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Neurotensin in different dermatoses

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Abstract

Background: Neurotensin (One of the many skin-related physiological functions is that of a vasoactive neuropeptide (NT), which is involved in wound healing, pain regulation, and inflammation. Stress causes the secretion of NT, making it a potential biomarker and connection in mental-cutaneous problems. Discovering NT's function in the skin might lead to new understandings of disease mechanisms and possible treatment avenues. The purpose of this essay is to show how NT is involved in various dermatoses. Its goal is to investigate the physiological role of NT and the processes that lead to its dysregulation. In conclusion, NT is a key molecule with several functions in the field of dermatology. Its altered expression levels and signalling pathways provide light on stress-related skin illnesses, including rosacea, melanoma, psoriasis, vitiligo, alopecia areata, and atopic dermatitis. The discovery of new treatments for various dermatoses may be possible via targeting NT.

Key words: Neurotensin is a blood pressure regulator, inflammatory skin condition, stress biomarker, and potential treatment target.

1. Introduction

Neurotensin (N-terminal tridecapeptide (NT) is a bioactive molecule that is present in several peripheral organs and the brain. Three neurotensin receptors mediate the activities of NT (NTSRs). NTSR1 and NTSR2 are GPCRs that have seven transmembrane domains and are conventional neuropeptide receptors (TMs). NTSR3, a member of the Vps10p-containing domain receptor family, goes by the name sortilin and is a type I receptor that is not linked to G proteins. [1]

The primary NT mediator, neurotensin receptor 1 (NTR1), launches a signalling cascade that allows NT to participate in cell survival, migration, invasion, and proliferation. SR48692, an NTSR1 antagonist, and SR142948A, a generic antagonist that binds to NTSR1 and NTSR2 with equal affinity, may both inhibit NTSR1-signalling. In contrast to NTSR3, whose expression is more diffuse, NTSR2 is primarily found in the brain. One mechanism by which neurotensin inhibits cell death is via raising levels of the anti-apoptotic B-cell lymphoma 2 (Bcl-2) messenger RNAs and proteins [2]. This activity has two sides: it protects cells against cytotoxic substances, which is good, and it hinders the proliferation of cancer cells, which is bad. [1] The impact of stress on skin immunity may be better understood via the interactions of NT, Corticotrophin-releasing hormone (CRH), and mast cells. For stress-induced inflammatory dermatoses, potential treatment targets include NTR and/or Corticotropin-releasing hormone receptor 1 (CRHR1) antagonists, mast cell blockers, and others. [3]

The purpose of this piece is to show how NT plays a part in many skin diseases. Its goal is to investigate the physiological role of NT and the processes that lead to its dysregulation.

Interactions between neurotensin and other neurotransmitters

The stress hormones neurotensin (NT) and corticotropin-releasing hormone receptor 1 (CRHR-1) are inversely related; NT promotes the expression of functional CRHR-1, whereas CRH promotes the production of NTR genes and proteins. [3] It has also been shown that a neurotensin-dependent mechanism is responsible for the skin vascular permeability that CRH induces on mast cells. There may be receptor interactions between NT and substance P (SP) [4]. SP receptor antagonists and N-acetyl-NT both inhibit NT's ability to cause colonic mast cell degranulation and SP's influence on the skin's vascular system. [3]

Effects of neurotensin on various skin cells

A variety of skin cells, including keratinocytes, dermal vascular endothelial cells, dermal dendritic cells, Langerhans cells, fibroblasts, and mast cells, bind to neuropeptides that are produced by peripheral sensory neurons.

It's worth noting that keratinocytes, melanocytes, fibroblasts, mast cells, and other immune cells in the skin produce more CRH and neurotensin when exposed to cutaneous stress [5]. Dendritic cells in the skin are known to express neurotensin receptors [6]. (NTR1 and NTR3). Inflammation causes a downregulation of these receptors, yet the production of neurotensin from these cells is conditional on inflammation, indicating the presence of paracrine activities. [7]

