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Opiorphin- Inhibitors of Enkephalins by Inactivating Ectopeptidases

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ABSTRACT

The unpleasant physical sensation caused by illness or injury is called pain and substances which are used in reducing or giving relief in pain are called analgesics. Human saliva is a natural pain killer which is six times more potent than morphine and consists of enkephalins inhibiting enzymes in human neutral ecto endopeptidase and ectoamino peptidase. Without directly interacting with an opioid receptor opiorphin extracts with antinociceptive effect by activating of mu and delta receptor. Opiorphin and its derivatives treated with the disorder that included pain and mood-related disorder. Gene coding opiorphin can be the biomarker of erectile dysfunction. Glutamine is the first position that is crucial for its pharmacological actions on gastrointestinal motility. Opiorphin play physiological roles in follicular growth, ovulation, and embryo implantation processes including maternal-fetal including control of the local concentration of NEP & AP- NSensitive. It also helps in the modulation of lachrymal homeostatic by increasing the bioavailability of enkephalins.

INTRODUCTION

Pain is defined as an unpleasant emotional and sensory experience associated with actual and potential tissue damage[1]. Pain is rarely of two types chronic and acute that differs from each other based on etiology and pathophysiology. Chronic or persistent is non-independent and treated imperfectly. Whereas acute pain is independent pain which is consistent with the level of tissue damage[2] substance which helps in reducing or giving relief towards acute and chronic pain by the help of different mechanism in the body called Analgesics. The treatment of severe acute and chronic pain is done pharmacologically by prescribing various agents which contain non-steroidal anti-inflammatory drug [NSAIDS]. The symptoms are diminished and severe pains are moderately treated by Opioid receptor antagonists such as morphine. Mu, kappa and delta are the receptors that produce analgesic effects[3-5]. Their agents are recorded to provide short term relief to varied pain like diabetic neuropathy, peripheral neuropathy, postherpetic neuralgia, osteoarthritis, and rheumatoid arthritis[5].

The most easily obtainable biological fluid, human saliva is a natural pain killer which is six times more substantial than morphine[6]. Saliva is extracted through an oral cavity for sublingual, parotid glands and submandibular[7]. Besides containing several electrolytes, small organic molecules, proteins, enzymes, Saliva constitutes 99% of water[8]. Human saliva consists of enkephalins inhibiting enzymes in human neutral ectoendopeptidase and human ectoaminopeptidase. Opiorphin naturally available is detected to inhibit their growth. Morphine and this peptide exhibit almost similar analgesic potent[9]. From a physiological point, its innovation is of great curiosity. Opiorphin has recorded to minimize symptoms of pain effectively. The progression of adaptation intervened by enkephalins, besides nociception is also inhibited by it. Opiorphin works by the activation of endogenous opioids dependent transmission, which is often referred to as 'The modulator of opioids pathways in humans'. On being stimulated by enkephalins, Opiorphin produces its effect by affecting the specific opioid receptor restricted pathway, as a response to the nature, extent, and stimuli of pain. Due to their high-efficiency enkephalins act on both mu and delta-opioid receptors, they usually required a few receptors when compared to that of morphine, which exhibits some analgesic effect[10].

HISTORY

Since the first publication in 2006, by Wisner et al on the first discovery of opiorphin, there have been more than 30 research papers in the last 10 years. This gathered data helps in

justifying, summarizing, discussing and evaluating the results obtained. The importance of opiorphin is further highlighted by remembering the most prescribed therapeutically applied analgesic drug, Morphine which has a wide range of side effects on the body including nausea, dyspnea, constipation, tolerance, and dependence. The use of opiorphin started by the publication of a paper of Rougeot and his co-workers, where it was stated for the first time that, human opiorphin is “a naturally obtained antinociceptive modulator of opioid-dependent pathways". Opiorphin is a peptide of 5 different amino acids found distinctively under two forms of sequence Gln-Arg-Phe-Ser-Arg and pGlu-Arg-Phe-Ser-Arg (Fig.1). It was characterized by a biochemical approach from human saliva when it was first extracted and purified. Dickinson et al. first identified this gene, currently named PROL1 gene, coding the PRL1 precursor protein of opiorphin mature peptide product in 1996. The author also reported that the gene is present in human lachrymal and salivary glands. After almost 20 years this peptide was found in large quantities besides saliva and human lacrimal tears; in seminal fluid, milk, blood, and urine of adults, showcasing that it is synthesized, secreted and later distributed as paracrine/autocrine and/or exocrine peptide messenger. Several types of research on the human transcriptome reveals that PROL 1 gene is secreted in both male and female reproductive systems, also in the human brain as a neuroendocrine messenger. Before the characterization of human opiorphin, two similar acting natural inhibitors of the rat membrane-bound neutral endopeptidase and analgesic activities were also recorded as spinorphin, a heptapeptide extracted from the spinal cord in bovine and the functional homolog of human opiorphin in rat, called sialorphin QHNPR-peptide[11-15].

