distinct phenomena**. Dependence is masked until the opioid drug is removed from its receptors, either by stopping the drug or by giving an opioid receptor antagonist such as naloxone. A withdrawal or abstinence response then occurs. The withdrawal response is very complex and involves many brain regions. Dependence occurs much more rapidly than tolerance, and naloxone-precipitated withdrawal can be seen after a single dose of morphine in humans.

The treatment for opioid addiction is time consuming and often unsuccessful but, recovery is possible. There is an estimate of 400,000 deaths per year due to alkaloid addiction in the United States alone. Opioid addiction therapy includes successful detoxification, rehabilitation, and sometimes **methadone** maintenance. Physical, mental, and emotional pain usually accompany an individual trying to obtain abstinence from potent opiates such as morphine. Research has shown that when addicted animals go off drugs, levels of dopamine become extremely low very quickly. This is accompanied by withdrawal symptoms such as shaking, sweating, and vomiting.

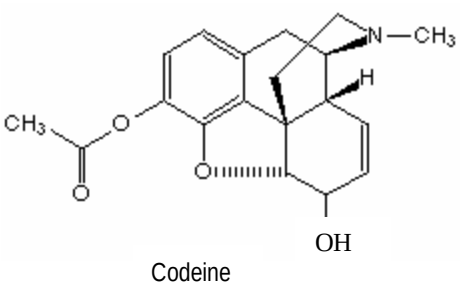
IV – Chemistry of morphine

Modifications at the 3- and 6-hydroxyl groups:

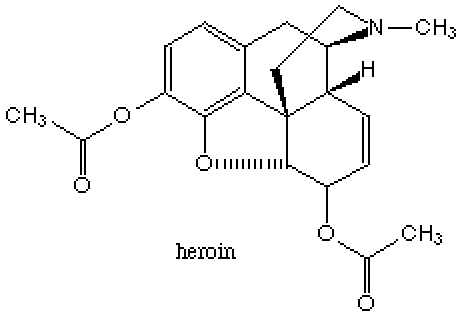


Morphine

- Conversion of the 3-OH to a 3-OCH3, yielding **codeine**, reduces activity to 15% of morphine. Groups larger than a methoxy reduce activity dramatically.



Codeine

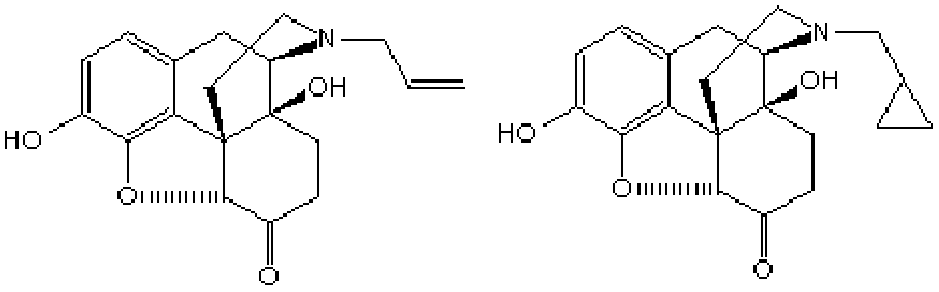


heroin

- Acetylation of both the 3- and 6-OH produces 3,6-diacetylmorphine, also known as **heroin**. Heroin is 2-3 times more potent than morphine. Most of this increase is due to **increased lipid solubility**, which leads to enhanced and rapid penetration into the central nervous system (CNS).

Antagonists

- There are two agents in the morphine class which are marketed as **morphine antagonists**. These agents, **naloxone** and **naltrexone**, are shown below. Naloxone is a **pure antagonist**, and is commonly used to treat narcotic overdose. Naltrexone is a similar agent, but does possess **weak agonist activity**, and is used to treat former narcotic addicts.



naloxone (Narcan®) naltrexone (Trexan®)

Narcotic antagonists are especially useful in cases of overdose because they can reverse the CNS depression caused by opiate agonists. Naloxone is the most often used, most effective, and prototypal narcotic antagonist. Naloxone, nalmefene, and nadide are among several other compounds used to antagonize morphine receptors.