Environmental and emotional stress may activate skin mast cells via the action of hormones, neuropeptide cytokines, and chemokines. Paracrine and autocrine responses are triggered when NT stimulates mast cells, which in turn increases vascular permeability. [8] The genes for vascular endothelial growth factor (VEFG) are induced by NT, and LAD2 mast cells release VEFG. By increasing CRHR-1 expression in human LAD2 mast cells, it enhances CRH's impact on mast cells as well. Histamine, granule-stored heparin, mast cells, tryptase, and tumour

necrosis factor are among the several mediators secreted with rapid activation of mast cells (TNF). Then, between six and twenty-four hours after that, chemokines (CCL2, CCL5, and CXCL8), cytokines (IL-5, IL-6, IL-31, IL-33, and TNF), and prostaglandin D2 are produced. Degranulation is not necessary for mast cells to secrete some mediators including serotonin, IL-6, and VEFG. Mast cell-released interleukin-33 enhances the action of neuropeptides like NT on these cells. By rapidly degrading NTs with their proteases, expressing NT receptors, secreting bioactive NT-like peptides, and synthesising a neurotensin precursor, mast cells tightly control NT activity [9]. [4]

Neurotensin is a part of the " brain-skin" connection

There the skin's immune system and the central nervous system are connected in a two-way circuit: The immune system communicates with the central nervous system through chemical messengers called cytokines. The central nervous system controls the immune response through the hypothalamic-pituitary-adrenal (HPA) axis. Immune system cells contain receptors for adrenaline. Lastly, organs within the immune system are innervated by the autonomic nervous system through sympathetic and parasympathetic nerves. The immune system is influenced by neuropeptides via the regulation of cytokine balance and HPA activation. [10]

Neurotensin as a connection between emotional and dermal stress

Skin and mental health issues communicate with each other in a two-way street. The skin becomes a neuro-immuno-endocrine organ when mental stress stimulates the HPA axis. In inflammatory dermatoses, the skin largely produces TNF and IL-6, two pro-inflammatory cytokines. Both dendritic cells and these latter cells are able to penetrate the blood-brain barrier, which is already compromised due to stress. This is because psychological stress causes glutamatergic hypertone, which in turn leads to the upregulation of proinflammatory cytokine signalling, the generation of reactive oxygen species (ROS), and oxidative damage. These mediators set in motion a series of molecular signalling processes in the CNS that are involved in the development of depression. [11]

Function of neurotensin in neurogenic inflammation of the skin (CNI)

Acute and chronic dermatological disorders including eczema, psoriasis, and atopic dermatitis are brought on by the activation of certain signalling pathways known as cutaneous neurogenic inflammation. [8]

Pathophysiological cutaneous neurogenic inflammation (CNI) occurs when neuropeptides, neurotrophins, cytokines, and vasoactive amines interact with specific receptors through feedback mechanisms; this process is based on a complex communication network between peripheral nerve endings and different immune and structural skin cells. By boosting the quantity and activity of mast cells—dubbed "gatekeepers" because to their close proximity to nerve endings—NT serves an essential signalling function in CNI. [11]

Dermatoses caused by stress: the role of neurotensin

In the pathophysiology of psychiatrically manifested dermatologic diseases such as rosacea, psoriasis, acne vulgaris, vitiligo, alopecia areata, seborrheic dermatitis, and neurotensin plays a part.

[12]

(I)Psoriasis

Among the many inflammatory skin illnesses, psoriasis stands out. NT and CRH, which are both released by the skin in response to stress, clearly have a role in the pathophysiology of psoriasis. [13]

Increased densities of nerve fibres and local concentrations of calcitonin gene-related peptide (CGRP), SP, NT, vasoactive intestinal peptide (VIP), and Nerve Growth Factor (NGF) all contribute to the persistence of psoriatic plaque by facilitating the subsequent enhancement of T cell and keratinocyte proliferation, mast cell migration, degranulation, and memory cell chemotaxis in response to the NGF effect.

[14]

(II)Seborrheic dermatitis and acne vulgaris

Psychological stress is the primary component that triggers or worsens acne vulgaris, a psychosomatic and somatopsychic condition. As a consequence of neuropeptides caused by stress, the sebocyte-level peripheral HPA axis is activated, leading to an increase in lipogenesis, testosterone metabolism, and pro-inflammatory cytokines. [11]

Inflammation, stress-induced skin barrier failure, delayed wound healing, and increased susceptibility to certain bacterial infections are all factors in cutaneous neurogenic inflammation (CNI), which is exacerbated by neurotensin, a stress-induced neuropeptide. [11] People who suffer from acne vulgaris often have elevated levels of NT serum. Additionally, there is a clear correlation between the psychological effect of acne and a greater NT level. [15]

