2018

Opioids Pharmacology

This is the second of a four-part Drug Testing Matters series on opioids.

Opioid Pharmacology - Pain Management

Opioid analgesics are the most effective and commonly used modality for the alleviation of moderate to severe pain. Opioids are characterized by their important pharmacological differences derived from the complex interaction with three opioid receptor types: *mu* or μ, *kappa* or κ, and *delta* or δ. These receptors belong to the G-protein-coupled receptor family and signal via a second messenger (e.g., cyclic adenosine monophosphate [cAMP]) or an ion channel. G-protein-coupled receptors have the following features: an extracellular N-terminus, a seven-transmembrane helical structure with 6 loops (3 intra- and 3 extracellular), and an intracellular C-terminus (1). Once a receptor is activated, it releases a portion of the G-protein, which diffuses within the membrane until it reaches its target (enzyme or ion channel). These targets alter protein phosphorylation via cAMP within the cell, resulting in the activation of protein kinases (short term) or gene transcription proteins and/or gene transcription (long term).

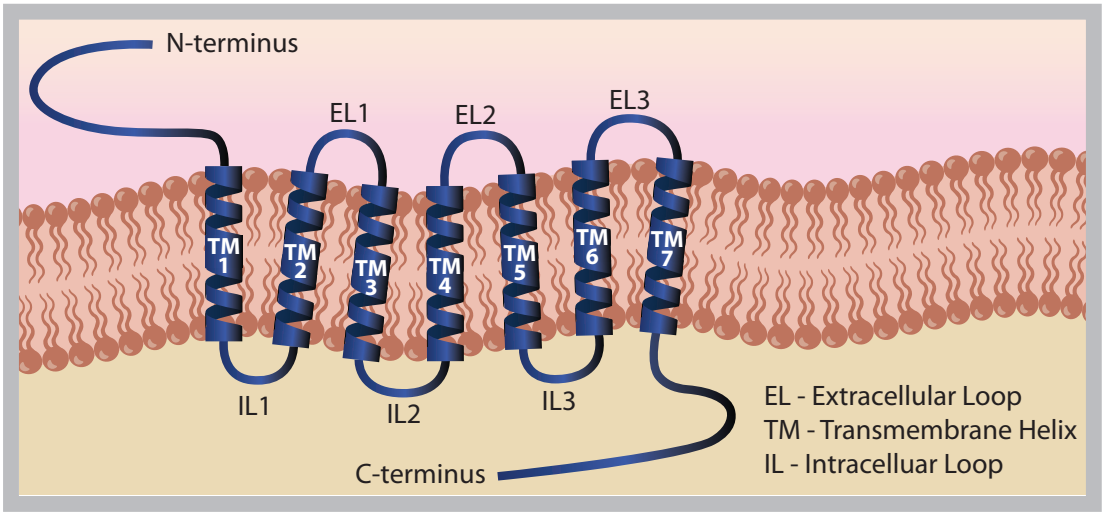

Figure 1. Opioid Receptor Structure. Adapted from A.M. Trescot, S. Datta, M. Lee, and H. Hansen, Opioid Pharmacology, Pain Physician 2008: Opioid Special Issue (11) S133-S153 (2008).

There are opioid receptors within the central nervous system and throughout the peripheral nervous system. These receptors are normally stimulated by endogenous peptides produced in response to noxious stimuli. The Greek letters used to identify the opioid receptors are based on the prototype agonists. Mu receptors, whose prototype agonist is morphine, are found in the brain stem and medial thalamus. Ketocyclazocine is the prototype agonist for kappa receptors, which are found in the limbic and other diencephalic areas, brain stem, and spinal cord. [D-Pen^2,D-Pen^5] enkephalin (DPDPE) is the prototype agonist for delta receptors (2), located largely in the brain.

