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Nerve growth factor and its role in immuno-inflammatory and endocrine metabolic diseases

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Ildikó Molnár

Immunoendocrinology, EndoMed, Debrecen

Correspondence: Ildikó Molnár, Immunoendocrinology, EndoMed, Debrecen, Bem tér 18/C., H-4026 Debrecen, Hungary, Email molilendomed@gmail.com

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Abstract

NGF is a neurotrophin essential for the maintenance, differentiation and growth of peripheral sympathetic and sensory neurons. The regulation of NGF and its secretion in allergy, Graves' ophthalmopathy, obesity and menopausal metabolic changes such as osteoporosis may provide new perspectives for their therapeutic approach. NGF plays a crucial non-neural regulatory role in immune and hematopoietic cells, modifying inflammatory processes and self-secretion. Local sympathetic and sensory neuronal activity could be enhanced by the release of active mediators, cytokines and active peptides from mast cells in allergic diseases. NGF is involved in the development of Th2 dominance, hypertrophy and apoptosis in Graves' ophthalmopathy. Pancreatic beta cells are the source of insulin synthesis and secretion. NGF co-secretion with insulin has been demonstrated in response to glucose levels. Obesity and postmenopause are associated with increased sympathetic activity and a greater tendency to develop increased insulin resistance, type 2 diabetes mellitus and metabolic syndrome. The specific neuronal action of NGF is to modulate nociception by altering receptor sensitization, gene expression and local neuronal sprouting associated with chronic pain, neuropathic pain, fibromyalgia and cancer pain. Several anti-NGF antibody therapies are available and have shown some success.

Keywords: nerve growth factor, chronic pain, allergy, Graves' ophthalmopathy, obesity, menopausal osteoporosis

Introduction

Nerve growth factor (NGF) is one of the four neurotrophic factors [brain-derived neurotrophic factor (BDNF), neurotrophin-3 and neurotrophin-4/5]. NGF is essential for the maintenance, differentiation and growth of peripheral sympathetic and sensory neurons and basal forebrain cholinergic neurons. Its neuronal origin and role is characterized by the modulation of nociception by altering receptor sensitization, gene expression and local neuronal sprouting.[1] In turn, NGF is characterized by a broad spectrum of non-neuronal regulatory effects showing interactions with immune-hematopoietic (T and B lymphocytes, monocytes/macrophages, eosinophils, basophils, neutrophils), parenchymal cells (adipocytes, pancreatic beta cells, thyrocytes, keratinocytes, osteoblasts, mesenchymal cells) and structural cells (fibroblasts, vascular stromal cells).[2] Two NGF receptors are known, a high-affinity, tropomyosin-related receptor with tyrosine kinase A activity (TrkA) and a low-affinity p75 receptor (p75NTR).[3,4] NGF is synthesized from proNGF after intracellular enzymatic cleavage by furin or extracellular enzymatic cleavage by plasmin or matrix metalloproteinases. The TrkA receptor activates three major signaling cascades: the mitogen-activated protein kinase (MAPK/ERK) pathway, the phospholipase C-γ (PLC γ) pathway and the phosphoinositide 3-kinase (PI3K) pathway. These pathways are responsible for proliferation, cell differentiation, synaptic plasticity and survival. p75NTR activation induces an apoptotic signaling pathway with caspase 3, 6 and 9 activities.[5] The expression of TrkA and p75NTR is cell specific and depends on local levels of NGF, inflammatory cytokines and drugs. NGF-null mice showed severe loss of sympathetic and sensory neurons, particularly peptidergic small and medium diameter dorsal root ganglion (DRG) neurons.[6] Hereditary sensory and autonomic neuropathy type V (HSAN V) is caused by a point mutation of the NGF gene at nucleotide 661, cytosine to thymine.[7] The mutation reduces sensitivity to cold and heat, but sweating remains normal. The mutation at nucleotide 680 (cytosine to adenosine) resulted in complete insensitivity to pain with anhydrosis, mild mental retardation and immune deficiency.[8]