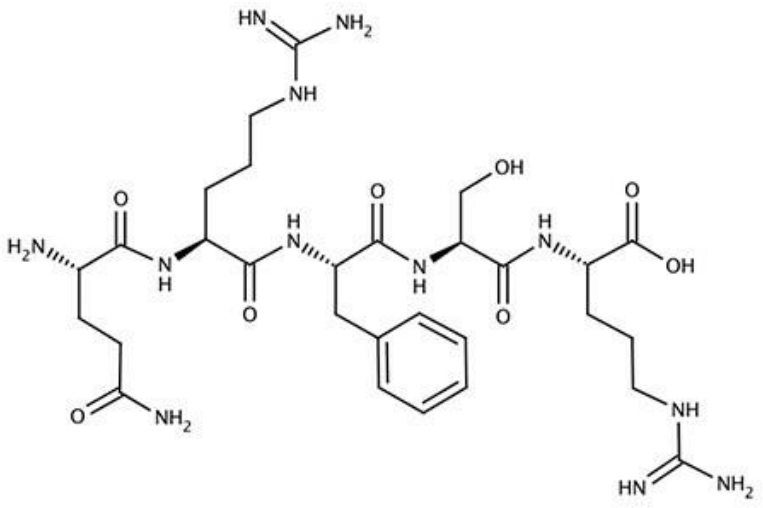

FIGURE NO. 1: CHEMICAL STRUCTURE OF OPRIOPHIN[16]

HOW OPIROPHIN WORKS

Opiorphin works by the breaking up enkephalins, the natural pain-killing opioids in the spinal cord. *In vitro* bioassay, it was found that Opiorphin is completely blocked by naloxone and beta-funaltrexamine[17]. Also, Opiorphin leads to the induction of a contractile response by Met-enkephalins. Various studies also indicated the involvement of both mu and delta opioids receptors, those are evoked by Opiorphin[18].

