

**CURRENT KNOWLEDGE AND FUTURE TRENDS OF ENDOGENOUS OPIOIDS: THEIR PHYSIOLOGICAL ROLE AND RECEPTORS**

*Anupama Koneru<sup>1\*</sup>, Sreemantula Satyanarayana<sup>2</sup>, Shaik Rizwan<sup>1</sup>*

<sup>1</sup>Department of Pharmacology, Sultan-ul-uloom College of Pharmacy, Hyderabad - 034, India.

<sup>2</sup>College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 003, India.

**Summary**

The Endogenous Opioid system includes a large number of opioid peptides that are ligands for numerous types of opioid receptors. Three distinct families of endogenous opioid peptides have been well characterized - Endorphins, Enkephalins, and Dynorphins. More recently, two additional short peptides, Endomorphin-1 and Endomorphin-2 that display a high affinity and selectivity for  $\mu$  opioid receptors have been identified. The Endogenous opioid peptides bind to three primary opioid receptor types that mediate analgesia, designated  $\mu$ ,  $\kappa$ , and  $\delta$ . Preferentially, Enkephalins interact with the  $\delta$  receptor, Dynorphins interact with the  $\kappa$  receptor, and Endorphins bind to both  $\mu$  and  $\delta$  receptors with comparable affinity.

**Key Words:** Opioid receptors, Endogenous Ligands, Endorphins, Enkephalins, Dynorphins, Endomorphins.

**\*Author for Correspondence**

Anupama Koneru  
Sultan-ul-uloom College of Pharmacy  
Road No. 3, Banjara Hills  
Hyderabad-500 034  
Andhra Pradesh  
India  
Email: [anupamakoneru@ymail.com](mailto:anupamakoneru@ymail.com)

## Introduction

The complex effects, both beneficial and adverse, of opioid analgesics can be traced to the interaction of these agents with endogenous opioid systems. Opioid compounds and their receptors exist throughout the central and peripheral nervous systems and in other tissues. Opioid systems are involved in a diverse array of homeostatic functions and movement control as well as the processing of noxious sensory input. The antinociceptive system, involved in pain modulation, is itself exceedingly complex. Information about endogenous opioid system is useful background for an understanding of the effects of opioid analgesics.<sup>[1]</sup>

## Endogenous Opioid Peptides

Opioid peptides that are produced in the body include:

- Endorphins
- Enkephalins
- Dynorphins
- Endomorphins

Each family derives from a distinct precursor protein and has a characteristic anatomical distribution. The precursors, prepro-opiomelanocortin (POMC), preproenkephalin, and prodynorphin which are encoded by three corresponding genes code for the enkephalins, endorphins, and dynorphins respectively.

Each precursor is subject to complex cleavages and post-translational modifications resulting in the synthesis of multiple active peptides. The major opioid peptide encoded by pre-proopiomelanocortin is  $\beta$ -endorphin. In addition to  $\beta$ -endorphin, the proopiomelanocortin precursor encodes the nonopioid peptides adrenocorticotrophic hormone (ACTH),  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), and  $\beta$ -lipotropic pituitary hormone ( $\beta$ -LPH). Pre-proenkephalin encodes multiple copies of Met-enkephalin, including two extended forms of Met-enkephalin (a heptapeptide and an octapeptide), and a single copy of Leu-enkephalin. Pre-prodynorphin encodes three opioid peptides of various lengths that all begin with the Leu-enkephalin sequence: dynorphin A, dynorphin B, and neoendorphin. The opioid peptides share the common amino-terminal sequence of **Tyr-Gly-Gly-Phe-(Met or Leu)**, which has been called the *opioid motif* [3]. This motif is followed by various C-terminal extensions yielding peptides ranging from 5 to 31 residues.<sup>[2,3,4]</sup>

## **Endorphins**

Endorphins are endogenous opioid polypeptide compounds. They are produced by the pituitary gland and the hypothalamus in vertebrates during strenuous exercise,<sup>[5]</sup> excitement, pain and orgasm and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. Endorphins work as "natural pain relievers." They can be found in more than twenty different parts in the body, such as the pituitary glands as well as in many parts of the brain and nervous system.<sup>[6,7]</sup>

The term "endorphin" implies a pharmacological activity as opposed to a specific chemical formulation. The term endorphin is a general name for many opioid-like proteins. (It consists of two parts: endo and orphin; these are short forms of the words endogenous met-enkephalin which means "a morphine-like substance which is produced by the human body").<sup>[8]</sup>