The role of NGF in chronic pain (e.g. osteoarthritis, fractures, cancer pain, neuropathic pain and fibromyalgia) has led to the search for agents that block the binding of NGF to its receptors. Several neutralising autoantibodies against the NGF protein have been developed (anti-NGF monoclonal antibodies: tanezumab, fulranumab and fasinumab).[9] The previous positive effect in reducing pain has been associated with adverse effects such as cartilage damage, tibial osteophytes, and subchondral bone sclerosis). The involvement of NGF in cancer progression and cancer pain may represent a new therapeutic perspective in the next decade.[10]

The non-neuronal regulation of NGF and its production in allergy, autoimmune thyroid diseases, particularly Graves' ophthalmopathy, obesity and menopausal metabolic disorders, and osteoporosis show a broad disease spectrum. The role of NGF in these diseases is discussed and new perspectives for the therapeutic approach are presented.

Allergy: allergic rhinitis, rhinoconjunctivitis, asthma and atopic dermatitis

NGF plays a central role in allergic events as an important mediator and participant in the maturation, survival and activation of mast cells, eosinophils, T and B lymphocytes and airway hyperresponsiveness. NGF is a link in the interaction between neural and immune cells in Th2-related inflammation.[11] Increased NGF secretion can be caused by emotional and physical stress as well as increased sympathoadrenal activity. The involvement of NGF in inflammatory processes leads to a shift towards Th2 dominance. The process of allergic inflammation consists of two steps: 1. The acute-phase hypersensitive reactions (skin edema, redness, indurated swelling, bronchial smooth muscle contraction, mucus hypersecretion, skin eruption or urticaria), 2. The late-phase reactions (angiogenesis, fibrosis and wound healing). In the acute-phase reactions, mast cells are the main source of NGF production and also become a target for NGF action.[12] Binding of NGF to the TrkA receptor on mast cells induces cell degranulation with release of inflammatory mediators such as histamine, tryptase, serotonin, substance P (SP), leukotrienes, calcitonin gene-related peptide (CGRP), platelet-activating factors (PAF), IL-4, IL-5, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNFα), kinin, prostanoids. The neuropeptides SP and CGRP promote neuronal sensitization of sensory neurons enhancing neurogenic inflammation and inducing hyperalgesia.[13,14] SP has proinflammatory activity, while CGRP acts as a potent vasodilator in neurogenic inflammation. NGF is involved in the recruitment of eosinophils, basophils and neutrophils to the site of the allergic region. Locally, NGF exerts a trophic effect inducing neural outgrowth and branching. The late-phase reactions are IgE-independent processes, in which allergic reactions are initiated by numerous mediators released by eosinophils, basophils and mast cells (*Figure 1*).

