DIVERSE ROLES OF NEUROPEPTIDES-A REVIEW

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Abstract: Neuropeptides are a group of compounds which act as neurotransmitters and are short-chain polypeptides. Role of neuropeptides in several conditions has been under constant observation and its significance is being realized recently after immense research. Not only in mammals, but also in the lower organisms like hydra they are functionally important. They respond to various conditions varying from inflammatory response to healing after injury. Different varieties/groups of neuropeptides have proven to perform multiple functions during normal physiology and during pathology as well. The aim of this study is to have a quick review of the various roles played by neuropeptides in the human system.

Abbreviations & key words:

Neuropeptides-NPs

Substance P-SP

Neuropeptide Y-NPY

Neuropeptide F-NPF

Calcitonin gene related peptide-CGRP

Pituitary adenylatecyclase-activating polypeptide-PACAP

Peripheral nervous system-PNS

Central nervous system-CNS

Polymorphonuclear leukocytes-PMNs

Diabetes mellitus-DM

Vasoactive intestinal peptide-VIP

Thyrotrophin releasing hormone-TRH

Diabetes mellitus-DM

Introduction:

NPs are a variety of peptides found in neural tissue. They communicate with the neural tissues of the brain. These NPs are of various types and they have functions in almost in all the organs of the body. The most important or striking function of NPs is their role in regeneration in various organisms. Therapeutic significance of NPs is remarkable. They form an integral part of regulation and growth too.Different types or classes of NPs have different functions. Apart from its functions during normal physiological conditions,NPsalso come into action as rescuers post injuries and diseases. They are present in in the afferent nerves which on stimulation releases large amounts of NPs. In the skin surface they act through the activation of receptors present in cells like keratinocytes,fibroblasts,mast cells etc,.NPs are exclusively produced in the cell soma and in most instances encoded by a single mRNA.[1]

BASICS OF CERTAIN NPs:

Some of the common NPs and a brief introduction of them are as follows:[1]

NEUROPEPTIDE	SPECIFICATIONS	SYNTHESIS	OCCURRENCE
Substance P	1.11-amino acid peptide 2.structurally related to tachykinins	Dorsal nerve root ganglia	CNS,PNS,skin,GIT,respiratory tract
NPY	Composed of 36 amino acids		CNS,PNS,heart,immunecells,endothelial cells
CGRP	37 amino acid peptide	By the alternative splicing of calcitonin gene	CNS,PNS,heart,liver,spleen,skeletalmuscle,lung,lymphocytes

- NPF

Recently certain amidatedNPs(NPY,PACAP) have been identified with the potential to promote neuronal proliferation apart from developmental and regenerative properties in the mammalian olfactory epithelium. This review highlights the role of NPs according to recent researches and studies.

NPs AND WOUND HEALING:

Repair of injured tissues requires interactions between cells and the cellular microenvironment. Neurogenic stimuli has profound effect in inflammation,proliferation and regulation of immune cells. The PNS acts through the NPs,relays information to the CNS and also plays an important role in inflammation,proliferation and reparative processes after injury.The participation of NPs in many inflammatory responses has been proved to be crucial for wound healing[1].

EFFECTS OF NPs ON THE IMMUNE CELLS:

NPs have been associated with the inflammatory responses such as vasodilation. They act as a link between the immune and nervous systems. These perform as the host inflammatory orchestra following tissue injury. Certain NPs actions on various immune cells which are noteable have been discussed below[1].

SPs action:

It exerts direct chemotactic action on the PMNs. Certain NPs like VIP and somatostatin have been reported to both inhibit and stimulate neutrophil chemotaxis. On the monocytes and macrophages, SP seems to exhibit proinflammatory actions including activation of arachidonic acid metabolism,chemotaxis and oxidative burst. It affects the synthesis and release of cytokines in mononuclear phagocytes. There are several contradictions with the action of SP in inducing the release of IL-1,IL-6. NPs render the mononuclear cells sensitive to secondary stimulation.SP promotes T-lymphocyte endothelial cell adhesion. In the mast cells,SPs bind to them and activate the mast cells,which results in degranulation and histamine release[1].

