Saving the Synapse: Assessing Opioid Receptors as Therapeutic Targets in the Management of Opioid Addiction

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CHEM 495 – Drug Discovery

Background

- Opioids are analgesic drugs that can agonize endogenous opioid receptors at the neuronal synapse and inhibit signal transduction through nociceptive (pain) modulatory pathways, making opioids a popular drug choice for clinical pain management. [1]

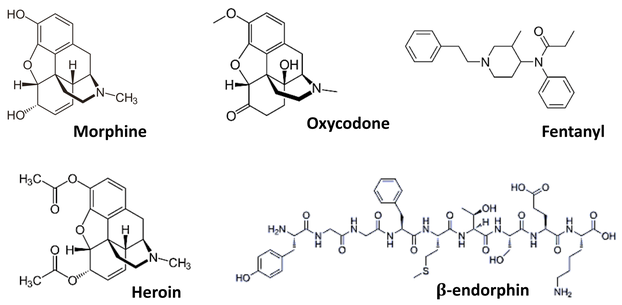

Figure 1. Structures of common opioids

- There are three main classes of opioid receptors: mu (MOR), delta (DOR), and kappa (KOR) receptors. Each receptor type varies in its physiological and psychological effects as well as its binding affinity to specific drugs. [2]

Table 1. Opioid binding selectivity and physiological effects for MOR, DOR, and KOR

		MOR	DOR	KOR
Opioids	Morphine	+++	+	+
	Oxycodone	+++	+	++
	Fentanyl	+++	+	-
	Heroin	+++	+	-
	β-endorphin	+++	+++	+++
Effects	Analgesia	+++	+	++
	Respiratory Depression	+++	++	-
	Euphoria	+++	-	-
	Dysphoria	-	-	+++
	Physical Dependence	+++	-	+

Pharmacodynamics at the Synapse

- Small agonists (like morphine) interact with conserved residues in the bottom of the binding pocket, forcing an active receptor confirmation (Fig. 2)
- Small antagonists can occupy the bottom of the binding pocket without forcing an active confirmation

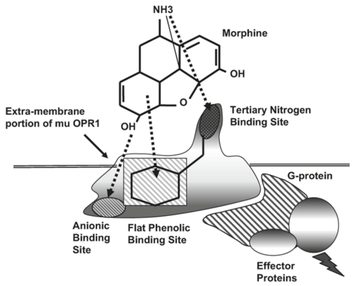

Figure 2. SAR for pharmacophore of mu-receptor agonist.

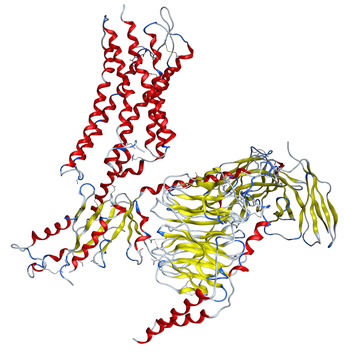

Figure 3. Crystal structure of mu opioid receptor with G-protein.

- ORs = G-coupled proteins (Fig. 3)
- ORs are ~60% identical - greatest conservation in transmembrane helices and the greatest diversity in their extracellular loops [2]
- Upon activation, G-protein α and $\beta\gamma$ subunits interact with second messenger to stimulate K^+ efflux, inhibit voltage-gated Ca^{2+} channels, and inhibit adenylyl cyclase
- Inhibits nociceptive signal transduction

- Chronic exposure to opioids induces physical and chemical changes in the synapse [3]
- β-arrestin sterically displaces G-protein and triggers receptor internalization and desensitization (Fig. 4)
- Chronic presence of opioid agonist result in decreased endogenous neurotransmitter synthesis

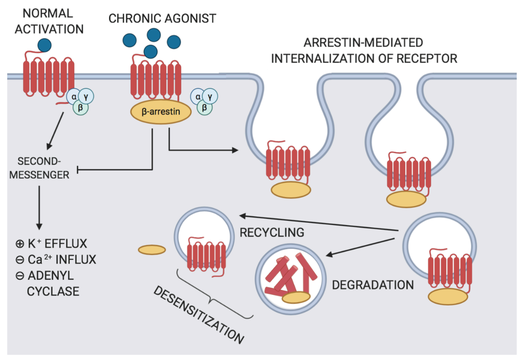

Figure 4. Chronic opioid exposure induces β-arrestin-mediated internalization of opioid receptor. Cell becomes desensitized to opioid presence, results in increased tolerance.

- These physiological changes are difficult to reverse thus increasing drug tolerance, fostering physical dependence, and contributing to addiction and withdrawal symptoms. [3,4]

Combating Opioid Addiction

CURRENT AAPROACHES:

- Need to control over-prescription of opioids in clinical setting
- Requires understanding of physical dependence as well as behavioral conditioning of drug use [4]
- Treating physical dependence:
  - Methadone (full mu receptor agonist)
  - Buprenorphine (partial mu receptor agonist and kappa receptor agonist)
  - Naltrexone (extended-release mu receptor antagonist and kappa receptor antagonist)
  - Naloxone (antagonist to all receptors)

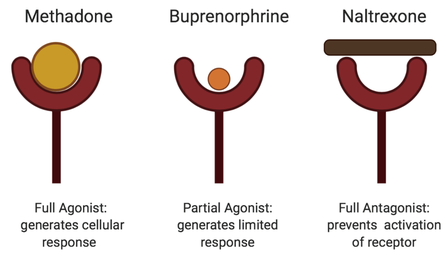

Figure 5. Comparison of agonist activity of Methadone and Buprenorphine and antagonist activity of Naltrexone

MORE RESEARCH NEEDED:

- Easing symptoms of withdrawal to make antagonist drugs more desirable
- Selectively targeting conformation of PNS opioid receptors [4]
- Prevention or diminishing of receptor internalization [3]
- Combined agonist/antagonist regiment

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References:

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4. Stein, C. 2018. New concepts in opioid analgesia. *Expert Op. on Inves. Drugs,* 27(10):765-775.