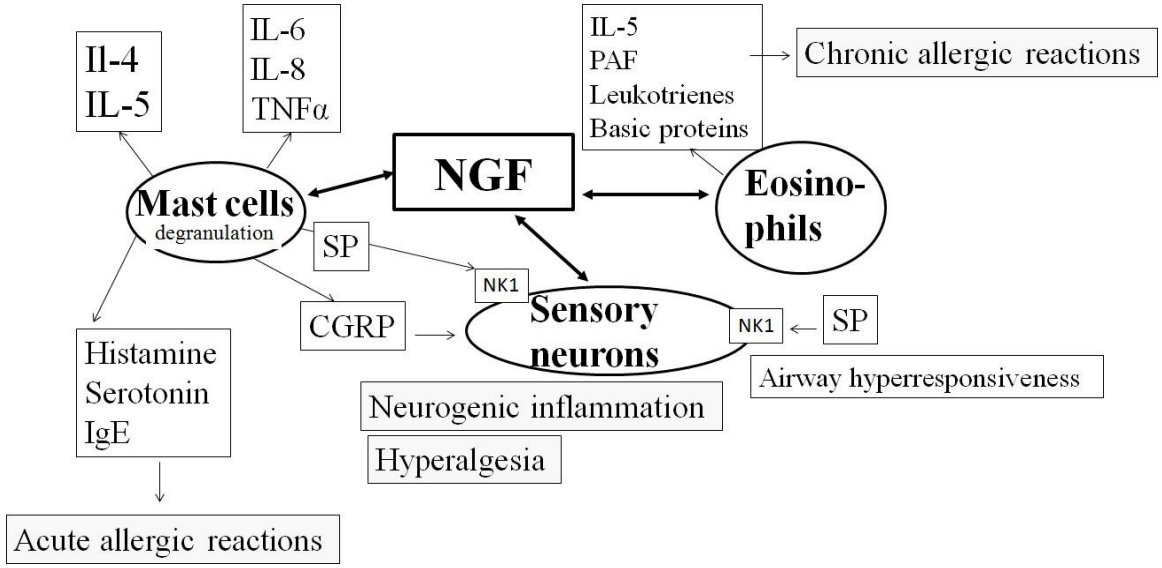

Figure 1: NGF-induced mast cell degranulation leads to the release of active mediators and cytokines that promote allergic inflammation, neurogenic inflammation and pain. Mast cells are mainly involved in acute allergic reactions, but eosinophils are involved in chronic allergic reactions and all cells are also sources of local NGF release.

NGF: nerve growth factor; NK1: neurokinin-1 receptor; SP: substance P; CGRP: calcitonin gene-related peptide; TNFα: tumor necrosis factor α; IL: interleukin; PAF: platelet-activating factor; IgE: immunoglobulin E.

In allergic dermatitis, a positive correlation has been shown between epidermal thickness and NGF nerve fibres in the skin.[15] Anti-NGF treatment reduced NGF expression in a mouse model.[16] In allergic rhinitis, NGF expression was increased in submucosal glands and nerve bundles after provocation in the nasal mucosa. In a study, patients had higher NGF levels in serum and nasal discharge.[17] In asthma, elevated levels of SP and NGF have been demonstrated in BALF (bronchoalveolar lavage fluid) highlighting their role in bronchoconstriction, vasodilation and mucus secretion.[18,19] Human lung fibroblasts, bronchial epithelium and smooth muscle cells are able to co-secrete NGF with immune cells present in the airways.[20] NGF contributes to airway hyperresponsiveness through a neurokinin-1 receptor-dependent mechanism.[21] Neurokinin-1 (NK1) is expressed on sensory neurons and activated by SP. Anti-NGF treatment inhibited allergen-specific airway hyperreactivity and reduced the number of eosinophils, neutrophils and macrophages in BALF.[22] In allergic conjunctivitis, a positive correlation has been found between the number of mast cells and increased serum NGF levels.[23] The development of allergic conjunctivitis in response to histaminergic and non-histaminergic (NGF) activation may be initiated by the release of inflammatory mediators and neuropeptides from mast cells and eosinophils. Sensory neuron activation by SP and CGRP leads to extravasation with prolonged mechanical and thermal hyperalgesia and increased itch.[24]

Graves' disease with and without orbitopathy

NGF regulates the survival of various immune cells, potentiates the proliferative response of T and B lymphocytes to mitogens, and modulates B lymphocyte-mediated immune responses and immunoglobulin secretion by promoting the differentiation of B lymphocytes into immunoglobulin-secreting plasma cells.[25,26] It is therefore not surprising that elevated serum NGF levels are associated with several autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, type I diabetes mellitus, multiple sclerosis, autoimmune encephalitis and autoimmune thyroid diseases.[27]

In our study, contained of 95 patients with Graves' disease, 19 patients with Hashimoto's thyroiditis and 20 controls, serum NGF levels were significantly higher in patients with thyroid autoimmunity than in controls.[28] In hyperthyroid Graves' patients, serum NGF levels were significantly higher than in euthyroid patients. Surprisingly, NGF levels were significantly reduced in Graves' patients with orbitopathy. A positive correlation was found between serum NGF and FT_3 levels in Graves' hyperthyroidism. In hyperthyroid Graves' disease, TSH receptor antibody positive patients had significantly higher NGF levels than those who were TSH receptor antibody negative. The results highlighted the regulatory role of NGF in Graves' hyperthyroidism, which is associated with inflammatory events. The accumulation of adipose tissue, the enlargement of the eye muscle by fibroblast proliferation in orbitopathy may lead to neuronal degeneration associated with reduced NGF levels. Human conjunctival epithelium expresses the p75NTR low-affinity NGF receptor. In conjunctival reconstruction method during transplantation, the proliferative capacity of conjunctival epithelial stem cells could be enhanced or inhibited by the addition of exogenous NGF or proNGF.[29] Corneal ulceration, one of the severe ocular symptoms of Graves' orbitopathy, could be cured by exogenous NGF.[30] The above cases confirmed that reduced serum NGF levels in Graves' orbitopathy may be associated with neurogenic damage, therefore NGF plays a neuroprotective role in orbitopathy.[31]

