Chemistry of Opioid Analgesics

PHA 422 - Neurology Pharmacotherapeutics

Optional reading assignment: Wilson and Gisvold, pgs. 629-656.

Opioid analgesics are well known for their ability to reduce the perception of pain without a loss of consciousness. The original opioids were derived from opium, which is a partially dried latex harvested from the opium poppy, *papaver somniferum*. Opium contains morphine, codeine, noscapine, papaverine, and thebaine. Thebaine is a convulsant drug that produces no analgesia, and as such it is not used clinically. However, it is an important synthetic intermediate in the production of semisynthetic opioids.

Opium is a less effective analgesic than pure morphine, because it is slowly absorbed, and has been historically used for its constipating action (paregoric). Morphine itself, which was discovered in 1809, has a variety of effects, among which are an increase in the tolerance to pain, somnolence, euphoria, an antitussive effect, respiratory depression, constipation and emesis. In addition, morphine has a high addiction liability. Derivatives of morphine have been sought that retain the analgesic activity of the parent, but that have improved oral bioavailability and a reduction in addiction liability and other deleterious side effects.

The structure of morphine is shown below. The rings are lettered A (aromatic), B (cyclohexane), C (cyclohexene), D (piperidine) and E (tetrahydrofuran). All of the derivatives of morphine which possess this basic ring structure have a high addiction liability which is proportional to their analgesic activity.

![Morphine structure](image)

**Structure/Activity Relationships of Morphine Analogues**

**Modifications at the 3- and 6-hydroxyl groups:**

- 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.
Conversion of the 6-OH to a 6-OCH3, yielding heterocodeine, results in a six-fold increase in activity.

Oxidation of the 6-OH to a ketone reduces activity when the 7,8-double bond is present (morphinone = 37% of morphine). However, as shown below, when the 7,8-double bond is saturated, a 6-keto will increase activity.

Removal of the 6-OH (6-desoxymorphine) increases activity 10-fold in the dihydro series.

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 CNS penetration.

If the ether linkage is opened up to afford a second OH on the aromatic ring, activity is reduced 90% (see below).

**Modifications at the 7,8-double bond:**

- Reduction of the 7,8-double bond results in a slight increase in activity, as in dihydromorphine and dihydrocodeine.
- As mentioned above, saturation of the 7,8-double bond has the greatest effect when combined with modifications at the 6-position (as in dihydromorphinone).

**Modifications of the nitrogen substituent:**

- Methyl is the optimal substituent for agonist activity, and ethyl is passable.
- If the nitrogen substituent is a hydrogen, analgesic effect is reduced 75%, and addiction liability is lowered.
Addition of a phenethyl substituent in place of methyl results in a 14-fold increase in activity over morphine.

- Quaternary ammonium derivatives such as N,N-dimethylmorphine have no analgesic activity, but do have significant curare-like activity.
- If the nitrogen substituent is a bulky alkyl group such as propyl, isobutyl, or especially allyl and cyclopropylmethyl, the compound becomes a narcotic antagonist.

**Nuclear (ring) substitutions:**

- Opening up the ether linkage (E ring) to form the catechol-type ring system shown below will reduce activity by 90%.

![Diagram 1](image)

- Addition of a 14-beta-OH results in a dramatic increase in activity in the dihydromorphinone series, as shown below.

![Diagram 2](image)

- If the 6 position is substituted with a methylene substituent, as in the structure above (6-methylene-dihydromorphine), the resulting analogue has 80 times the potency of morphine.
Representative Morphine Analogues

The oripavine derivative etorphine is a representative of a particularly potent class of morphine analogues. Etorphine is approximately 1000 times as potent as morphine, and arguably is too potent to be released for human therapy. It is currently used as a tranquilizer for large animals.

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.

The Morphine Rule

The following structural features are found in most opioid analgesic analogues, and are collectively referred to as the "Morphine Rule". As you will see later, there are some exceptions to this 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.

**Structure/Activity Relationships of Morphinans**

The *morphinans*, which were first introduced by Grewe in 1946, are similar in structure to the morphine analogues, but lack the E ring found in the naturally occurring opioids, as well as the 6-OH and the 7,8-double bond. Their general structure is represented by levorphanol, which is shown below.