CGRPs actions:

These profoundly prevent macrophage activation and inhibit their ability to produce H2O2. Furthermore,CGRP exerts direct action on stimulating the monocyte population. They have the ability to inhibit the proliferation of mononuclear cells which induces the above said proliferation action. CGRP also exerts an inhibitory effect on certain proliferative factors of the T-lymphocytes[1].

All these actions of the NPs are carried by their receptors. There are evidences of NPs in angiogenesis in inflammation and wound healing.

ROLE OF GASTROINTESTINAL (GI) NPs:

Effects of GI NPs on pancreas growth & regeneration:

SP:

Scattered immunoreactivefibers are present in the pancreatic blood vessels and ganglion. But its appropriate role has not been identified **[3]**

VIP:

VIP immunoreactivefibers terminate around the acinarcells,ducts and blood vessels. The hydrolactic action of VIP is less potent than secretin's actions in rat,dog and humans. VIP alone cannot stimulate the growth of pancreas. It needs the help of secretin like action as VIP and a peptide with CCK-like effect,potentiate both ecretion and growth of pancreas. In pancreas carcinomas,VIP stimulates the growth of receptors and lessens the intensity of spread of tumor cells[3]

PACAP:

PACAP was observed in both exocrine and endocrine parts of rat and mouse pancreas and they come into action through receptors of subtypes. Its selective and specific in its action. PACAP receptors established patterns of the NPs in human tumor cells. But studies were not able to establish the efficient trophic factor on human cancer cell population[3].

CGRP:

The CGRP positive fibers were found in the rat pancreas. It inhibits the CCK-stimulated pancreatic secretion thereby inhibiting the growth of pancreas[3].

PANCREAS REGENERATION:

Investigations on regeneration of pancreas in higher mammals is associated with cell cycle activation. It has so far been demonstrated only in the pig pancreas[3].

PERIPHERAL NERVE REGNERATION:

Regeneration of peripheral nerves is a complex process which involves interaction between axons and Schwann cells. CGRP is critical for this collaboration which is synthesised by local axons. CGRP receptors and their activity in modifying proteins were expressed on Schwann cells,from where they were available for signalling. These findings indicate the critical behaviour of CGRP for partnering with the intra-axonal translation during the regrowth of adult peripheral nerves[4].

ROLE OF NP HEAD ACTIVATOR (HA) IN MAMMALS:

HA in mammals was isolated mainly from hypothalamus and intestine. HA is a factor required for a nerve cell to become determined in its action. In addition to brain,which is the chief site of HA production, it is also of endocrine origin. It is not only found in humans but also in insects,birdsetc,. Apart from being present in normal cells and tissues,it occurs in tumor cells too. HA occurs in the following human tissues:

- Cerebral cortex
- Cerebellum
- Pons
- Medulla
- Thalamus
- Hypothalamus
- Retina

In addition to the above cells,it is also found in the huma placental cells, in elevated levels during 3-4months of gestation and also in the milk of lactating mothers. These facts suggest that HA acts as a growth factor in normal development. Like other NPs HA may therefore be a mediator in various responses[5].

NPs IN DIABETIC WOUND HEALING:

Diabetes mellitusis a threat for the public health worldwide, especially in the developed nations. Prolonged occurrence of type 1 & type 2 DM results in complications of the neuronal and vascular systems. Diabetic foot ulceration (DFU) is a common condition prevalent in the diabetic patients. NPs act as mediators of wound healing and potential therapeutic agents for chronic and non-healing ulcers such as the DFU[1].

Angiogeneseis & vasculogenesis in diabetic wound healing:

Angiogenesis is the formation of new blood vessels. Patients with diabetes have abnormal angiogenesis in various organs. Impaired angiogenesis is observed in diabetes along with abnormal wound healing and blunted inflammatory response.

Vasculogenesis refers to the formation of new vascular system or new vessels by endothelial cell progenitors. Vasculopathiesin diabetic patients include increase in blood vessel formation,atherosclerosis leading to coronary artery disease and cerebrovascular diseases[1].