The regulatory role of NGF may be reflected in the increased prevalence of allergic symptoms in Graves' disease. In our other study, the prevalence of respiratory and food allergen-specific IgE levels was investigated in 259 patients, of whom 149 had Graves' disease, 110 had Hashimoto's thyroiditis and 65 were controls.[32] Allergic rhinitis was more frequent in Hashimoto's thyroiditis than in Graves' disease. On the other hand, allergic conjunctivitis was more frequent in Graves' disease than in Hashimoto's thyroiditis. The concordance between the month of thyroid onset and seasonal allergic attacks was significantly overlapping in Graves' disease. Patients with Graves' disease had an increased prevalence of tree (alder, birch and hazel) and weed (mugwort, plantain and ragweed) allergen-specific IgE levels compared to those found in Hashimoto's thyroiditis. Food allergen-specific IgE levels to soybeans and walnuts had a modifying effect on thyroid peroxidase antibody levels, increasing them.

In conclusion, NGF is an important activator of the cells (B and T lymphocytes, mast cells, fibroblasts, adipocytes) that play a central role in the development of Graves' orbitopathy. Both NGF receptors are expressed in orbital tissues. Catecholamines have the ability to induce apoptosis, which could be inhibited by NGF. IGF-1 (insulin-like growth factor-1) and NGF represent a balance between cell death and survival. NGF induces the differentiation of conjunctival fibroblasts into myofibroblasts and supports the Th2 dominance associated with chronic inflammatory processes. In hyperthyroidism, catecholamines are the central mediators of sympathetic innervation and their chronic stimulatory effect on the β-adrenergic receptor is responsible for myofibroblast and adipocyte hypertrophy (*Figure 2*). Graves' orbitopathy is characterized dominantly by inflammatory and immune responses, hypertrophy, Th2 dominance and apoptosis.

Obesity

The modulatory role of NGF in metabolic homeostasis includes its interactions with immune cells, pancreatic beta cells, adipose tissue, angiogenesis, gonadal steroid hormones and chronic sympathetic hyperactivity of the nervous system.[33] Pancreatic beta cells are the source of insulin synthesis and secretion. NGF is co-secreted with insulin in response to glucose levels.[34] Not only pancreatic beta cells, but also vascular cells, immune cells and neurons are capable of NGF production. Both NGF receptors are expressed in pancreatic islets. The effect of NGF is to promote pancreatic islet survival via the TrkA receptor. Beta cell damage is associated with increased NGF secretion, whereas decreased NGF levels induce beta cell apoptosis.[35] Endoplasmatic reticulum and oxidative stress, inflammatory cytokines and hyperglycemia can cause beta cell dysfunction and apoptosis.[36] Adipose tissue is a major source of NGF production with the release of pro- and antiinflammatory cytokines (IL-1, TNFα, IL-10, TGFβ), and adipokines (leptin, adiponectin). NGF regulates the development and health of sympathetic innervation by controling the inflammatory response of adipose tissue. Mast cells, which express both NGF receptors, are the main regulators of local immune processes, angiogenesis and regeneration. Mast cells are involved in adipose tissue hypertrophy, inflammation and insulin resistance.[37] Serum glucose levels are negatively correlated with serum NGF levels in the metabolic syndrome.[38] The synthesis and secretion of steroid hormones is controled by NGF regulation. The main source of NGF is granulosa cells in women and Leydig cells in men.[39,40] Patients with PCOS have elevated serum NGF levels, which are involved in hyperandrogenism and insulin resistance.[41] The low serum NGF levels in men are associated with decreased testosterone levels and reproductive and metabolic dysfunction.[42]

Our results confirmed the decreased serum NGF levels in metabolic events of obesity.[43] The studies highlighted the interactions between thyroid dysfunction and serum monocyte chemoattractant protein-1 (MCP1) and NGF levels in obesity. Serum NGF levels were significantly higher in obese patients compared to postmenopausal women and controls. There was a positive correlation between increased serum NGF levels and decreased FT_4 levels in MCP1- and NGF-positive obese patients compared to postmenopausal women. The results showed that the regulatory role of NGF affects thyroid dysfunction and increases the incidence of subclinical hypothyroidism due to crosstalk between the thyroid and adipose tissue.[44]