Opioid receptors are located on presynaptic terminals of nociceptive C-fibers and A delta fibers. When activated by opioid agonists, they indirectly inhibit voltage-dependent Ca^{++} channels, decreasing cAMP levels and blocking the release of pain neurotransmitters, such as glutamate, substance P, and calcitonin-related peptide, from the nociceptive fibers. This results in analgesia. At the cellular level, there are three mechanisms of opioid actions (1):

1) A decrease in Ca^{++} entry that results in a decrease in presynaptic neurotransmission release (substance P) from the primary afferents in the spinal cord and dorsal horn

2) An increase in K^+ ion efflux that results in hyper-polarization of postsynaptic neurons, causing a decrease in synaptic transmission

3) The inhibition of GABAergic transmission in a local circuit in the brain stem where GABA (gamma-aminobutyric acid) acts to inhibit pain inhibitory neurons.

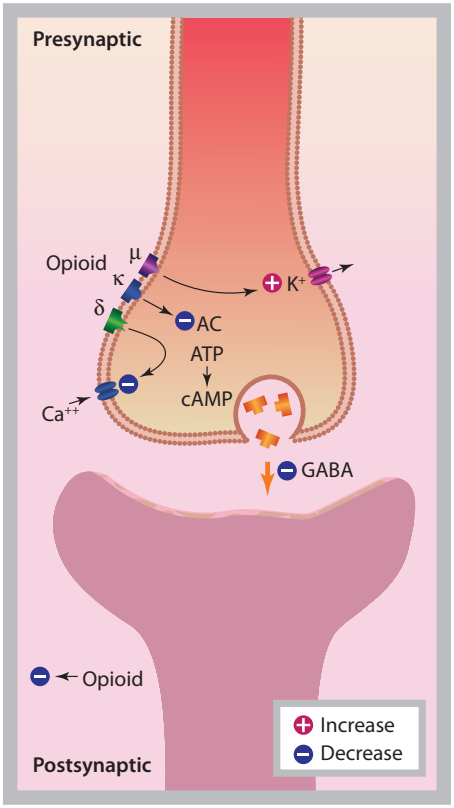

Figure 2. Cellular Mechanisms of Opioid Analgesic Action. Adapted from A.M. Trescot, S. Datta, M. Lee, and H. Hansen, Opioid Pharmacology, Pain Physician 2008: Opioid Special Issue (11) S133-S153 (2008).

Opioid Pharmacology—Addiction

Drug addiction is defined as a chronically relapsing behavioral disorder characterized by compulsive—at times, uncontrollable—drug craving, seeking, and use that persist even in the face of negative consequences (3). Addictive drugs produce behavioral effects by initiating a cascade of neurochemical events that ultimately make the organism seek the drug. There are three general cellular mechanisms related to the dopamine receptor, which is tied to the "reward" mechanism in the brain, that encompass all drugs of abuse (3):

1) Direct stimulation of dopamine neurons

2) Drug binding to GABAergic-inhibiting afferents to dopamine cells, leading to decreased GABA release and disinhibited dopamine neuronal action

3) Drug binding to presynaptic receptors, increasing presynaptic release of dopamine by blocking its reuptake or promoting its release by reverse transport.

The mechanism of action of opioids for drug addiction is characterized by the second model. Opioids activate presynaptic receptors on GABA neurons, which inhibit the release of GABA in the ventral tegmental area (VTA). The inhibition of GABA allows dopaminergic neurons to fire more vigorously, and the extra dopamine in the nucleus accumbens is intensely pleasurable.

In Figure 3, the normal state with no drug present is depicted on the left, and the situation that occurs when an opioid is present is shown on the right (4). In the normal state with no drug present and no binding to the opioid receptor, GABA is released and binds to GABA receptors, thereby inhibiting the release of dopamine and resulting in overall modulation and normal release of dopamine. The diagram on the right shows what occurs when an opioid is present. The opioid binds to the opioid receptor, inhibiting GABA release. Less binding of GABA means no inhibition of dopamine release, resulting in an increase of dopamine in the nucleus accumbens, which causes a feeling of intense pleasure (1,3).