### ***Types of Endorphins:***

Four types of endorphins are created in the human body. They are named alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ) and sigma ( $\sigma$ ) endorphins.<sup>[9]</sup> The four types have different numbers and types of amino acids in their molecules; they have between 16 and 31 amino acids in each molecule. More endorphins are released in the pituitary gland during times of pain or stress. Exercise increases the endorphin release too. For the same reason, exercise results in a better mood.  $\beta$ -endorphins are the most powerful endogenous opioid peptide neurotransmitters and are found in the neurons of both the central and peripheral nervous system. They are present abundantly in the hypothalamus and pituitary gland. They are released when the body encounters any sort of stress or pain. During severe pain the endorphins in our body cause an analgesic effect to occur, to lessen the pain that is inflicting our body. But during stress, endorphins act differently. They are released in the limbic system which reduces the extent of anxiety that our body is feeling. Not only does the opiate cause the pain to decrease it also causes the feelings of euphoria to occur as well as the release of many sex hormones.<sup>[10]</sup>

### ***$\beta$ -endorphins:***

Sequence: "Tyr Gly Gly Phe Met Thr Ser Glu Lys Ser Gln Thr Pro Leu Val Thr Leu Phe Lys Asn Ala Ile Ile Lys Asn Ala Tyr Lys Lys Gly Glu."<sup>[11]</sup>

### ***Mechanism of action and Physiological role***

Endorphins act through opiate receptors.  $\beta$ -endorphins have the highest affinity for the  $\mu_1$ -opioid receptor, slightly lower affinity for the  $\mu_2$ - and  $\delta$ -opioid receptors and low affinity for the  $\kappa_1$ -opioid receptors. Classically,  $\mu$ -receptors are presynaptic, and inhibit neurotransmitter release; through this mechanism, they inhibit the release of the inhibitory neurotransmitter GABA, and decreases the inhibition of dopamine pathways, causing more dopamine to be released. By hijacking this process, exogenous opioids cause inappropriate dopamine release, and lead to aberrant synaptic plasticity, which causes addiction.

Endorphins may have a role in preventing obesity, diabetes and psychiatric diseases too. Athletes also produce high levels of endorphins. They get a "runners high" when the athlete has done a very hard and strenuous exercise. The term "runners high" has been adopted in refer to feelings that endorphins allow humans to feel a sense of power and control over themselves that allows them to persist with activity for an extended time [9].

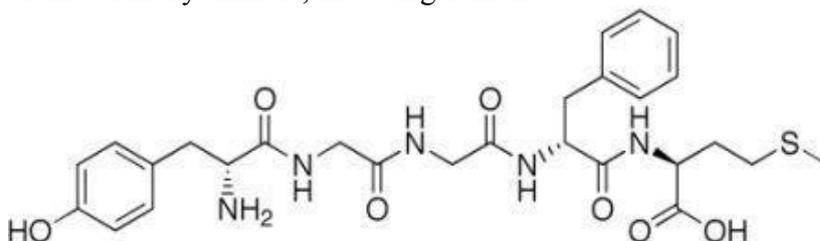
### Enkephalins

Enkephalins are pentapeptides involved in regulating nociception in the body. Discovered in 1975, two forms of enkephalin were revealed, one containing leucine ("leu"), and the other containing methionine ("met"). Both are products of the proenkephalin gene.<sup>[12]</sup>

- Met-enkephalins has Tyr-Gly-Gly-Phe-Met.
- Leu-enkephalins has Tyr-Gly-Gly-Phe-Leu.

#### *Met-enkephalins*

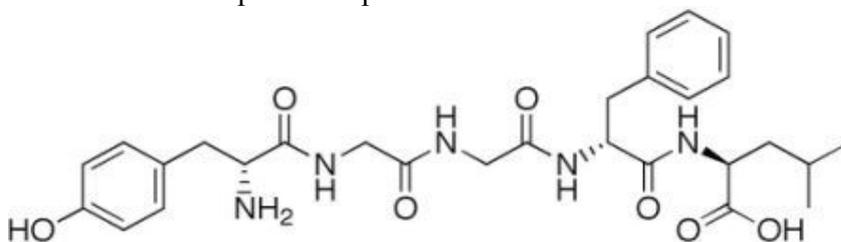
Met-enkephalins are endogenous opioid peptide neurotransmitter found naturally in the brains of many animals, including humans.



Molecular formula: C<sub>27</sub>H<sub>35</sub>N<sub>5</sub>O<sub>7</sub>S

#### *Leu-enkephalins*

Leu-enkephalins produce pharmacological effects at both the  $\mu$  and  $\delta$  opioid receptors. They have much higher selectivity for  $\delta$  opioid receptors than  $\mu$  receptors and have little to no effect on  $\kappa$  opioid receptors.