Adipose tissue is an endocrine organ involved in lipid metabolism, insulin sensitivity, glucose and vascular homeostasis, and immune and inflammatory processes. Under stress, the adrenal glands and the HPA axis can modulate adipose tissue function through the release of NGF, hormones (catecholamines, cortisol, hypogonadism, hypothyroidism, hyperprolactinemia) and cytokines (TNFα, IL-1, IL-6, IL-8, IL-10, TGFβ). Increased sympathetic activity initiates lipolysis, hyperinsulinemia, adipocyte proliferation and hypertrophy and the development of the metabolic syndrome[45] (*Figure 3*).

Postmenopausal metabolic changes and postmenopausal osteoporosis

Postmenopause represents altered immune and metabolic processes due to estrogen deficiency. Estrogen receptors are expressed in immune cells (macrophages, T and B lymphocytes, dendritic cells, eosinophils, mast cells).[46] The protective role of estrogen in energy, glucose and hematopoietic homeostasis is gradually lost in the postmenopausal period, leading to life-threatening diseases such as osteoporosis, cardiovascular diseases, tumors, immune and hematopoietic disorders). Estrogen acts directly on glucose and lipid metabolism leading to increased visceral fat and lipid accumulation with decreased lipid utilisation and suppressed expression of glucose transporter 4 (GLUT4).[47] Therefore, the propensity for insulin resistance and type 2 diabetes mellitus, together with sympathetic neuronal activity, is very high in postmenopausal women. Estrogen deficiency leads to changes in the structure of the vasculature and endothelium promoting the release of several mediators [IL-6, MCP-1, RANTES (regulated on activation normal T cell expressed and secreted) chemokine, VEGF (vascular endothelial growth factor)]. Upregulation of VEGF is associated with hypertrophy of vascular smooth muscle cells. The renin-angiotensin system is inhibited by estrogen, the absence of which results in increased atherogenesis and hypertension.[48] Postmenopause is characterized by the development of low-grade inflammation, insulin resistance, obesity and vascular lesions.

The metabolic and endocrine changes that occur in the postmenopausal period are associated with increased sympathetic neuronal activity and low-grade inflammation, in which NGF plays a role. This study investigated NGF in postmenopausal osteoporosis. The balance of bone remodeling shifts towards osteoclastogenesis in the postmenopausal period. Postmenopausal osteoporosis is a T lymphocyte-mediated inflammatory process in which increased proinflammatory cytokines, particularly TNFα and IL-17, promote osteoclastogenesis. Our study investigated serum NGF and MCP1 levels in 60 postmenopausal women.[49] Dual-energy X-ray absorptiometry (DXA) was used to measure bone mineral density (BMD), and T-scores at the lumbar spine. The results showed significantly increased serum NGF levels in postmenopausal women with osteoporosis (T-score below -2.5) compared to those with normal or osteopenic T-score values. NGF levels were positively associated with MCP1 levels and negatively associated with bone mineral density using multiple regression analysis. Age was not included in the model. Three regions, total lumbar spine, total forearm and femoral neck, were measured by DXA scan. Elevated serum NGF levels were associated with osteoporosis of the lumbar spine, but not of the total forearm and femoral neck. NGF has been detected in osteoprogenitor cells, bone marrow stromal cells, osteoblasts, chondrocytes, endothelial cells, skeletal muscle and the periosteal matrix of fracture callus.[50] Mesenchymal stem cells are also capable of producing NGF, highlighting their role in bone repair and regeneration.[51] Treatment with anti-NGF antibodies is available.[52] Their use attenuated cutaneous hypersensitivity and musculoskeletal discomfort, but resulted in only a small increase in lumbar spine BMD in osteoporotic mice.