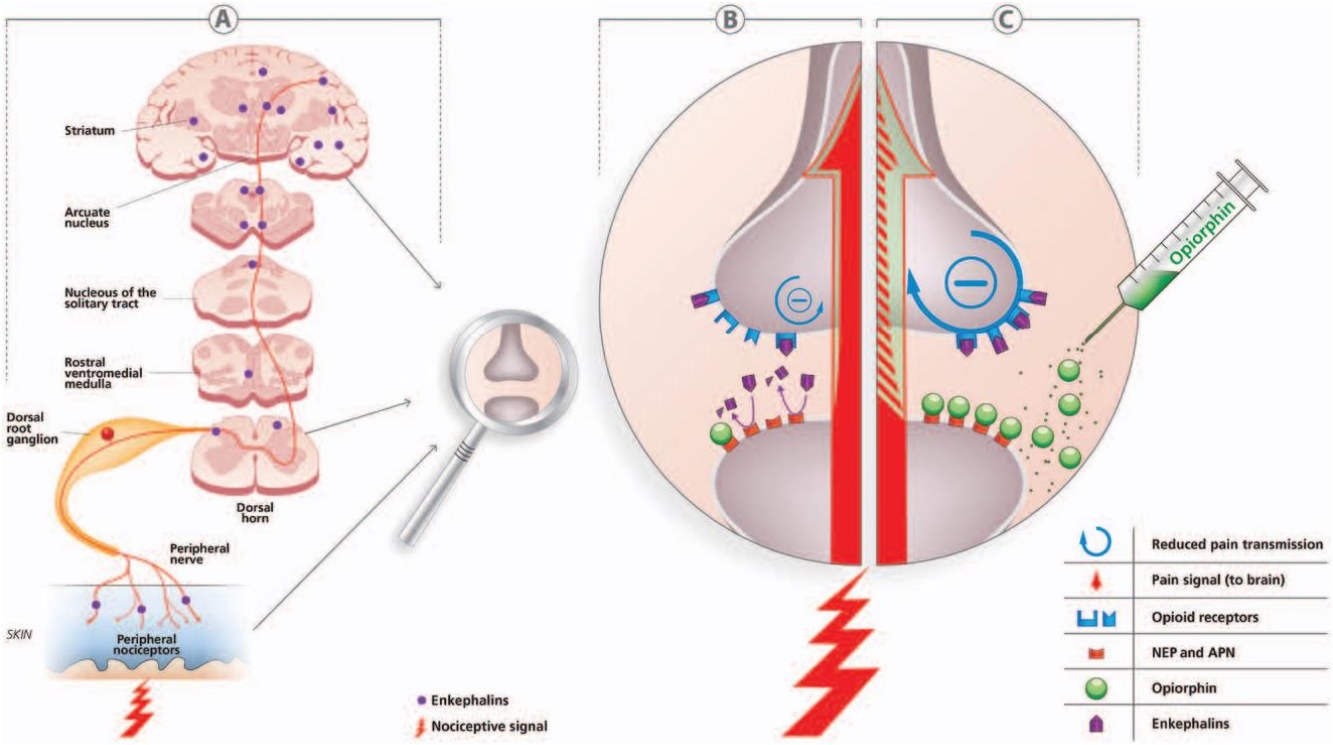

FIGURE NO. 2: SCHEMATIC DIAGRAM SHOWING THE MECHANISM OF OPIORPHIN IN ENKEPHALIN RELATED OPIOID PATHWAY [19]

OPRIOPHIN-ENHANCER OFENKEPHALIN-MEDICATED CONTROL OF PAIN PERCEPTION

The pain inhibitory effect of opiorphin on several enkephalin catabolizing ectopeptidases was first presented. On several substrates including physiological or fluorogenic and detection methods, the data states that the inhibitory capacity of opiorphin for hNEP and hAP-N was almost half, ranging from 10 to 50 M, depending on enzymes associated. Opiorphin prolongs the short-lasting associated. Opiorphin prolongs the short lasting activation of enkephalin peptides, found on opioid receptors by protecting Met-enkephalin from degradation, by membrane-anchored enzymes. Without directly interacting with an opioid receptor, opiorphin

exerts antinociceptive effect, at par with morphine, in rat brain membrane opiorphin increases by 40-60% the affinity of opioid labeled peptides [H3] MERF(Tyr-Gly-Glyphe-Met-Arg-phe) and [H3] MEGV (Met-enkephalin-Gly6-Tyr7) in rats when compared with other complementary inhibitors like cocktails containing bestatin, captopril, thiorphan and, bactrian. Studies suggest that 1 mg/kg i.v. or 5 mg/kg i.c.v. Opiorphin has equal effect to 2-3 mg/kg i.v. or 10 g/kg i.c.v. morphine in rats. Certain *In vivo* experiments showcase that opiorphin are not addictive, neither produces antiperistalsis administration. Opiorphin requires activating endogenous enkephalin-related MOR and DOR pathways to function[20-25].

HUMAN ORIOPHIN NATURALLY OCCURRING ANTI-DEPRESSENT ACTING SELECTIVELY IN THE ENKEPHALINS–DEPENDENT DELTA-OPIOID PATHWAY

Human opiorphin protects enkephalins from any damage by endopeptidase and aminopeptidase-N and thus reduces pain perception in its different models. Besides this, it also implicates the modulation of emotion-related behaviors. In locomotors, activity test sedation or hyperactivity was also reported. The report suggests that 1mg IV doses of opiorphin works by activating endogenous opioidergic pathways. The treated rats did not report any development of either hypo or hyperactive response in this test. Also, opiorphin did not show either anxiolytic or anxiogenic responses in the defensive burying test. Thus, it can be concluded that opiorphin can produce antidepressant drugs like effects when supported by the opioid receptor, by the modulation of concentration of endogenous enkephalin released as a result of a psychological stimulus. Thus opiorphin or its derivatives is a promising drug to treat disorders that include pain and mood-related disorders, mainly comprising of depression[26].

ORIOPHIN, A MODULATOR OF ENKEPHALIN-MEDICATED EMOTION AND SMOOTH MUSCLE CONTRACTION

Most of the opiorphin investigations were done based on its anti-nociceptive action by activation of mu-opioid or delta-opioid pathways [26]. A potential action of opiorphin in emotion-related behaviors (such as depression, panic), contraction of smooth muscles, were explored after the discovery of encephalin-dependent opioid pathways implicate the modulation of these behaviors. The standard rat models of forced swim describe the antidepressant effect of human opiorphin. Antidepressant alike effects were obtained with 1-2 mg /kg human opiorphin i.v. doses which turned to be reversible by delta-opioid receptor