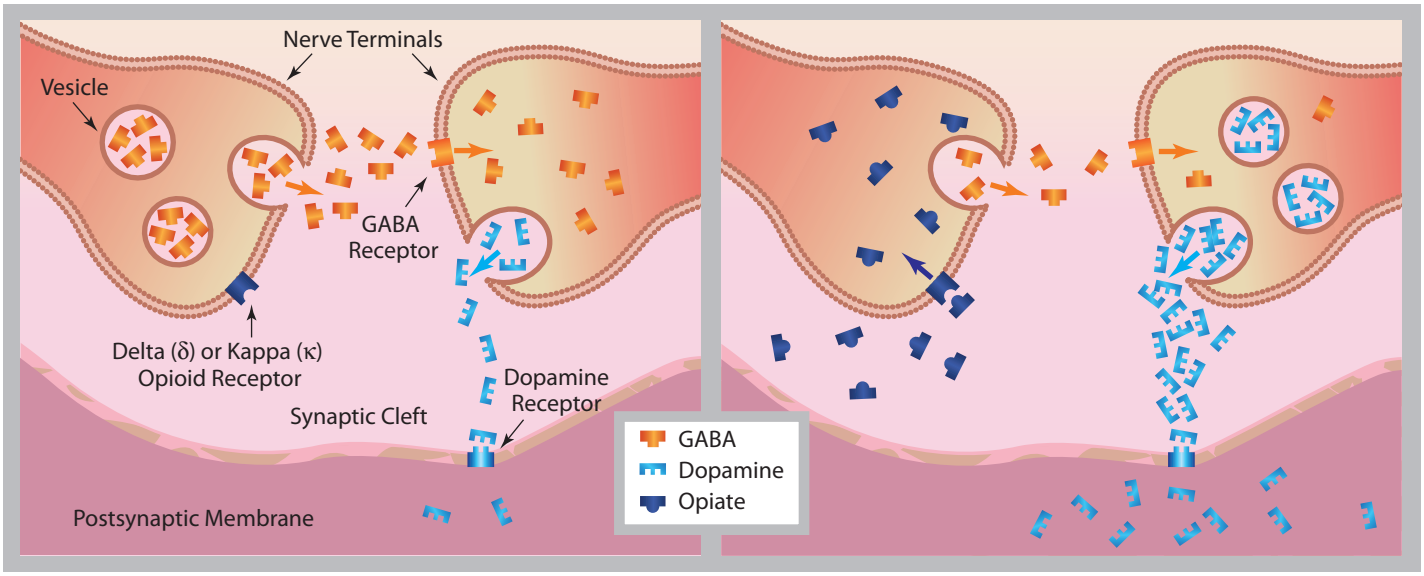

Figure 3. Cellular Mechanisms of Opioid Addictive Action. Adapted from CNSforum Image Bank (4).

References

1. A.M. Trescot, S. Datta, M. Lee, and H. Hansen, Opioid Pharmacology, *Pain Physician 2008*: Opioid Special Issue (11) S133-S153 (2008).

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3. H.S. Smith and S.D. Passik, *Pain and Chemical Dependency*, Oxford University Press, New York, NY, 2008.

4. Lundbeck Institute, CNSforum Image Bank. The mechanism of action of heroin at the delta (δ) and kappa (κ) opiate receptors [Online image] Available http://www.cnsforum.com/imagebank/item/moa_heroin_delta_kappa/default.aspx, January 10, 2012.

The author of the February 2012 Drug Testing Matters article, Opiates Pharmacology, was James Bourland, Ph.D., F-ABFT. This article was revised and updated in August 2018 by staff and consultants of RTI International.

The author of the May 2012 Drug Testing Matters article, Opiates Pharmacology, was James Bourland, Ph.D., F-ABFT. ***This article was revised and updated in August 2018 by:***

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