Molecular formula: C<sub>28</sub>H<sub>37</sub>N<sub>5</sub>O<sub>7</sub>

**Dynorphins**

Dynorphins arise from the precursor protein prodynorphin. When prodynorphin is cleaved during processing by proprotein convertase 2 (PC2), multiple active peptides are released: dynorphin A, dynorphin B [13]. Dynorphin A, Dynorphin B contains a high proportion of basic amino acid residues, particularly lysine and arginine as well as many hydrophobic residues. Dynorphins are produced in many different parts of the brain, including hypothalamus, hippocampus, midbrain, medulla, pons, and the spinal cord, and has many different physiological actions, depending upon their site of production. For example, dynorphins that are made in magnocellular vasopressin neurons of the supraoptic nucleus are important in the patterning of electrical activity. Dynorphins produced in magnocellular oxytocin neurons cause negative feedback inhibition of oxytocin secretion. Dynorphin produced in the arcuate nucleus and in orexin neurons of the lateral hypothalamus affects the control of appetite. Dynorphins are stored in large (80-120 nm diameter) dense-core vesicles that are considerably larger than vesicles storing neurotransmitters. These large dense-core vesicles differ from small synaptic vesicles in that a more intense and prolonged stimulus is needed to cause the large vesicles to release their contents into the synaptic cleft. Dense-core vesicle storage is characteristic of opioid peptides storage.<sup>[13]</sup>

***Mechanism of action and Physiological role***

Dynorphins primarily exert their effects through the  $\kappa$ -opioid receptor and act as modulators of pain response, maintain homeostasis through appetite control and circadian rhythm, weight control and regulation of body temperature.

**Endomorphins**

Endomorphins are of two types of tetrapeptides - Endomorphin-1 (Tyr-Pro-Trp-Phe-NH<sub>2</sub>) and Endomorphin-2 (Tyr-Pro-Phe-Phe-NH<sub>2</sub>).

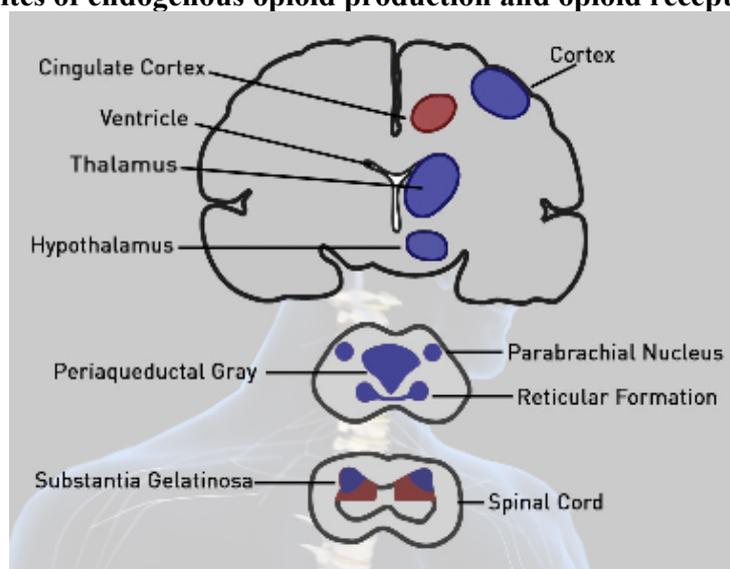
***Mechanism of action and Physiological role***

Endomorphins have the highest known affinity and specificity for the  $\mu$  opioid receptor. Endomorphin-1 is widely and densely distributed throughout the brain and upper brainstem and is particularly abundant in the nucleus accumbens (Nac), the cortex, the amygdala, the thalamus, the hypothalamus, the striatum, the dorsal root ganglia, the nucleus of the solitary tract, the periventricular hypothalamus, and the dorsomedial hypothalamus, where it is found within histaminergic neurons and may regulate sedative and arousal behaviors. In contrast, Endomorphin-2 is more prevalent in the spinal cord and lower brainstem. They play important role in perception of pain, responses related to stress, and complex functions such as reward, arousal, and vigilance, as well as autonomic, cognitive, neuroendocrine, and limbic homeostasis.<sup>[14]</sup>

### Opioid Receptors

Opioid receptors ( $\mu$ ,  $\kappa$ , and  $\delta$ ), like other G protein-coupled receptors, are characterized by 7 transmembrane domains.<sup>[1,15]</sup> High densities of opioid receptors are located in all areas of the CNS known to be involved in integrating information about pain—the brainstem, the medial thalamus, the spinal cord, the hypothalamus, and the limbic system. Opioid receptors also have been identified in the periphery.

