INTRODUCTION

Neuropeptides represent a heterogeneous group of molecules ranging from very small molecules containing only 2 amino acids to large ones containing 40 or more amino acids. They represent a class of extremely potent molecules acting on a variety of target cells by binding to specific receptors ***(Hokfelt et al., 1990).***

Neuropeptides are present in neurons of both the central and peripheral nervous systems where they appear to be critical mediators of different processes. They act as neuromodulators, neurotransmitters, hormones and neurohormones in the skin, nervous and immune systems ***(Masahiko et al., 2002; Zouboulis et al., 2005).***

For a substance to be accurately classified as a neurotransmitter, it must meet several criteria. First, it must be produced and stored presynaptically; in addition, it must be released into the synapse upon depolarization of the neuron. Finally, when released into the synaptic cleft, it must act postsynaptically to change the properties of the postsynaptic cell and must be subsequently inactivated in a specific way ***(Lynch and Snyder, 1986).*** Synthesis of neuropeptides starts on ribosomes in the neural cell body in the form of precursors, then transformation to the active form occurs in storage granules during axonal transport to the nerve terminal ***(Toyoda and Morohashi, 2001).***

The major neuronal peptides of human skin include substance P (SP), substance K (SK), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), peptide histidine methionin (PHM), neuropeptide Y (NPY), somatostatin (SOM), neurotensin (NT), pituitary adenylate cyclase activating polypeptide (PACAP), proopiomelanocortin (POMC)-derived peptides and neurokinin A ***(Eedy, 1993).*** Substance P/ CGRP fibers are most abundant in fingers and toes. VIP fibers and NPY fibers are localized in the deeper parts of the dermis around blood vessels and acini of sweat glands. Fibers contaning these neuropeptides are also most common in fingertips and toes. VIP occurs in relatively high amounts in skin from the axilla, whereas NPY in this region was found to be below detection limit. Somatostatin-immunoreactive fibers were found in low concentrations in tissue extracts ***(Wallengren et al., 1987)***.

Neuropeptides were found to play a role in the pathogenesis of certain skin diseases such as psoriasis ***(Artemi et al., 1997)***, atopic dermatitis ***(Pincelli et al., 1990)***, prurigo nodularis ***(Vaalasti et al., 1989),*** rosacea ***(Kurkcuoglu et al., 1991)***, vitiligo ***(Liu et al., 1996)***, eczema ***(Anand et al., 1991)*** and various inflammatory skin disorders ***(Walsh et al., 1992; Pincelli et al., 1993)***.

There is current evidence that regulatory neuropeptides with hormonal and non-hormonal activity controls the development of clinical inflammation in acne.

Numerous substance P immunoreactive nerve fibers were detected in close opposition to the sebaceous glands ***(Toyoda et al., 2002 ; Zouboulis et al., 2005)***. Substance P contains numerous lipid droplets. These disintegrate to form an acellular sebum secretion that stimulate sebaceous gland cells, even in the peripheral area of the glands. These observations indicate that SP can accelerate lipid synthesis and increase the number of sebum vacuoles in each differentiated sebaceous cell. Substance P actively increases the release of sebaceous gland secretions which are the main events occuring in the pathogenesis of acne ***(Toyoda and Morohashi, 2001).***

AIM OF THE ESSAY

The aim of this essay is to revice the chemical properties and mechanism of action of neuropeptides and to evaluate their role in the pathogenesis of acne vulgaris aiming to throw more light on these important chemical substances.

NEUROPEPTIDES

Neuropeptides (NPs) are defined as heterogeneous group of several hundred biologically active peptides that are present in neurons of both the central and peripheral nervous systems and that are involved in the transmission of signals, not only between nerve cells, but also in the immune system where they appear to be critical mediators of different processes ***(Scholzen et al., 1998)***. They act as neuromodulators, neurotransmitters, hormones and neurohormones, and can manifest immunomodulatory activity. They contribute to the cross talk between the nervous and immune systems in the skin ***(Masahiko et al., 2002)***.