SP in diabetes:

Studies have proved that in type1 diabetic persons, depletion of SP occurs in the nervous system. The number of positive SPs are found to decrease in the dermis as well. Patients with diabetic neuropathy were found to have deficient neuro inflammatory signalling and impaired wound healing.SP and other tachykinins were found to have the ability to cause vasodilation. Their efficiency was decreased in patients with diabetes[1].

NPY in diabetes:

The levels of NPY was elevated in diabetic patients in their CNS, particularly in the hypothalamus whereas, the levels were decreased in the dermis of such patients. NPY has pleiotropic effects(production by a single gene of apparently unrelated multiple effects at the clinical or phenotypic level) on both the innate and acquired immune systems. These effects range from modulation of cell migration to production of antibodies. Certain factors which are not activated by NPY mediate angiogenic effects of NPY. Block in NPY-induced angiogenesis causes delayed wound healing. Thus, NPY is important for both inflammatory and angiogenic phases of wound healing in diabetes[1].

CGRP in diabetes:

CGRP is reduced in the sites of its occurrence in diabetic animal models. CGRP is known to induce neurogenic inflammation, formation of new vessels and is important during wound healing. It influences inflammatory pathways while it can be induced by inflammation as well. The involvement of CGRP in wound healing is mediated through angiogenesis[1].

NPs IN LIGAMENT HEALING &SKELETAL MUSCLES:

Ligaments are bundles of fibrous connective tissues connecting two or more bones,cartilages,or other structures. NPs have been found to be highly effective in stimulating repair of ligaments after injury due to trauma, ligament disease or other diseases resulting in the damage. Active pharmaceutical composition of ligament healing includes

- CGRP
- NPY
- CCK
- Dynorphin
- Neurotensin
- SP
- VIP
- TRH
- Enkephalin
- Somatostatin

One of the above NP is administered along with the suitable pharmaceutical carrier to the individual with degenerative ligament disease or repair. Healing, at the cellular level includes cell migration and proliferation and involves detachment and re-attachment around the site of injury. It is evident that local NPs from the PNS play an important role in these inflammatory responses. Ligament healing and grafting are being carried out without considering the role of NPs and peripheral nerves. These facts prove that the administration of NPs hastens the process of ligament healing and also the intact maintenance of undamaged ligaments[6].

NPs are found in human skeletal muscles at rest and after exercise. The occurrence of CGRP was detected with the pain related to heavy eccentric exercise. It is associated with the stimulation of tissue regeneration. While CGRP exerts nociceptive effects, NPY seems to show opposite effects to CGRP-(i.e)it acts as a vasoconstrictor and exerts anti-nociceptive effects. These results were concluded after in vivo techniques in human skeletal muscle at rest and after exercise[7].

Apart from all the above said role and actions, which have not been paid attention in the clinical practices, NPs also play marked roles in the regeneration of skin an dermis associated structures.

CONCLUSION:

Gene therapies, molecular studies and researches which gain momentum day by day, keep updating about the NPs and their significance in various organs. The benefits of NPs to mankind is innumerable. In an age of increasing traumas and tumors, NP administration can save time and lives of people to a considerable extent. Techniques of administration are still under research which in time would emerge enormous.

REFERENCES:

1.The Open Circulation and Vascular Journal, 2010, 3, 43-55 43 1877-3826/10 2010 Bentham Open Open AccessInflammatory and Angiogenic Abnormalities in Diabetic Wound Healing:Role of Neuropeptides and Therapeutic PerspectivesAna Tellechea#,1, Ermelindo Leal#,1, Aristidis Veves2 and EugéniaCarvalho*,1

2. Journal of Neuroscience Research 66:1–7 (2001) Mini-ReviewRegulation of Olfactory Neurogenesis by Amidated NeuropeptidesDonna E. Hansel,1 Betty A. Eipper,2 and Gabriele V. Ronnett1,