**Fig 1. Major sites of endogenous opioid production and opioid receptors.**



**$\mu$  Receptor-** The receptor is characterized by its high affinity for Morphine. It is the major receptor mediating action of morphine and its congeners. Endogenous ligands for  $\mu$  receptor are Endomorphins-1 and Endomorphin-2, found in mammalian brain, produce biological effects ascribed to this receptor. Other opioid peptides like  $\beta$ -endorphins, Enkephalins and Dynorphins bind to  $\mu$  receptor with lower affinity.<sup>[16]</sup>

Two subtypes of  $\mu$  receptors have been proposed:

**$\mu_1$ :** Has higher affinity for morphine, mediates supraspinal analgesia and is selectively blocked by naloxone.

**$\mu_2$ :** Has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action.

**$\kappa$  Receptor** is defined by its high affinity for ketocyclazocine and Dynorphin A. Norbinaltorphimine is a selective  $\kappa$ - antagonist. Two subtypes of  $\kappa$  receptors  $\kappa_1$  and  $\kappa_3$  are functionally important. Analgesia caused by  $\kappa$  agonist is primarily spinal ( $\kappa_1$ ) or supraspinal ( $\kappa_3$ ).<sup>[16]</sup>

**$\delta$  Receptor** has high affinity for leu/met Enkephalins which are its endogenous ligands. The  $\delta$  mediated analgesia is mainly spinal ( $\delta$  receptors present in dorsal horn of spinal cord). Naltrindole is a selective  $\delta$  antagonist.<sup>[3,16]</sup>

**ORL 1 Receptor** is discovered recently and is structurally similar to the opioid receptors.<sup>[2]</sup> The natural ligand has been termed orphanin FQ (OFQ), or nociceptin. The physiology of this system is yet poorly understood. It appears to be involved in the central modulation of pain but does not appear to be implicated in respiratory depression. The various opioid receptors location and responses mediated by them are given Table 1 and their agonists and antagonists in Table 2.

**Table-1: Opioid receptors, location, and responses mediated by them**

Receptor	CNS Location	Response on activation
<b>μ</b>	Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)	<b>μ<sub>1</sub></b> – supraspinal analgesia, physical dependence; <b>μ<sub>2</sub></b> – Respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
<b>K</b>	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
<b>δ</b>	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria, physical dependence

CNS – Central nervous system

Receptor Subtype	ENDOGENOUS LIGAND	SELECTIVE LIGAND		NONSELECTIVE LIGAND	
		Agonist	Antagonist	Agonist	Antagonist
<b>μ</b>	Endorphins Endomorphins	DAMGO Morphine Methadone Fentanyl Dermarphin	CTOP	Levorphanol Etorphine	Nalaxone Naltrexone β funaltrexamine

**Table 2. Opioid Receptors – their agonists and antagonists and endogenous ligands.**

<b>κ</b>	Dynorphin A	Spiradoline U50,488	Nor-BNI	Levorphanol Etorphine EKC	Nalaxone Naltrexone
<b>δ</b>	Enkephalins	DPDPE Deltorphin DSLET	Naltrindole NTB BNTX	Levorphanol Etorphine	Nalaxone Naltrexone

BNTX -7 benzylidenenaltroxone; EKC - ethylketocyclazosine; NTB - benzofuran analog of Naltrindole; nor-BNI - nor-binaltorphimine; DAMGO - [D-Ala 2, MePhe 4, Gly(ol) 5]enkephalin; DPDPE - [D-Pen 2, D-Pen 5]enkephalin; DSLET 0 [D-Ser 2, Leu 5]enkephalin-Thr 6; CTOP - D-Phe-Cys-Tyr-D-Trp Orn-Thr-Pen-Thr-NH<sub>2</sub>.

### **Opioid Receptor Transducer Mechanism**

All the three types of opioid receptors ( $\mu$ ,  $\delta$ ,  $\kappa$ ) are all G-protein coupled receptors located mostly on prejunctional neurons. They generally exercise inhibitory modulation by decreasing release of the junctional transmitter. As such various monoaminergic (NA, DA, 5-HT), GABA, Glutamate (NMDA/AMPA) pathways are intricately involved in opioid actions.

Opioid receptor activation reduces intracellular cAMP formation and opens  $K^+$  channels (mainly through  $\mu$  and  $\delta$  receptors) or suppresses voltage gated N type  $Ca^{2+}$  channels (mainly  $\kappa$  receptor). These actions result in neuronal hyperpolarization and reduced availability of intracellular  $Ca^{2+}$   $\rightarrow$  decreased neurotransmitter release by CNS and myenteric neurons. However different mechanisms and second messengers may also be involved, particularly in the long-term.<sup>[16]</sup>

### **Conclusions**

The physiologic modulation of noxious stimuli involves a highly complex system that integrates the actions of multiple opioid receptors and endogenous opioid peptides. The interaction of this system with different opioids is similarly complex. Future research that elucidates the pharmacology and molecular biology of the endogenous system holds great promise for development of new selective drugs, rational selection of treatments for individual patients, and fashioning of novel drug combinations to optimize the benefit and minimize the risks associated with opioid therapy.

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