THE OPIOID CRISIS

Understanding Opioid Receptors, Addiction, and Alternatives

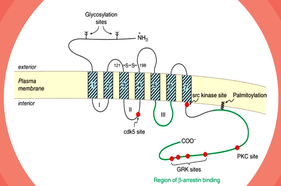
Nearly **100** deaths per day in the U.S. are opioid related[1]

Drug overdose is the leading cause of death of Americans under 50[1]

Nearly **1/2** of all U.S. opioid overdose deaths involve a prescription opioid[2]

Opioids could kill nearly **500,000** Americans in the next decade[1]

GENERAL STRUCTURE OF AN OPIOID RECEPTOR

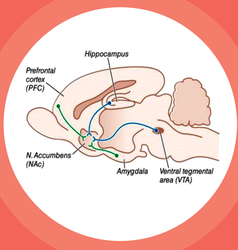


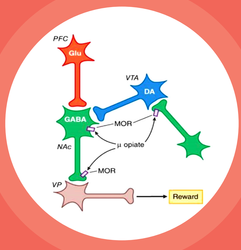
Each of the opiate receptors consists of an extracellular N-terminus, seven TM helices, three extra- and intracellular loops, and an intracellular C-terminus characteristic of the G-protein-coupled receptors (GPCRs).

PATHWAYS OF THE REWARDING PROPERTIES OF OPIATES

The positive, rewarding effects of opiates are considered to be the driving component for initiating the recreational use of opiates.

This sagittal section of rat brain shows DA and GABA inputs from the VTA and PFC, respectively, into the NAc.





Neurons are labeled with their primary neurotransmitters. At a cellular level, μ-opioid receptor (MOR) agonists reduce excitability and transmitter release at the sites indicated by inhibiting $Ca2+$ influx and enhancing $K+$ current. Thus, opiate-induced inhibition in the VTA on GABAergic interneurons or in the NAc reduce GABA-mediated inhibition and increase outflow from the ventral pallidum (VP), which appears to correlate with a positive reinforcing state (enhanced reward).

A NOVEL NONOPIOID TREATMENT FOR PAIN

Myriad marine toxins target GPCRs, neurotransmitter transporters, and ion channels; a number (i.e., tetrodotoxin, saxitoxin, kainic acid, and various venoms from cone snails) have been useful to basic scientists (Sakai and Swanson 2014). One that has become an FDA-approved treatment of chronic pain is ziconotide.

Ziconotide is a synthetic copy of a neuroactive cone snail toxin, a 25–amino acid basic polypeptide with three disulfide bridges. The molecule is hydrophilic and readily soluble in water and isotonic saline.

Ziconotide Mechanism of Action

Ziconotide binds to and blocks N-type $Ca2+$ channels on nociceptive afferents in the dorsal horn of the spinal cord. This leads to blockade of the release of excitatory neurotransmitter involved in nociception (Patel et al., 2017).

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Content and figures excerpted from Goodman & Gilman's: *The Pharmacological Basis of Therapeutics*, 13th Edition, Edited by Laurence L. Brunton, Randa Hilal-Dandа, Björn C. Knollmann.

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References:

[1] https://www.statnews.com/2017/06/27/opioid-deaths-forecast/

[2] https://www.cdc.gov/drugoverdose/data/overdose.html