The neurogenic activation of sebum secretion is one approach to the pathophysiology of seborrheic dermatitis. There are a number of neuropeptides released by sensory neurons that enhance sebaceous gland production. These include neurotensin, somatostatin, substance P, nerve growth factor (NGF), and proopiomelanocortin peptide. [10]

(III)Vitiligo

The inactivation of melanocytes is one of several symptoms of vitiligo, a complex condition. According to the "convergence hypothesis," which posits a neuro-immuno-endocrine relationship, many processes may collaborate in vitiligo to cause melanocyte loss. [16]

Many people who suffer from vitiligo say that they were under a lot of emotional pressure just before their condition started. It is via hormones and neurotransmitters that stress may exacerbate inflammatory and autoimmune illnesses. The release of

catecholamines is triggered by stress via the activation of the HPA axis. [10]

Melanocytes secrete more CRH and neurotensin in response to cutaneous stress.

[6] There are heightened levels of tumour necrosis factor alpha in the peri-vitliggos zones because neurotensin causes melanocytic synthesis of the protein to rise. [17]

According to scientific evidence, neurotensin is associated with the pathogenic processes of COVID-19 and is a component of the "vasoactive peptide storm" concept. When exposed to NT, immune cells and mast cells produce mediators such as matrix metalloproteases and pro-inflammatory cytokines, which in turn increase microvascular hyperpermeability. [18]

Vitiligo has been reported in many cases as a result of COVID-19 infection. More research is required to confirm a connection between the COVID-19 virus and the development of vitiligo [19]. Yet, NT's role in the disease's pathogenic processes raises the possibility of NT as a connecting component that needs more investigation. (IV)

Areas of hair loss

The autoimmune disorder known as alopecia areata causes temporary thinning of the hair. Autoimmune and apoptotic pathways are involved in the processes of stress-induced AA. Degranulation of mast cells close to hair follicles is facilitated by stress-induced neuropeptides (CRH, NT, and SP). Upon mast cell degranulation, neurogenic inflammation is induced within the hair follicle, leading to the breakdown of the hair follicle immune privilege (HFIP). This, in turn, causes the development of cytotoxic CD8+ T cells and accelerates the hair follicle's evolution into the early catagen phase. [20] The expression of 1093 genes in human dermal papilla cells is controlled by NT (HDPC) [21]

Inflammatory skin disease

Psychological stress triggers the release of CRH and the HPA axis in the brain, which in turn increases the production of VEFG and pro-inflammatory mediators by brain mast cells (especially cytokines such as IL-5, IL-6, IL-31, IL-33, and TNF). In order to release these mediators into the peripheral circulation, they enhance microvascular permeability at the level of the blood-brain barrier (BBB). NT plays a significant role in mast cell activation by upregulating CRHR1 on human brain mast cells at the hypothalamus and meningeal levels, inducing VEFG gene expression and release from LAD2 mast cells, and so on. Similar to how the peripheral cutaneous HPA axis and CRH release are activated in response to stress in the brain, this process is amplified in the skin. [11]

Lesional skin of atopic dermatitis patients has elevated neurotensin gene expression, leading to blood levels of neurotensin that are greater than those in healthy individuals. [22]

(VI)Rosacea

It is clear that psychological stress may cause or worsen rosacea, a prevalent chronic inflammatory skin condition. Neuropeptides CRH and NT are produced in response to stress; when their levels are elevated, they disrupt the HPA axis and cause inflammatory reactions. Two aspects of rosacea pathophysiology mediated by CRH and NT include angiogenesis, cutaneous neurogenic inflammation, and mast cell degranulation. [8]

Function of neurotensin in vasculitis

Damage to blood vessels and a reduction in cardiovascular events are symptoms of vasculitis, an inflammatory disease of the blood vessels. Many complex elements, including the vasculature and systemic factors like the immune system, as well as systemic problems caused by primary illnesses like diabetes mellitus, contribute to the causes of vasculitis. CRH primarily acts on corticotropin-releasing factor1, which has a role in the development of vasculitis (CRF1). The primary way CRF1 is seen in vasculitis is as a major pro-inflammatory factor that regulates the migration of vascular smooth muscle cells (VSMCs), influences angiogenesis, affects vascular permeability, and influences inflammatory cells. [23]