IV – Mechanism of action of morphine

Opioid drugs like morphine act in both the **central and peripheral nervous systems**. Within the central nervous system, opioids have effects in many areas, including the spinal cord. In the peripheral nervous system, actions of opioids in both the myenteric plexus and submucous plexus in the wall of the gut are responsible for the powerful constipating effect of opioids. In peripheral tissues such as joints, opioids act to reduce inflammation.

Major advances have been made in understanding the mechanism of action of the opioids. The most important recent advances have been the **cloning and characterisation of the receptors** acted upon by opioids (opioid receptors), increased knowledge of the cellular action of opioids and identification of the sites of action of opioids in the brain.

IV.1 – Endorphins and enkephalins

Discovery

Generally speaking, if a molecule acts on cells, it`s because it is recognized by these cells, which possess specific receptors. This general reasoning process led four scientists to look for

morphine receptors in the nervous system, on the neurons surface. But why do the brains of vertebrates would contain receptors for alkaloids derived from the juice of poopy seeds? Hanz Kosterlitz, a scotish searcher, had the idea that if animal cells such as neurons can express receptors for a natural substance, it could mean that this substance simply mimicks molecules that are normally present in the bodies of vertebrates. This hypothesis resulted in a public outcry, and yet it was true.

Indeed the breakthrough came in 1975 when John Hugues and Kosterlitz isolated two peptides with opiatelike activity from pig brains. These related pentapeptides, called **methionine enkephalin** and **leucine enkephalin** , are abundant in certain nerve terminals. They participate in the integration of sensory information pertaining to pain.

- Met Enképhaline : $^{+}H_3N$-Tyr-Gly-Gly-Phe-Met-COO^{-}

- Leu Enképhaline : $^{+}H_3N$-Tyr-Gly-Gly-Phe-Leu-COO^{-}

A year later, Roger Guillemin isolated longer peptides called a **-endorphins** and b **-endorphins**, from the intermediate lobe of the pituitary gland. The name **endorphin**, coined by Choh Li of the University of California at Berkeley, refers to "morphine within", and was given to the **endogenous morphine-like peptides** that originate from the pituitary hormone.

Facts

It has been shown later that endorphins and enkephalins are derived from a 91 amino acid pituitary hormone called b **-lipotropin**. On release it is cleaved to form four major active products: residue 61-65 is the **met-enkephalin**, residue 61-77 is called g **-endorphin**, residue 61-91 is the b **-endorphin**, and residue 61-76 is the a **-endorphin**. Beta-endorphin is the most active and gives the most euphoric effect to the brain. It can produce dependence and tolerance. All these peptides show a high morphinelike activity inducing analgesic pharmacological effects, and bind to opiate receptors. Their high activity and specificity make endorphins attractive compounds from a clinical view, but most are active only if injected into the blood (or the cerebrospinal fluid). This is because peptides are digested in the stomach, decomposed by proteolytic and other enzymes. This is the basis for an old Perry Mason episode where the murderer, knowing his victim had an ulcer, spiked a bottle of wine with rattlesnake poison and drank it with him. It killed the man with the ulcer by passing

directly into the blood through the ulcer, but not the murderer with an intact stomach. Also, because of their size and structure, they have difficulty passing into the brain. Thus, despite the low oral to parenteral ratio of many morphine derivatives, they will probably not be replaced by small-chain peptides anytime soon.

Enkephalins and endorphins are commonly called "**opioids**". ("**Opiates**" is mainly used to describe the traditional drugs, morphine and its analogues). These compounds are hundreds of times more potent than morphine on a molar basis. Because of this potency, their concentrations in vivo are low, and it has taken recent advances in experimental neuroscience to elucidate the chemistries of these hormones. These include radioimmunoassay and microdialysis.