antagonist, naltrindole some tests state that by modulation of concentrations of endogenous encephalin released as a response to the psychological stimulus, opiorphin helps relieve certain mood disorders, mainly related with depression without hypo or hyperactive, anxiogenic-nor anxiolytic and amnesic behavioral responses. After central administration of 1-6 gm. i.c.v /mouse effect produced by opiorphin affected MOR and DOR in the forced swim test in mice. However, opiorphin is avoided by co-administering several delta-opioid receptor antagonists, naltrindole or selective mu-opioid antagonist, Beta-funaltrexamine. Rats that came in contact with opiorphin did not have any convulsive behavior. Also, a panicolytic alike effect was attributed with opiorphin when used centrally in dorsal perioquaductal gray (5 nmol, Intra dPAG) or systematrally (2 mg/kg i.v.). These responses were studied using the elevated Tmaze and dPAC, electrical stimulation tests in rats. As it is antagonized after local pretreatment with certain MOR antagonist, CTOP (1 nmol) the anti-panic effect opiorphin is supported by MOR. In the gastrointestinal and urogenital tracts, opiorphin affects the motility of smooth muscles. It is seen that opiorphin causes colonic contraction dependent on others, using in vitro bioassay. The effect of opiorphin is however blocked by naloxone and partially stopped by beta-funaltrexamine and the MOR and DOR antagonist. Demonstrating the involvement of enkephalin dependent opioid pathway in the opiorphin evoked colonic motility, opiorphin significantly responses. Few years later another team studied the distinctively comparative effect of human opiorphin, and rat sialorphin each, in two natural forms: glutamine 1(Gln1-Arg-Ser-Arg) and (Gln1-His-Asn-ProArg) and pyroglutamate 1(pGlu1-Arg-Phe-Ser-Arg) and (PGlu1-His-Asn-Pro-Arg) on mice ileum motility. However, studies indicate that only glutamine 1 forms of opiorphin and sialorphin are increased in the electrical field in a dor-dependent manner. This shows that glutamine is the first position that is crucial for its pharmacological actions on the gastrointestinal motility. Met-enkephalin and mice sialorphin work simultaneously to destroy the upper gastrointestinal transit of mouse, with doses of opiorphin. Their effects were also seen in particular corporal smooth muscles in the male genital tissue. When compared with normal volunteers, the level of PRO1 gene alongside opiorphin in these corpora canvernosa tissue waves severely down to those with erectile dysfunction. Thus, Gene coding opiorphin can be the biomarker erectile dysfunction[27-35].

SECRETION OF ORIOPHIN IN HUMAN MILK

Milk which is a major source of naturally obtained active peptides with opioid inhibition action functions as modulators of the different regulatory processes in neonatal progression, varying

from gastrointestinal actions to central and peripheral neuroendocrine functions. Technologies like Affymetrix Genechips provide tissue-related data for the PROL1 gene, dealing with the opiorphin precursor, which in females is secreted also besides of mammary gland in the ovary, uterus as amniotic fluid. NEP and AP N membrane-bound cells serve as targets for opiorphin, are also secreted by different cells in the human breast, ovarian granulosa, endometrial and chorionic placental cells along with fetal membrane. These researches suggest that opiorphin play physiological roles in follicular growth, ovulation, and embryo implantation processes including maternal-fetal including control of local concentration of NEP & AP- NSensitive[36-40].

SECRETION OF OPRIOPHIN IN HUMAN TEAR

Tears, a crucial body fluid present in the eyes, contain a large variety of molecules alongside peptides, which is expressed by lachrymal glands. Tear fluid constitutes contribute as a defense mechanism of the eyes and related functional ocular surface with the central nervous system, lachrymal gland neural network, which is important in maintaining the health of the ocular surface. Met5 and Leu5 enkephalin, Proenkaephalin A derived peptides, with their cognitive receptors are found and their importance in endogenous enkephalin in the lachrymal functions, acts as an inhibitor to the lachrymal function is recorded. The study also indicates the presence of lachrymal tissue and secretion of opiorphin in tears from normal adults. A role of opiorphin in the modulation of lachrymal fluid homeostasis by an increase in bioavailability of enkephalin. For example, certain causes of epiophora are evoked. A paracrine is a proposed and autocrine role of opiorphin in the ocular surface in the lachrymal system. Any further studies indicate several new hints for the molecular understanding of the concerned gland's function and regulation[41-43].

TABLE NO. 1: OPRIOPHIN LEVEL IN HUMAN BODY

OPIORPHIN LEVEL,NG/ML MEDIAN (RANGES)[13]			
	MEN	**NON PREGNANT**	**PREGNANT WOMEN MONTH PREGNANCY**
Urines	7(4-27)n=15	4(1-6)n=15	
Milks		8.3(3-23)n=7	
Tears	(<2-183)n=9	220(2-1109)n=15	
Saliva(basal condition)	53(7=196)n=23	30(6-129)n=10	78(20-237)n=8
Saliva(stimulated condition)	163(80-1057)n=18	158(24-1091)n=13	60(34-205)n=10

CONCLUSION

The review suggests that opiorphin acts as an antidepressant drug which works in coordination with the opioid receptor, by controlling the concentration of endogenous enkephalin released. All different appendages of the human opiorphin family of genes can modulate erectile physiology. Human opiorphin is comparable with Morphine, a commonly prescribed pain killer, having similar effects in almost equal quantities.

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CONFLICT OF INTEREST

We declare that I have no conflict of interest.

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