Since 1950, more than 100 peptides have been identified in neurons of many tissues and occur with classical neurotransmitters such as acetylcholine, noradrenaline and dopamine ***(Hokfelt et al., 1990).*** Neuropeptides and their receptors have been identified in different tissues such as the nervous system, intrinsic neurons of gastrointestinal tract ***(Lynch and Snyder, 1986)***, lungs in both small and medium size bronchi ***(Harrison and Geppetti, 2001)***, skin in primary sensory neurons and in many other locations such as cardiac and cerebral arterioles, and urinary tract ***(Oida et al., 1995).***

For a substance to be accurately classified as a neurotransmitter, it must fulfil several criteria: first, it

must be produced & stored presynaptically and released into the synapse on depolarization of the neuron. Then, when released into the synaptic cleft, it must act post synaptically to change the properties of the post synaptic cell. Its action is highly localized to the synaptic region, with a duration of milliseconds. Termination of its action is accomplished by removal of the transmitter, either by enzymatic degradation or via a reuptake mechanism into the presynaptic terminal (Fig.1) ***(Harrison and Geppetti, 2001).***

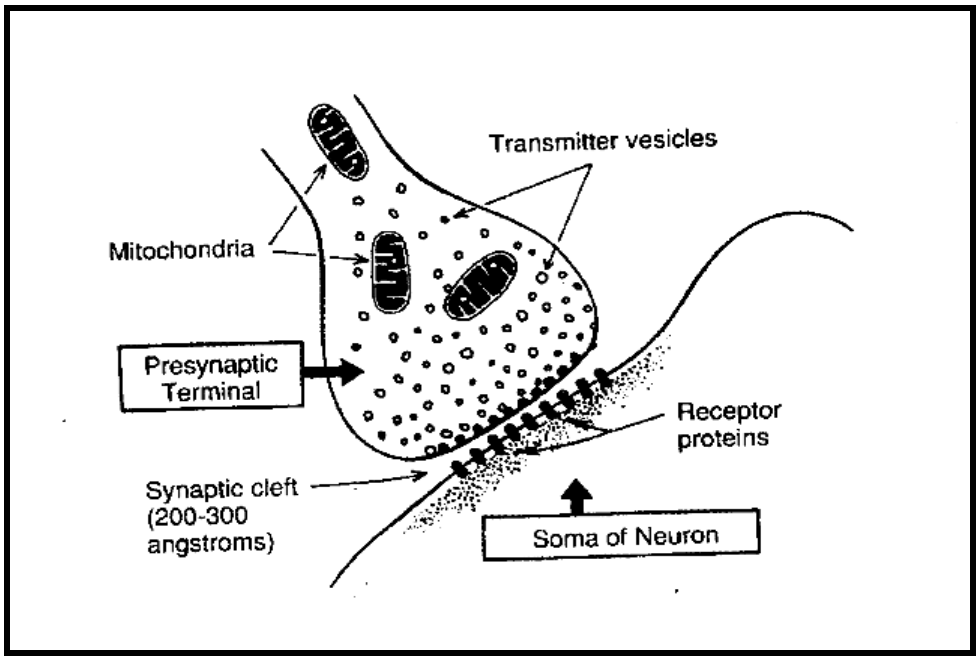

Fig. (1): Physiologic anatomy of the synapse
(Guyton and Hall, 1996).

Peptides are low molecular weight proteins that yields two or more amino acids on hydrolysis. Peptides are the constituent parts of proteins and are formed by loss of water from the NH2 and COOH groups of adjacent amino

acids to form peptide bonds. Over 100 unique biologically active peptide sequences have been purified from biological sources; their sizes range from 2 eg: carnosine (Fig.2) to over 40 amino acids eg: corticotrophin-releasing hormone [CRH] and growth hormone-releasing hormone [GH-RH]. Most of the other known active peptides fall within these size limits. By convention, peptides greater than 90 amino acids in length (about 10,000 molecular weight) are considered proteins ***(Owens et al., 2000).***