Function of opioids

The functions of these small protein molecules appear to be as **natural analgesics** (pain killers) and they are associated with those systems that react to stress. Excessive production and release of these agents can result in euphoria and actions remarkably similar to those of the opiates. They stimulate their receptors on nerves mainly to decrease the chances of the nerve firing or to decrease the release of an **excitatory transmitter**, such as **acetylcholine**, by reducing the availability of essential calcium ions in the nerve ending. Such actions account for their physiology, pharmacology and therapeutic uses, as well as those of morphine, etc., to cause analgesia, narcosis, respiratory depression, tolerance, addiction (dependence), pin-point pupil, constipation and, of course, the relief of diarrhoea. But without them it would be difficult to explain the effectiveness of acupuncture, massage, the pain relieving ability of the hot water bottle or heat lamp or thrill or the euphoria that some people experience when jogging.

Finally the effectiveness of analgesic opiate derivatives such as opium, morphine, and heroin is an accidental side effect that derives from the ability of these substances to bind to neurohormone receptors despite their very different structure

IV.2 – Opioids (and opiates) receptors

Classes of receptors

Opiate receptors of **several varieties** are responsible for the major pharmacologic effects. These subtypes are given Greek names like m (analgesia, euphoria), s (dysphoria, cardiac stimulation), k (sedation, spinal cord analgesia, miosis), d, etc. Antitussive properties, emesis (vomiting), and anticholinergic (constipation) effects also occur, indicating a wide variety of receptor types and actions. Indeed opiate use causes nausea and vomiting. Tolerance for this effect is built up very quickly. Opiates effect the digestive system by inhibiting intestinal peristalsis. Long before they were used as painkillers, opiates were used to control diarrhea. There is also a concentration of opiate receptors in the respiratory center of the brain. Opiates have an inhibiting effect on these cells and in the case of an overdose, respiration can come to a complete halt. Opiates also inhibit sensitivity to the impulse to cough.

Morphine has considerably **higher affinity for** m **receptors** than for other opioid receptors. The opioid antagonist, **naloxone**, inhibits all opioid receptors, but has highest affinity for μ receptors. All receptors produce analgesia when an opioid binds to them. However, activation of κ receptors does not produce as much physical dependence as activation of μ receptors. Lastly β endorphin interacts preferentially with μ receptors too, and the enkephalins with δ receptors.

Recently, the main opioid receptors have been cloned, and their molecular structures described. These receptors belong to the large family of receptors which possess 7 transmembrane-spanning domains of amino acids.

Similarities

It is, however, important to note that all classes of opioid receptors share key similarities. First, the receptors have a **common general structure**. Cloning demonstrates that the receptors are usually G protein-linked receptors imbedded in the plasma membrane of neurons. Once the receptors are bound, a portion of the G protein is activated, which allows it to diffuse within the plasma membrane. The G protein moves within the membrane until it reaches its target, which is either an

enzyme or an ion channel. Most often, the targets alter protein phosphorylation and/or gene transcription, which alter the short-term and long-term activity of the neuron, respectively.

A second similarity is that activation of any type of opioid receptors **inhibits adenylate cyclase**, which is an enzyme responsible for catalyzing numerous chemical reactions in neurons. Activation of each type of receptor appears to shares a common property, which allows them to alter adenylate cyclase activity. The common properties may explain why different types of opioid receptors occasionally have the same effect on a neuron. Even though opioid receptors share the ability to inhibit adenylate cyclase, each receptor subtype has unique series of effects that can not be produced by any other type of opioid receptor.

A final similarity is that all types of opioid receptors are present both **presynaptically and postsynaptically in neurons**. When acting at presynaptic receptors, the peptides function as neuromodulators affecting the release of neurotransmitters. At postsynaptic receptors, the peptides act as neurotransmitters by directly altering membrane potentials. The overall effect of opioids on a particular tissue depends upon the concentration and location of particular opioid receptors in the area.

