Pharmacological Reports 69 (2017) 438–447

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Neuromedin: An insight into its types, receptors and therapeutic opportunities

Saumitra Gajjar, Bhoomika M. Patel*

Institute of Pharmacy, Nirma University, Ahmedabad, India

ARTICLE INFO

Article history:
Received 9 August 2016
Received in revised form 26 December 2016
Accepted 18 January 2017
Available online 22 January 2017

Keywords:
Neuromedin
Neuromedin receptors
Cancer
Pain

ABSTRACT

Neuropeptides are small protein used by neurons in signal communications. Neuromedin U was the first neuropeptide discovered from the porcine spinal and showed its potent constricting activities on uterus hence was entitled with neuromedin U. Following neuromedin U another of its isoform was discovered neuromedin S which was observed in suprachiasmatic nucleus hence was entitled neuromedin S. Neuromedin K and neuromedin L are of kanassin class which belong to tachykinin family. Bombesin family consists of neuromedin B and neuromedin C. All these different neuromedins have various physiological roles like constrictive effects on the smooth muscles, control of blood pressure, pain sensations, hunger, bone metastasis and release and regulation of hormones. Over the years various newer physiological roles have been observed thus opening ways for various novel therapeutic treatments. This review aims to provide an overview of important different types of neuromedin, their receptors, signal transduction mechanism and implications for various diseases.

Contents

Abbreviations: ACTH, Adrenocorticotrophic hormone; CRH, Corticotrophin releasing hormone; FSH, Follicle stimulating hormone; GIT, Gastrointestinal tract; GPCRs, G-Protein Coupled Receptors; GRP, Gastrin releasing peptide; LH, Luteinizing hormone; NMB, Neuromedin B; NMC, Neuromedin C; NMK, Neuromedin K; NML, Neuromedin L; NMS, Neuromedin S; NMU, Neuromedin U; NMULIR, NMU like immunoreactivity; PVN, Paraventricular nucleus; RIA, Radioimmunoassay; RT-PCR, Reverse Transcriptase-Polymer Chain Reaction; SCN, Suprachiasmatic nucleus; TRH, Thyroid releasing hormone.

* Corresponding author.
E-mail addresses: drbhoomikampatel@gmail.com, bgoyal@rediffmail.com (B.M. Patel).

http://dx.doi.org/10.1016/j.pharep.2017.01.009
1734-1140/

Introduction

Neuropeptides are small protein related structures (peptides) which are used by the neurons to communicate with each other. Neuropeptides present in the brain influence the brain in many aspects by neuronal signaling thus implicating themselves in various physiological processes. A search of novel neuropeptides has been a newer interest for researchers or scientists in this decade. Although many neuropeptides have been isolated with defined functions, a powerful method of isolating novel neuropeptides took place in the early nineties [1]. Human genomic sequence study shows that there are hundreds of G protein coupled receptors present and matter of fact is that yet their ligands are yet to be discovered [2]. The unidentified GPCRs have same alikeness with the known GPCRs ligands which has opened the ways for the discovery of newer neuropeptide agents. The biggest advantage of human genomic sequencing is that it helps in identifying neuropeptides with its related receptors, leading to the development of novel neuropeptides over a large scale in this decade. Ten newer neuropeptides have been discovered being endogenous ligands for orphan GPCRs [3] "Neuromedin" one such novel discovery.

Neuromedin peptides are basically divided into 4 classes (1) Bombesin comprising of Neuromedin B and Neuromedin C, (2) Kanassin comprises of Neuromedin K and Neuromedin L, (3) Neurotensin comprises of Neuromedin N, (4) Neuromedin U and Neuromedin S. Isolation of the first neuromedin took place in the 1980s from porcine spinal cord which had large amount of vasoconstrictor properties which was Neuromedin U [4–9] the first neuropeptide of all, later on its different isoforms were discovered. Neuromedin U was found in brain and periphery and has many physiological aspects which include constrictive effects on the smooth muscles, control of blood pressure, pain sensations, hunger, bone metastasis and release and regulation of hormones [10–17]. This review aims to provide an overview of important different types of Neuromedin, their receptors, signal transduction mechanism and implications for various diseases.

Types of neuromedins, structure, location, receptors, signal transduction

A brief overview of Neuromedin U, Neuromedin B and Neuromedin S has been summarized in Table 1.

Neuromedin U

Neuromedin U a novel neuropeptide having various physiological roles is obtained from the spinal cord of the porcine species which had the ability to cause potent constriction of skeletal smooth muscle. It was first administered in the uterus and caused potent vasoconstriction hence was entitled with Neuromedin U. Being synthesized in vasculature of endothelial cells on being released operates in paracrine fashion. NMU is a highly conserved neuropeptide. Purification of NMU led to the discovery of two of its isoforms having same biological activity. This consisted of NMU-25 (icosapentapeptide) other one NMU-8 (octapeptide). The rodents which include rat consist of NMU-23. In recent times many newer types such as NMU-17 is isolated of Chinese red belly toad, *Bombina maxima* from their skin secretions [18], different variants NMU-21, NMU-38 have been isolated from goldfish brain. One of the peptides produced by *Drosophila hugin* gene pyrokinin-2 possessing myostimulatory activity resembles mammalian NMU-8 [19]. The human NMU-25 is icosapentapeptide having 174 amino acid precursors which contain NMU peptide inside C-terminus (carboxy terminus) which is split into 25 amino acids. NMU is obtained from various species having different amino acid homology. The SAR has been preserved against evolutionary pressures.

The amino acid sequence of human which is contained in the C-terminus NMU-25-Phe-Arg-Val-Asp-Glu-Glu-Phe-Gln-Ser-Pro-Phe-Ala-Ser-Gln-Ser-Arg-Gly-Tyr-Phe-Leu-Phe-Arg-Pro-Arg-Asn-NH_2.

Immunocytochemistry or Radioimmunoassay (RIA) studies show that neuromedin receptors are widely distributed in the regions of the brain and also the gastrointestinal tract (GIT). Radioligand studies did not detect any circulating NMU-like

Table 1
Comparisons of different types of Neuromedin.

	Neuromedin U	Neuromedin B	Neuromedin S
Structure	Octapeptide/Icosapentapeptide	Decapeptide	Hexatricontapeptide
Location	Pituitary and GIT	Pituitary and GIT	Suprachiasmatic nucleus of Brain
Receptors	NMU receptors	BB receptors	NMU receptors
Subtypes	NMU-1 and NMU-2	BB-1 and BB-2	NMU-2
Type	G-protein coupled receptors	G protein coupled receptors	G protein coupled receptors
Signalling	Phosphoionositol pathway/MAP-ERK pathway	Phosphoionositol pathway/ Adenyl cyclase pathway	Phosphoionositol pathway
Molecular Formula	$C_{141}H_{203}N_{41}O_{38}$	$C_{52}H_{73}N_{15}O_{12}S_1$	$C_{173}H_{265}N_{53}O_{44}$
Molecular Weight	3080.37	1132.300	3791.33
Agonist	Nonselective-NMU Selective-NMS for NMU-2 receptor, Hexapeptide analogues, icariin, EUK2010	NMB, Bradykinin, Leptin	NMU, NMS, Leptin a-melanocyte stimulating hormone, corticotrophin releasing hormone
Antagonist	R-PSOP, [D-Pro^6]-HMU-8, [D-Leu^3, D-Pro^6]-MNU-8,Astressin	Somatostatin analogues (SS-14. SS-28), PD 168368, BIM-23127	R-PSOP, SHU9119 (antagonist for α-MSH), α-helical corticotropin-releasing factor-(9–41) (antagonist for CRH)