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Review

Deciphering intracellular localization and physiological role of nociceptin and nocistatin

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ABSTRACT

Nociceptin and nocistatin are endogenous ligands of G protein coupled receptor family. Numerous techniques have been used to study the diverse parameters including, localization, distribution and ultrastructure of these peptides. The majority of the study parameters are based on their physiological roles in different organ systems. The present study presents an overview of the different methods used for the study of nociceptin, nocistatin and their receptors. Nociceptin has been implicated in many physiological functions including, nociception, locomotion, stressed-induced analgesia, learning and memory, neurotransmitter and hormone release, renal function, neuronal differentiation, sexual and reproductive behavior, uterine contraction, feeding, anxiety, gastrointestinal motility, cardiovascular function, micturition, cough, hypoxic–ischemic brain injury, diuresis and sodium balance, temperature regulation, vestibular function, and mucosal transport. It has been noted that the use of light and electron microscopy was less frequent, though it may be one of the most promising tools to study the intracellular localization of these neuropeptides. In addition, more studies on the level of circulating nociceptin and nocistatin are also necessary for investigating their clinical roles in health and disease. A variety of modern tools including physiological, light and electron microscopy (EM) are needed to decipher the extent of intracellular localization, tissue distribution and function of these peptides. The intracellular localization of nociceptin and nocistatin will require a high resolution transmission EM capable of identifying these peptides and other supporting molecules that co-localize with them. A tracing technique could also elucidate a possible migratory ability of nociceptin and nocistatin from one cellular compartment to the other.

Contents

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1. Introduction

Nociceptin (NC), a heptadeca-neuropeptide, also known as orphanin or FQ (N/OFQ), is a natural endogenous ligand of the G protein coupled receptors (GPCRs). GPCRs are one of the largest family of proteins that alter intercellular interactions and control a variety of biological activities in the human body, predominantly in the central nervous system (CNS). There are several GPCRs in living organisms. Many of these receptors are at present 'orphans'. The orphan receptor approach as the endogenous ligand of the oGPCR ORL-1 was demonstrated successfully with the discovery of the N/OFQ, [101,136]. Meunier et al. [101] used the term nociceptin for the novel peptide based on perceptible pro-nociceptive properties. At the same time, Reinscheid et al. [136] phrased it orphanin FQ, as a ligand of an orphan receptor, whose first and last amino acids are Phe (F) and Gln (Q), respectively. Nociceptin is similar to an opiod peptide and its receptors are called ORL-1 or nociceptin receptor (NOC/OP_4). *Albeit*, it resembles the opioid receptor but there is no affinity between opioid and nociceptin receptors [22]. After the first report in 1995, a series of publications have provided detailed depiction of its pharmacological, physiological and behavioral roles and anatomical distribution in the body. Over 50 reviews have been published in PubMed. Refs. [14,19,135] have highlighted their biological significance in the body.

1.1. Structure

Structurally, nociceptin is a heptadecapeptide that closely resembles dynorphin A (Fig. 1) in its amino acid sequence. Both peptides contain 17 amino acids bounded by pairs of basic amino acids important in their assembly from precursors. In addition, both have internal pairs of basic amino acid raising the likelihood of further processing. The opioid peptides share an YGGF pattern, where the fifth amino acid is either leucine or methionine (Fig. 2). The amino terminal of N/OFQ is composed of phenylalanine instead of tyrosine, followed by GGF. As a final point, both peptides contain the same last two amino acids at the carboxyl terminal. Similar to endogenous opioids, nociceptin is derived from a larger precursor (preproorphanin or preproOFQ), which contains additional neuropeptides that may have biological activity [59,116,125,161,186]. Mollereau et al. [186], Nothacker et al. [116], and Zaveri et al. [181] have elucidated the primary structure of rat and human preproorphanin. Since preproorphanin shares close structural homology to the endogenous opioid peptide precursors, prodynorphin and preproenkephalin, it has been suggested that a synchronized mechanism of evolution may have alienated the N/OFQ from the opioid systems [26,27,134].