Effects

Opiate receptors exert effects on synaptic transmission by presynaptically modulating the release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, and substance P. The latter compound is a peptide neurotransmitter involved in nociceptive (pain-related) neurons. Opiate receptors act on G-peptides, transmembranal macromolecules linked to post-synaptic intracellular enzymes (such as adenylyl cyclase) or ion channels (such as K^+, Ca^{++}). In high doses the opiates cause generalized CNS (central nervous system) depression sufficient for surgical anesthesia.

As shown next page, the opioid receptor is thought to have three main binding areas. There is an **anionic site** (8 by 6.5 angstroms) that bonds to the charged nitrogen of morphine, a **cavity** which accomodates the piperidine ring, and a **flat surface** for binding the aromatic portion of the molecule. All active agonists and antagonists must fit this receptor to some degree.

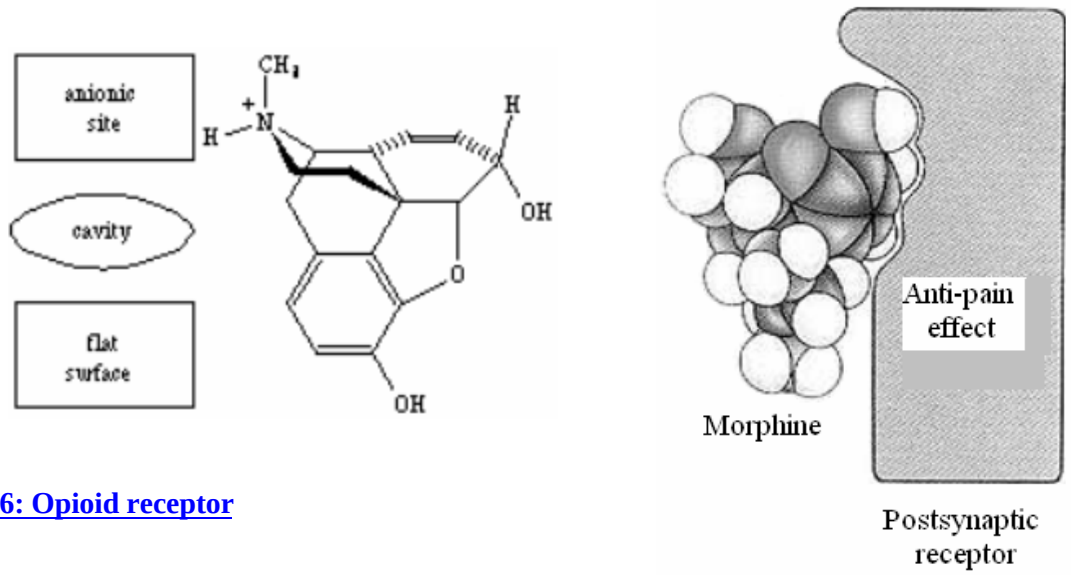


Fig 16: Opioid receptor

Conclusion

Morphine has brought about many moral and ethical questions. It has gone through phases of being outlawed and reinstated for therapeutical use several times. The potent morphine derivative, Heroin, is currently banned in the United States but it is used for medical treatment in other countries.

The prescribing of morphine, as recommended by the World Health Organization, is based on an individual's personal pain threshold. Indeed after my surgery I was asked regularly by the nurse to evaluate my pain on a scale from 0 to 10, and according to my answer he could decide whether he had to give me morphine or another less powerful analgesic. I think that this method is really efficient and wise.