The structure/activity relationships of the morphinans are very similar to those of the morphines:

- A 3-OH is optimal, and a 3-methoxy is less active.
- The nitrogen substituent produces the same activity as in the morphines.
- No other substituents may be added to the A ring.
- The C ring must be unsubstituted.
Representative Morphinan Analogues

The benzomorphans, which were first introduced by May in 1960, are also similar in structure to the morphine analogues, but lack the C and E rings found in the naturally occurring opioids. Their general structure is shown below.

The structure/activity relationships follow the same pattern as the morphinans:

- The nitrogen substituent (R3) follows the same rules as the morphinans and morphines. However, antagonist substituents produce analogues with a higher agonist/antagonist ratio.
- R1 and R2 substituents must be present to supply vestiges of the C ring. These are usually methyl, or a similar lower alkyl. R2 must be alpha for the analogue to have agonist activity. R1 can be alpha (cis), producing analogues with activity about equal to morphine, or beta
(trans), producing agents 4-30 times as active as morphine. The beta agents will support narcotic addiction, while the alpha series will not.

- R4 must be OH or methoxy.

**Representative Benzomorphan Analogues**

![Representative Benzomorphan Analogues](image)

**Structure/Activity Relationships of the 4-Phenylpiperidines**

The representative 4-phenylpiperidine, meperidine (Demerol, below) was first prepared as an antispasmodic, and in addition to this activity it was found to be analgesic at about 20% the potency of morphine. Note that the compound follows the morphine rule.

![Structure/Activity Relationships of the 4-Phenylpiperidines](image)

The structure/activity relationships of 4-phenylpiperidines are fairly simple:

- Both esters and reverse esters at the 4 position are active, as are the simple ketones. propyl is the optimal chain length (excluding the ester oxygen).
- The phenyl ring at the 4 position is necessary for activity, and must be able to assume the axial position, as shown above. Addition of a m-OH group will enhance activity; such analogues are called *bemidones*.
- If a reverse ester is combined with a 3-methyl, the analogues are known as *prodines* (see below). The methyl group may cause enantiomeric recognition by the opioid receptor.
The nitrogen substituent is a methyl in most cases. A phenethyl or its equivalent will increase activity. It is not possible to confer antagonist activity with a nitrogen substituent such as allyl.

**Representative 4-Phenylpiperidines**

- Dupenacril (Lunesta®)
  - no analgesia
  - sedation

- Illoretadine
  - 6.2 x meperidine

- Deletrine
  - 5.5 x meperidine

- Pinolinine
  - reverse action
  - 1800 x meperidine

- Temazepam (Searle®)
  - 1600 x meperidine
  - hypnotic - benzodiazepine (adjunct to general anesthesia)

- Nitrazepam
  - 300 x meperidine
Open Chain Opioid Analgesics

Open chain analogues which follow the morphine rule can also have significant analgesic activity. The general structure of these analogues appears below:

![General structure of open chain opioid analgesics](image)

The structure/activity relationships of open chain opioid analgesics is as follows:

- Both phenyl groups must be present.
- The nitrogen substituent R2 can vary, but the nitrogen should be tertiary. It is not possible to produce an antagonist in this class.
- A m-OH reduces activity.
- The (-)-isomers are most potent.
- R1 is usually propionyl.
- R3 is usually methyl, and the total aliphatic chain length is usually 7 carbons.

Methadone accumulates in lipid tissue outside of the CNS, and thus has a slow onset and long duration (24 hours). It is used for long term maintenance of addiction. Propoxyphene is a mild analgesic with a low addiction liability.
The Opioid Receptor

As shown above, 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. There appear to be four receptor subtypes, termed mu (the morphine receptor), sigma (the phencyclidine receptor), kappa (the ketocyclazocine receptor) and delta (the endorphin/enkephalin receptor).

Endorphins and Enkephalins

Endorphins and enkephalins are derived from a 91 amino acid pituitary hormone called beta-lipotropin. On release it is cleaved to form three major active products: residue 61-65 is called met-enkephalin, residue 61-77 is called gamma-endorphin, and residue 61-91 is called beta-endorphin. Beta-endorphin is most active, and is about 20 times as potent as morphine. It can produce dependence and tolerance.