Naloxone: Effects and Side Effects

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- Specificity
- Toxicology
- Unmasking Disease

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ARTICLE

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Crystal structure of the μ-opioid receptor bound to a morphinan antagonist

Aashish Manglik[1], Andrew C. Kruse[1], Tong Sun Kobilka[1], Foon Sun Thian[1], Jesper M. Mathiesen[1], Roger K. Sunahara[2], Leonardo Pardo[3], William I. Weis[1,4], Brian K. Kobilka[1] & Sébastien Granier[1,5]

Opium is one of the world's oldest drugs, and its derivatives morphine and codeine are among the most used clinical drugs to relieve severe pain. These prototypical opioids produce analgesia as well as many undesirable side effects (sedation, apnoea and dependence) by binding to and activating the G-protein-coupled μ-opioid receptor (μ-OR) in the central nervous system. Here we describe the 2.8 Å crystal structure of the mouse μ-OR in complex with an irreversible morphinan antagonist. Compared to the buried binding pocket observed in most G-protein-coupled receptors published so far, the morphinan ligand binds deeply within a large solvent-exposed pocket. Of particular interest, the μ-OR crystallizes as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6. These high-resolution insights into opioid receptor structure will enable the application of structure-based approaches to develop better drugs for the management of pain and addiction.

Opium extracts from the plant *Papaver somniferum* have been used that it may be possible to develop safer and more effective therapeutic

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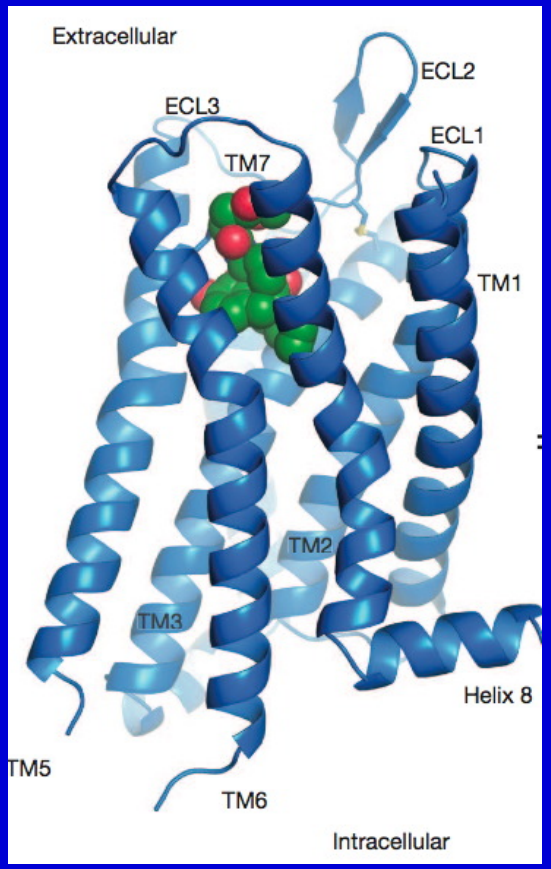

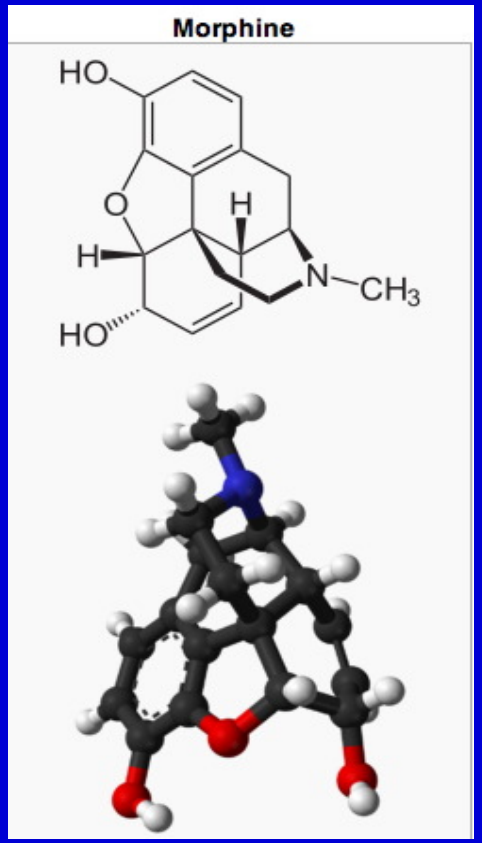

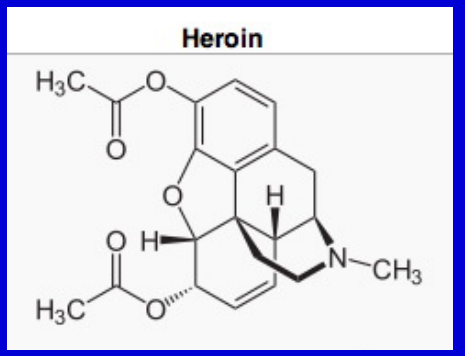

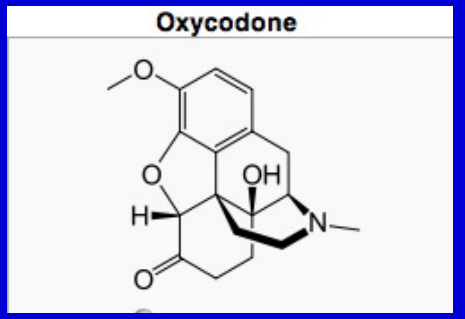

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Naloxone: Effects and Side Effects

N-ALLYLNOROXYMORPHONE:
A NEW POTENT NARCOTIC ANTAGONIST

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It has been known since 1915, when Pohl[17] described the antagonistic effect of N-allylcodeine on the codeine-induced respiratory depression that N-allyl derivatives of narcotic analgesics are capable of antagonizing nar-

production of controllable apnea during anesthesia (Foldes *et al.*[7]).

Recently the pharmacological effects of the N-allyl derivative of a potent narcotic analgesic, oxymorphone† (Numorphan (see Fig. 1), were investi-

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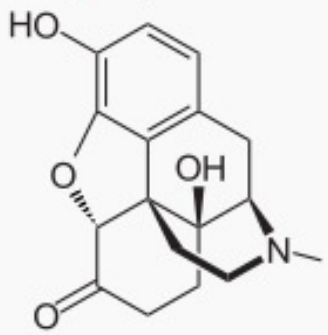
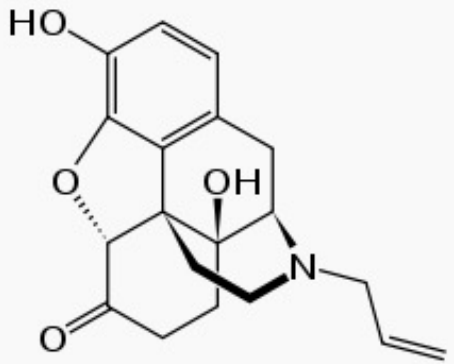
Oxymorphone



Naloxone



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