The current research on opiates is focused on the binding between the drug and the human receptors. Scientists are trying to find new ways of synthesis to provide analgesic effects without the side-effects and problem of addiction. Current research is also making an attempt to combat drug addiction and ease withdrawal symptoms. The rapid advancement of technology is making the synthesis of these drugs and their mechanisms for delivery possible. Devices are currently being developed that will be triggered by morphine to release naltrexone, a morphine antagonist. Cellulose acetatephthalate microspheres are coated with trilaurin which then disperse the naltrexone. Naltrexone is also dispersed in an noctyl half ester of methyl vinyl ether and maleic

anhydride copolymer and fabricated into a disk. This disk releases naltrexone over a two week period while the microspheres release it rapidly. The disk and microspheres are placed in a semi-permeable membrane that is activated by morphine. Morphine activates the devices causing the release of naltrexone. The naltrexone then binds to the morphine receptor instead of morphine. This technique seems to be useful in the treatment of heroin addiction.

Igenious ideas like these are what will provide some answers to the ethical and moral questions that morphine has caused. Scientific manipulation did cause the spree of heroin addiction to begin, but at the time it was one of the only available potent analgesics to prevent dreadful and unperceivable human pain and suffering. Today scientists are able to use state of the art technology, such as molecular modeling software, to make predictions about newly synthesized drugs. By having an understanding of structure, metabolism, and receptor-substrate binding, nonaddictive analgesics with little side effects could be developed. Eventually, the poppy could be used for its simple esthetic value!

References

- *Biochemistry*, third edition, Lubert Stryer , 19 , p 992-993
- The Chemistry of Morphine Alkaloids , K.W.Bentley , 1954
- Morphine and allied drugs, A.K.Reynolds, 1957 (Toronto)
- Recent findings on the mechanisms of action of morphine : implication for the development of new analgesics, O.Valverde, R.Maldonado, BL. Kieffer, CNS Drugs 98 vol 10 1-10
- The opium poppy, morphine, and verapamil, M.K Davies, A.Hollman, Heart (BMJ) 2002 vol88
- Rapid and simple method to determine morphine and its metabolites in rat plasma by liquid chromatography mass spectroscopy, D.Projean, The Minh Tu, J. Ducharme, Journal of chromatography B, vol 787, issue 2, april 2003, p243-253
- EXPERIMENTAL AND CLINICAL PHARMACOLOGY,Opioids, mechanisms of action Loris A. Chahl, Associate Professor, Discipline of Clinical Pharmacology, Faculty of Medicine and Health Sciences, University of Newcastle, Newcastle, N.S.W. (Aust Prescr 1996;19;66-7) http://www.australianprescriber.com/magazines/vol19no3/opioids.htm
- Molecular Expression, Gamma endorphins, Available: http://micro.magnet.fsu.edu/optics/olympusmicd/galleries/polarized/gammaendorphin1.html

- Centre l`Etape – La Morphine Available: http://www.etape.qc.ca/drogues/morphine.htm

- Columbia Encyclopedia, Sixth Edition, Copyright (c) 2002. Morphine
  Available: http://www.encyclopedia.com/html/m1/morphine.asp

- Constance Hammond, directeur de recherche, U29, INSERM
  Jean-Pierre Ternaux, Laboratoire Neurocybernétique cellulaire - UPR 90 – CNRS
  Available: http://www.inrp.fr/Acces/biotic/neuro/douleur/html/morphine.htm

- Pharmacology Central – Opiates narcotics, http://www.pharmcentral.com/narcotics.htm

- BRIAN CALLINGHAM Opium, from a travellers' remedy to the enkephalins
  http://www.quns.cam.ac.uk/Queens/Record/1999/Academic/Opium.html

- Didier Pol © 2002 – Petite histoire naturelle des drogues psychotropes
  http://wwwusers.imaginet.fr/~pol/8morph&h.htm

- Biotech (N.A.) – Natural power of endorphins
  http://www.biotech-usa.com/tellme.htm

- United Nation Office on drugs and crime: The quantitative determination of the morphine content of opium by paper chromatography and paper electrophoresis. A. Baerheim Svendsen, Kamilla Bergane 1958/01/01
  http://www.undcp.org/odccp/bulletin/bulletin_1958-01-01_4_page005.html