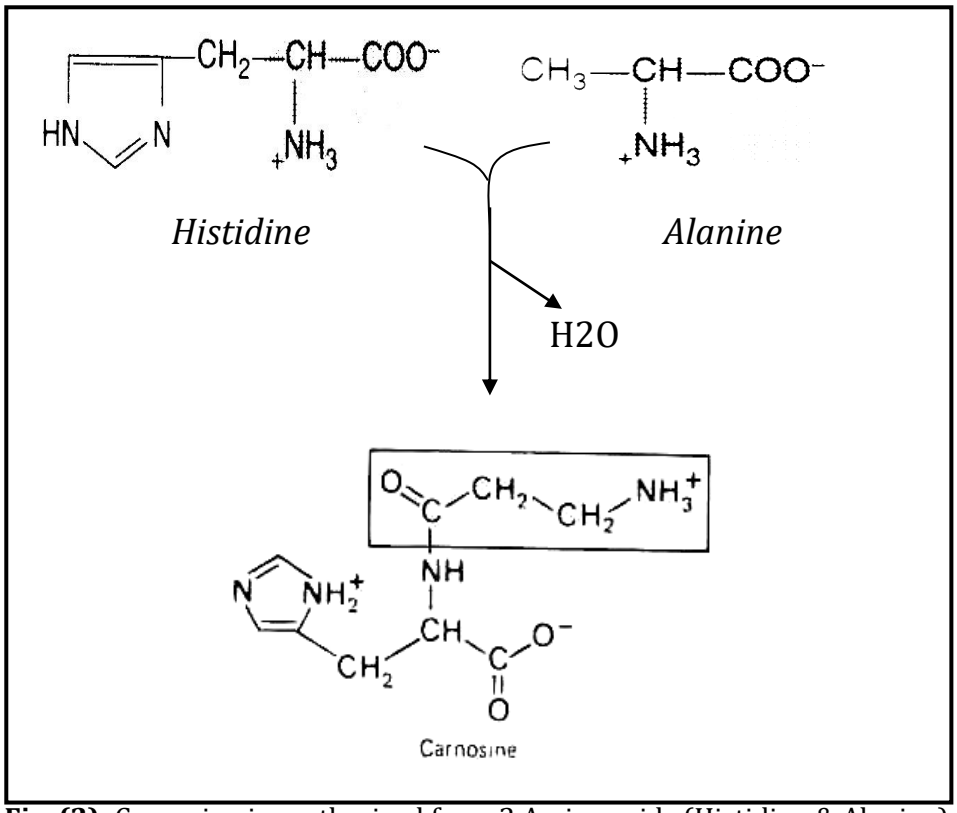

Fig. (2): Carnosine is synthesized from 2 Amino acids (Histidine & Alanine) ***(Rodwell and Kennelly, 1996).***

The past several decades have witnessed a veritable explosion of knowledge about the central nervous system (CNS), and in no area has this been as impressive as in peptide

neurobiology. Especially in the last twenty years, an ever-growing number of peptides have been added to the list of neurotransmitters. Numerous peptide neurotransmitter candidates have been identified and characterized, their CNS distributions mapped, and their genes cloned ***(Snijdelar et al., 2000).***

Neuropeptides have been implicated as chemical mediators in pathways subserving a variety of behavioral and physiological effects, including thermoregulation, food and water consumption, sex, sleep, locomotion, memory, learning, responses to stress and pain and emotions ***(Owens et al., 2000).***

In the skin, neuropeptides comprise a large family of regulatory molecules including tachykinins (substance P[SP], substance K (SK), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), peptide histidine methionin (PHM), neuropeptide Y (NPY), somatostatin (SOM), neurotensin (NT), pituitary adenylate cyclase activating polypeptide (PACAP), proopiomelanocortin (POMC)-derived peptides and neurokinin A ***(Luger, 2002).*** They are released from sensory or autonomic nerve fibers and certain neuropeptides such as POMC-derived peptides have also been produced by epidermal and dermal cells ***(Scholzen et al., 1998)***.

They exert a variety of modulatory actions on dermal and epidermal target cells. They induce changes directly on susceptible cells, or indirectly by activation of other cells,

for example, mast cells (MCs) ***(Misery, 1997).*** Keratinocytes and dermal endothelial cells are able to synthesize neuropeptides which are transported by nerve fibers or immune cells. Specific receptors for neuropeptides are also present on cutaneous cells. Neuropeptides intervene as neurogenic modulators of inflammatory reactions, and therefore participate in the pathogenesis of skin diseases ***(Claudy, 1996).***

The number of peptide neuromediators is large. Many of them co-exist with other neuromediators in the synaptic terminals. One to three types are sharing a particular ending with a well established neurotransmitter, in some cases they have shown to be present within the same synaptic vesicles ***(Zilles, 1994)***.

