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, NPs also 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]

<table>
<thead>
<tr>
<th>NEUROPEPTIDE</th>
<th>SPECIFICATIONS</th>
<th>SYNTHESIS</th>
<th>OCCURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance P</td>
<td>1.11-amino acid peptide 2.structurally related to tachykinins</td>
<td>Dorsal nerve root ganglia</td>
<td>CNS,PNS,skin,GIT,respiratory tract</td>
</tr>
<tr>
<td>NPY</td>
<td>Composed of 36 amino acids</td>
<td>CNS,PNS,heart,immune cells, endothelial cells</td>
<td></td>
</tr>
<tr>
<td>CGRP</td>
<td>37 amino acid peptide</td>
<td>By the alternative splicing of calcitonin gene</td>
<td>CNS,PNS,heart,liver,spleen,skeletal muscle,lung, lymphocytes</td>
</tr>
</tbody>
</table>

- NPF

Recently certain amidated NPs (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 notable 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].

CGRP 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 immunoreactive fibers are present in the pancreatic blood vessels and ganglion. But its appropriate role has not been identified [3]

VIP:
VIP immunoreactive fibers terminate around the acinar cells, 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 REGENERATION:
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, birds etc. 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 3-4 months 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 mellitus is 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. Vasculopathies in 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 type 1 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 vasconstrictor 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.

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