3.Journal Of Physiology And Pharmacology 2003, 54, Suppl 4, 127– 141 J.Morissot

4. Journal of Neuropathology & Experimental Neurology:March 2009 - Volume 68 - Issue 3 - pp 326-337doi: 10.1097/NEN.0b013e31819ac71bLocally Synthesized Calcitonin Gene-Related Peptide Has a Critical Role in Peripheral Nerve RegenerationToth, Cory C. MD, FRCPC; Willis, Dianna PhD; Twiss, Jeffery L. MD, PhD; Walsh, Sarah; Martinez, Jose A. MSc; Liu, Wei-Qiao MSc; Midha, Rajiv MD, FRCSC; Zochodne, Douglas W. MD, FRCPC

5. Development 1989 Supplement, 99-107 (1989) Printed in Great Britain ©The Company of Biologists Limited 1989-99Role of the neuropeptide head activator for growth and development in hydra and mammalsH. Chica Schaller, Sabine A. H. Hoffmeister And Stefan DubelZemrumfilrMolekulareBiologie, ImNcucnheimcr Feld 282, 6900 Heidelberg, FRG

6. Publication date Sep 9, 2005Inventors Ray Vanderby, Kelley DwyerApplicant Wisconsin Alumni Research Foundation, Ray Vanderby, Kelley DwyerUse of neuropeptides for ligament healingWO 2005082403 A1

7. Br J Sports Med. 2006 March; 40(3): 264–267.doi: 10.1136/bjsm.2005.022731PMCID: PMC2491989Calcitonin gene related peptide and neuropeptide Y in skeletal muscle after eccentric exercise: a microdialysis studyS Jonhagen, P Ackermann, T Saartok, and P A Renstrom

8.Cooper; Bloom; Roth: 'The Biochemical Basis ofNeuropharmacology', 2003, OXFORD UNIVERSITY PRESS pages 321 - 356

9. Dwyer Kelley W Et Al: "Blockade of the sympathetic nervoussystem degrades ligament in a rat MCL model." JOURNAL OFApplied Physiology, vol. 96, no. 2, February 2004 (2004-02),pages 711-718, XP002334713 ISSN: 8750-7587

10.Economic costs of diabetes in the U.S in 2007. Diabetes Care, 2008, 31, 596-615.

11. No author listed. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts. American Diabetes Association. Diabetes Care, 1999, 22, 1354-60.

12. No author listed. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia.The Global Lower Extremity Amputation Study Group. Br. J. Surg., 2000, 87, 328-37.

13. Falanga, V. Wound healing and its impairment in the diabetic foot. Lancet, 2005, 366, 1736-43.

14. Rothman SS, Wells H. Enhancement of pancreatic enzyme synthesis by pancreozymin. Am JPhysiol 1969; 216: 504-507.

15. Mainz DL, Black O, Webster PD. Hormonal control of pancreatic growth. J Clin Invest 1973;52: 2300-2304.

16. Solomon TE, Vanier M, Morisset J. Cell site and time course of DNA synthesis in pancreas after caerulein and secretin. Am J Physiol 1983; 245: G99-G105.

17. Rivard N, Guan D, Maouyo D, Grondin G, Bérubé FL, Morisset J. Endogenous cholecystokinin release responsible for pancreatic growth observed after pancreatic juice diversion. Endocrinology 1991; 129: 2867-2874.

18. Morisset J, Morisset S, Lauzon K et al. Pancreatic inflammation, apoptosis and growth:

sequential events after partial pancreatectomy in pigs. Pancreas 2000; 21: 321-325.

19. Fiorucci S, Bufalari A, Distrutti E et al. Bombesin-induced pancreatic regeneration in pigs is mediated by p46Shc/p52Shc and p42/p44 mitogen-activated protein kinase upregulation. Scand JGastroenterol 1998; 33: 1310-1320.

20. Friess H, Kleeff J, Isenmann R, Malfertheiner P, Buchler MW. Adaptation of the humanpancreas to inhibition of luminal proteolytic activity.Gastroenterology 1998; 115: 388-396.

21. Tsiotos GG, Barry MK, Johnson CD, Sarr MG. Pancreas regeneration after resection: does itoccur in humans? Pancreas 1999; 19: 310-313.