Neuropeptides are stored within dense granular synaptic vesicles of various sizes and appearances. They are distributed widely through the nervous system. Certian areas have higher concentration and larger numbers of different types ***(Nieuwenhuys, 1994).*** Neuropeptides have been postulated to be involved in the mechanisms of some dermatoses such as psoriasis ***(Chan et al., 1997),*** prurigo ***(Misery, 1997)***, vitiligo ***(Misery, 1997),*** eczema, atopic dermatitis and other inflammatory skin disorders ***(Walsh et al., 1992; Pincelli et al., 1993).***

Synthesis of Neuropeptides

Neuropeptides have a long phylogenetic history and are produced only in the nerve cell bodies without a local synthesis in the nerve endings. Numerous neuropeptides are encoded by a single continuous fragment of messenger ribonucleic acid (mRNA), which is translated into one protein precursor. These precursors, as other proteins, are synthesized in endoplasmic reticulum, then transported to the Golgi apparatus, where they are processed. When they leave this apparatus, they are transported to the nerve endings by a fast axon transport ***(Slominski and Wortsman, 2000 and Zegarska et al., 2006).*** Transformation into the active form of neuropeptides, probably occur in storage granules during axonal transport to nerve terminal (Fig.3) ***(Hokfelt et al., 1990)***. After release at the nerve terminal, no re-uptake mechanism is thought to exist, but rather hydrolysis occurs by exo or endopeptidases with broad specificity ***(Berry et al., 1995).***