The nociceptin receptor (NOP) polypeptide in man consists of seven transmembrane regions with 370 amino acids [106]. The N-terminal of nociceptin receptor polypeptide is a 44-amino acid unit with 3 adjoining sequences for glycosylation (Asn-X-Ser/Thr). In addition, protein kinase A and C can phosphorylate the polypeptide in the third and second intracellular loops, respectively. Many studies have highlighted the structure of NOP. Notable among them are those of Reinscheid et al. [135], Podstawka-Proniewicz et al. [129] and Thompson et al. [158].

2. Localization and distribution of nociceptin and nocistatin

The distribution of N/OFQ and NOP receptors has been well described [13,39,60,81,86,106,112,113,116,117,137,169]. Outside of the CNS, N/OFQ and NOP receptors are detectable in the intestine, vas deferens, spleen and immune system [54,80,163]. Nociceptin and nocistatin are usually localized in the central nervous system (CNS) but have also been identified in the peripheral nervous system (PNS), organs and systems. Table 1 depicts the localization and function of nociceptin, nocistatin and NOP in different body systems.

2.1. Localization/distribution of NOC receptors

NOP or OP4 receptors have been found in both CNS and PNS. However, it is more extensively expressed in CNS regions such as the cortical areas of brain, olfactory regions, hippocampus, amygdala and thalamus. The other region of CNS where NOP receptors have been detected include the brain stem and in both dorsal and ventral horns of the spinal cord [105,113]. NOP receptors co-express with mu opioid (MOP) receptors in midbrain regions such as periaqueductal gray mater and the nucleus raphe magnus [60]. The NOP receptor mRNA has been found in the PNS and several other organs as indicated earlier for nociceptin localization. The distribution patterns have suggested the involvement of the NOP receptor system in motor and balance control, reinforcement and reward, nociception, stress response, sexual behavior, aggression and autonomic control of physiological processes [113].

3. Nociceptin and opioids

Nociceptin and opioids have structural and functional dissimilarities as well as resemblances. The structural part had been discussed in earlier sections. Nociceptin shows resemblances in some cellular functions with opiates like inhibition of cAMP, activation of K^+ channels, inhibition of Ca^{2+} channels and several protein kinases [56] and furthermore, regulation of transmitter release, for example, it decrease dopamine release in the nucleus accumbens [109]. Anti-epileptogenic actions [53] and regulation of the function of cells involved in the immune response [42,172] are also common functions of both peptides in addition to analgesic and nociceptive functions.

3.1. Nociceptin as antiopiates

Nociceptin has been shown to have anti-opioid effects, for example antagonizing morphine analgesia. However, for true anti-opiates, the compound has to meet certain criteria and conditions [80] which are still controversial in terms of nociceptin and opiate relationship. Nociceptin is regarded as an anti-opiate peptide

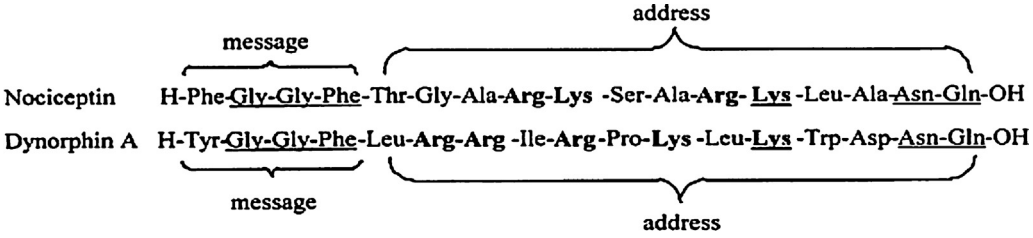

Fig. 1. Structural similarities between dynorphin A and N/OFQ amino acid sequences [52].