22. Niissalo S Et Al: "Neuropeptides in experimental and degenerativearthritis." Neuroendocrine Immune Basis Of The Rheumatic Diseases Ii: Proceedings Of The Second International Conference New York Academy Of Sciences, 2 East 63rd Street, New York, Ny, 10021, Usa Series : Annals Of The New York Academy Of Sciences (Issn 0077-892, 2002, Pages 384-399, Xp009050232 & Second International Conference On The Neuroendocrine Immune Basis Of The Rheumatic Diseases; Genova, Italy; September 21-23, 2001 Issn: 1-57331-392-0 1-57331-393-9

23. Ackermann P W, Li J, Finn A. *et al* Autonomic innervation of tendons, ligaments and joint capsules. A morphologic and quantitative study in the rat.J Orthop Res 2001.19372–378.378. [PubMed]

24. Ackermann P W, Finn A, Ahmed M. Sensory neuropeptidergic pattern in tendon, ligament and joint capsule. A study in the rat.Neuroreport 1999.102055–2060.2060. [PubMed]

25. Ljung B O, Forsgren S, Friden J. Substance P, and calcitonin gene-related peptide expression at the extensor carpi radialisbrevis muscle origin: implications for the etiology of tennis elbow. J Orthop Res 1999.17554–559.559. [PubMed]

26. Schafers M, Sorkin L S, Sommer C. Intramuscular injection of tumor necrosis factor-alpha induces muscle hyperalgesia in rats. Pain 2003.104579–588.588. [PubMed]

27. Carleson J, Lundeberg T, Appelgren B. Muscle and brain changes of calcitonin gene-related peptide in experimentally induced unilateral rat masseter myositis. J Orofac Pain 2004.18246–252.252. [PubMed]

28. Zhang L, Hoff A O, Wimalawansa S J. *et al* Arthritic calcitonin/alpha calcitonin gene-related peptide knockout mice have reduced nociceptive hypersensitivity. Pain 2001.89265–273.273. [PubMed]

29. Brain S D, Williams T J, Tippins J R. *et al* Calcitonin gene-related peptide is a potent vasodilator. Nature 1985.31354–56.56. [PubMed]

30. Hoffmann P, Mazurkiewicz J, Holtmann G. *et al* Capsaicin-sensitive nerve fibres induce epithelial cell proliferation, inflammatory cell immigration and transforming growth factor-alpha expression in the rat colonic mucosa in vivo. Scand J Gastroenterol 2002. 37414–422.422. [PubMed]

31. Onuoha G N, Alpar E K. Calcitonin gene-related peptide and other neuropeptides in the plasma of patients with soft tissue injury. Life Sci 1999.651351–1358.1358. [PubMed]

32.Payan DG Neuropeptides and inflammation: the role of substance P. Annu Rev Med. 1989;40341- 352

33.HökfeltTJohanssonOLjungdahlALundbergJMSchultzberg M Peptidergic neurones. Nature.

1980;284515- 521

34.JessellTMKellyDDKandelERedSchwartzJHedJessellTMed Pain and analgesia. Principles of Neural Science New York, NY Elsevier Science Inc1991;385- 399

35.FeltenDLFeltenSYBellinger DL et al. Noradrenergic sympathetic neural interactions with the immune system: structure and function. Immunol Rev. 1987;100225- 258

36.Holzer P Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. Neuroscience. 1988;24739- 768

37.HökfeltTedSchaibleHGedSchmidtRFed Neuropeptides, Nociception and Pain. Weinheim, Germany Chapman& Hall1994;

38.Kenins P Identification of the unmyelinated sensory nerves which evoke plasma extravasation in response to antidromic stimulation. NeurosciLett. 1981;25137- 141

39.SakamotoTBarnesPJChung KF Effect of CP-96,345, a non-peptide receptor antagonist, against substance P-induced, bradykinin-induced and allergen-induced airway microvascular leakage and bronchoconstriction in the guinea pig. Eur J Pharmacol. 1993;23131- 38

40.PerettiMAhluwaliaAFlowerRJManzini S Endogenous tachykinins play a pivotal role in IL-1-induced neutrophil accumulation: involvement of NK-1 receptors. Immunology. 1993;8073- 77