A neurotensin-dependent mechanism is responsible for CRH's impact on mast cells, as previously stated. The NT receptor antagonist SR48692 prevents CRH-induced vascular permeability, a step in the development of vasculitis, suggesting that NT plays a role in vasculitis indirectly. [4]

The Function of Neurotensin in Cancer

Evidence for NT's carcinogenic activity comes from its involvement in endocrine, autocrine, and paracrine tumour development stimuli. This activity is achieved by many methods, such as the anti-apoptotic impact of NT and the acceleration of cell motility, invasion, and proliferation. First, NTSR1 mediates the NT impact on cancer cells. A key regulator of cell cycle progression, cell death, and tumour development, NTSR1 is significantly expressed in melanoma cells. Antagonizing NT receptors, SR48692 decreases melanoma cells' ability to proliferate and self-renew [24], and it enhances the effectiveness of ionising radiation in treating prostate malignancies. [1]

As a result, NT and NTSRs have become pharmaceutical targets in addition to diagnostic and prognostic indicators for a number of malignancies. [24]

Excessive pigmentation and neurotensin interaction

Hyperpigmentation of the epidermis in dermatofibroma, urticarial pigmentosa, and post-inflammatory hyperpigmentation has been associated with NT-stimulated human mast cell degranulation and activation.

[25]

Recognized for its function in melanosome maturation, the protein glycoprotein nonmetastatic melanoma protein b (GPNMB) is generated by epidermal basal keratinocytes and shows noticeable

increase in reaction to histamine and downregulation in response to tryptase. The two sides of mast cells in pigmentary diseases are now explained. [26]

Hyperpigmentation and neurological variables may go hand in hand due to the fact that melanocytes and peripheral nerve networks both originate from the neural crest. Some studies have shown a correlation between an increased number of cutaneous nerve terminals and pigmentary diseases such as café au lait macules and congenital large pigmented nevus. Nerve fibres secrete specific neuropeptides that stimulate the growth of melanocytes. It has been shown that Becker's nevus has elevated levels of NT and NTSR2 expression (BN). [27]

Nervotensin and Health Problems

Among other things, neurotensin inhibits the growth of gram-positive and gram-negative bacteria, including Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. It also inhibits the growth of the yeast Candida albicans.

[28]

Healing wounds and neurotensin

In the inflammation, proliferation, and migration stages of the wound, a number of neuropeptides are associated with it. These include CGRP, SP, CRF, NT, α-melanocorticotropin releasing hormone (α-MSH), neurokinin A (NKA), and neuropeptide Y (NPY). [5]

It has been proposed that NT has a function in skin wound healing due to its capacity to boost the expression of epidermal growth factor (EGF) and downregulate the pro-inflammatory features of skin dendritic cells. [29]

If neurotensin (NT) is released early in an inflammatory process, it can reduce cells' ability to respond to inflammation, which can have harmful effects. However, NT can modulate the degree of inflammation, end inflammation, and promote wound healing through EGF production when released later in the inflammatory phase or during the migration-remodelling phases of wound healing. [7] For normal wound healing, neurotensin is a promising therapy option since it upregulates the immune activity of cells during the inflammatory phase of wound healing if administered promptly after damage, before the inflammatory process begins. On the other hand, NT has the ability to inhibit the immunological responses of cells when administered to wounds after damage, during an already active inflammatory process. It is possible to treat delayed wounds using antibodies that promote wound healing in certain cases. [7]

The process of skin regeneration

Some skin cells, including fibroblasts, keratinocytes, dermal vascular endothelial cells, Langerhans cells, and mast cells, may bind to receptors on neuropeptides such NT, SP, α-MSH, and CGRP, which then stimulate skin repair and regeneration. Restoring the sweat glands' innervation is a step in the healing cascade that ultimately helps with their rebuilding. Sweat gland regeneration is expedited by the vascular network that forms during wound healing, which carries oxygen and nutrients to the location and excretes metabolic waste. [30]

2.Conclusion

The brain and a number of other peripheral organs are common sites for the bioactive neuropeptide neurotensin (NT). In addition to playing a role in inflammation, pain modulation, and wound healing in the skin, NT also works on immune cells (leukocytes, mast cells, dendritic cells, and macrophages), triggering the production of cytokines and other immunomodulatory responses. Because it is released in response to stress, NT has the potential to serve as a biomarker and connecting factor in mental-cutaneous illnesses. Discovering NT's function in the skin might lead to new understandings of disease mechanisms and possible treatment avenues.

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