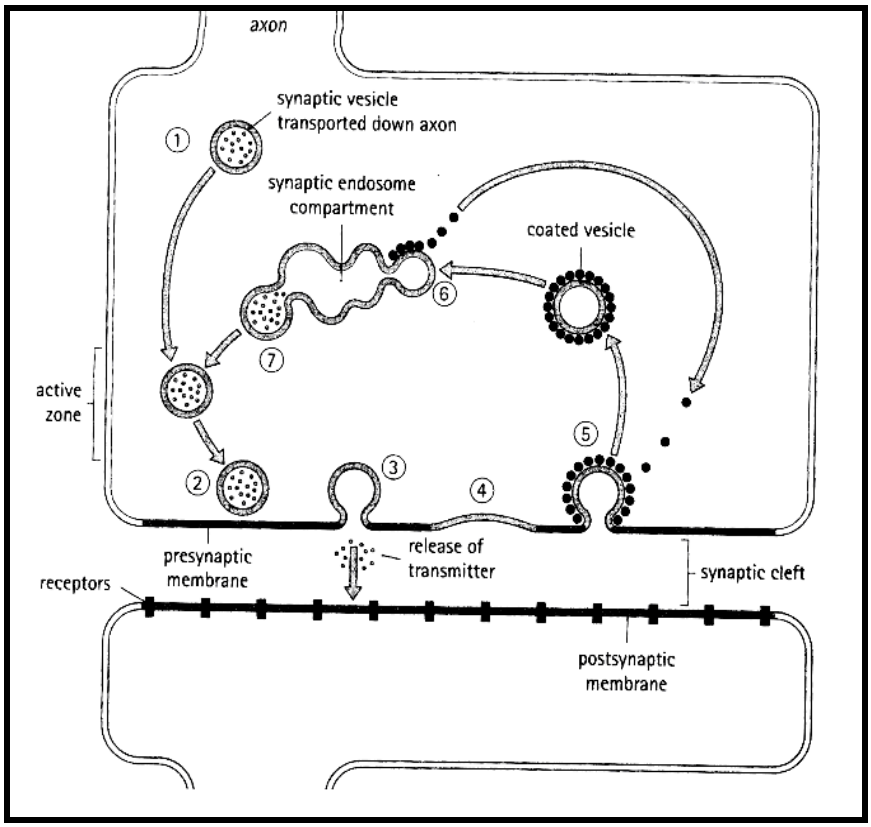

Fig. (3): Physiologic anatomy of the synapse ***(Alan and James., 1997).***

The majority of nerve endings are situated around blood vessels of the skin, sweat glands, hair follicles and in free nerve endings in epidermis (nociceptive afferent nerve fibers, including the fine myelinated A-delta fibers and unmyelinated C fibers) in the stratum papillare and nerve bundles deep in the skin ***(Slominski and Wortsman, 2000; Zegarska et al., 2006)***. Neuropeptides are present not only in skin nerve fibers, but also in skin cells, including: keratinocytes, microvascular endothelial cells, Merkel cells, fibroblasts, Langerhans cells, leukocytes,

eosinophils, mast cells, mononuclear cells and neutrophilic granulocytes ***(Steinhoff et al., 2003).***

Classification

Most of the neuropeptides are classified according to the site where they were first discovered, but some have been classified into a number of closely related families according to their chemistry, physiological properties, anatomical sites, or by being products of single or closely related genes. They are classified as peptidergic & non peptidergic neuromediators (Table 1) ***(Berry et al., 1995).***

Table (1): Summary of the main classes of non peptidergic and peptidergic neuromediators ***(Berry et al., 1995).***

(A) Non peptidergic neuromediators

1.Acetylcholine

2.Nitric oxide

3. Monoamines

- Noradrenaline
- Adrenaline
- Dopamine
- Serotonin
- Histamine

4. Amino acids

- Glutamate
- Aspartate
- Glycine
- Gamma aminobutyric acid (GABA)
- Taurine

5. Adenosine triphosphate (ATP)

(B)Peptides

1. Peptides first found in the gastrointestinal tract.

- Bombesin
- Cholecystokinins (CCK)
- Gastrin
- Glucagon
- Insulin
- Motilin
- Neurotensin (NT)
- Pancreatic polypeptide (PP)
- Substance P (SP)
- Substance K(SK)
- Vasoactive intestinal polypeptides (VIP)

Table (Continuation)

2. Peptides first associated with the hypothalamic-hypophyseal complex.

- Hypothalamic releasing hormones:

Somatostatin (SOM)
Corticotrophin-releasing factor (CRF)
Growth hormone releasing hormone (GHRH)
Leutinizing hormone releasing hormone (LHRA)
Thyrotropin releasing hormone (TRH)

- Neurohypophyseal peptide:

Vasopressin (arginine vasopressin; AVP)
Oxytocin (OXT)
Proopiomelanocortin (POMC) derivatives:
Corticotropin (ACTH)
Corticotropin like inter mediate lobe peptide (CLIP)
B-endorphins (-end)
B-lipotrpins (-LPH)
Gamma-lipotropins (LPH)
Methionine enkephalin (M-ENK)
Leucine enkephalin (L-ENK)
Alpha melanocyte stimulating hormone (α-MSH)
Gamma melanocyte stimulating hormone (γ-MSH)
Prodynorphin derivatives: Dynorphins (DYN) A & B;
Neodymorphins & (NE)

3. Other peptides

- Angiotensin II (ANGII)
- Bradykinin
- Calcitonin-gene releated peptide (CGRP)
- Neuropeptide Y (NYP)
- Carnosine
- Gallinine
- Natriuretic peptide
- Sleep peptides

4. Growth factors

- Nerve growth factor (NGF)
- Platelet derived growth factor (PDGF)

Mode of action

Evidence strongly supports the notion that neuropeptides are endogenous to the immune system and are used for intraimmune system regulation, as well as for bidirectional communication between the immune and neuroendocrine systems. Neuropeptides may exert their regulatory influence in one or more of the following ways:

- As components of the autonomic nervous system.
- Acting locally at peripheral sites.
- As being brain peptides, they may act on the central regulatory centers.
- As neuro-hormones reaching their target organs via the hypophyseal portal vessels (such as the releasing factors) or via the general circulation acting as hormones (oxytocin or vasopressin).
- In some instances, the central and peripheral actions are complementary**.**

(Eedy, 1993; Lotti et al., 1995)

Functions of Neuropeptides

Neuropeptides have both peripheral and immunological functions.