Conclusion

The regulatory role of NGF is associated with sympathetic neuronal activity and local inflammation involving immune, hematopoietic and bone marrow cells. The central role of mast cells is involved in the abundant production of NGF and the release of active mediators and cytokines for allergic and neurogenic inflammation leading to Th2 dominance. The action of NGF on adipose tissue, pancreatic beta cells, vascular endothelial cells, granulosa cells and Leyding cells alters glucose and insulin sensitivity and increases the propensity for insulin resistance, obesity, diabetes mellitus and metabolic syndrome. Similar low-grade inflammatory processes are initiated in postmenopausal women due to estrogen deficiency. Postmenopausal lumbar spine osteoporosis is associated with decreased serum NGF levels, showing the actual balance between bone loss and bone repair processes. Anti-NGF antibody therapy appears to be effective in reducing pain,

neuropathy and corneal ulcers or allergic events, but the serious side effects need to be addressed in new applications.

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Conflicts of Interest

None.

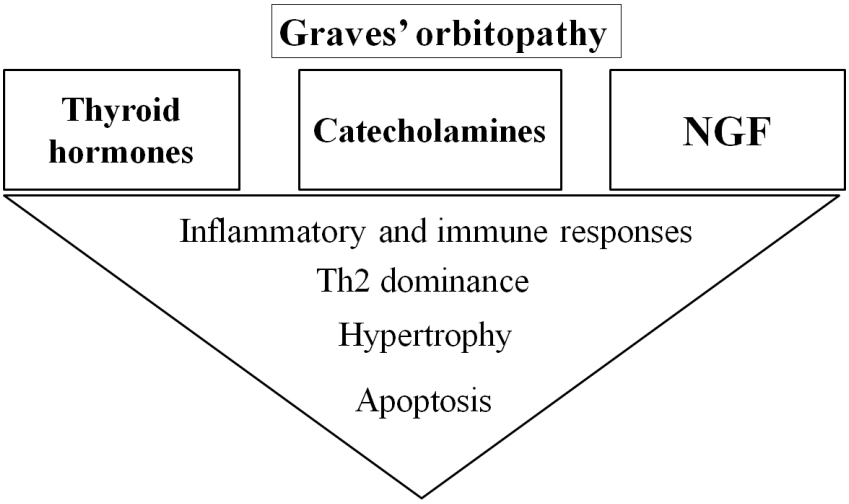

Figure 2: Concomitant increases in catecholamines and NGF due to accelerated sympathetic neuronal activity are responsible for hypertrophy of adipocytes, myofibroblasts and vascular smooth muscle cells, inflammatory and immune responses, Th2 dominance and apoptosis in hyperthyroid Graves ' orbitopathy.
Th2: T-helper 2 lymphocyte.

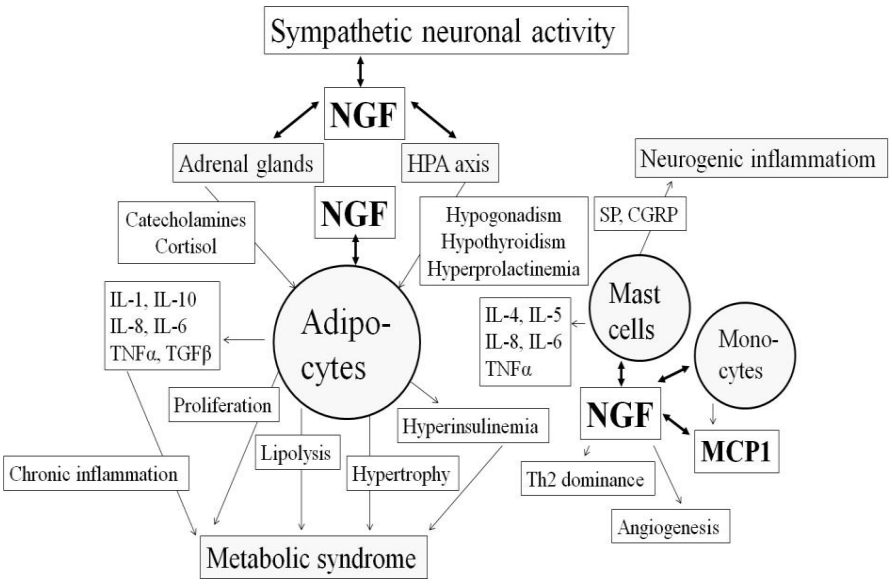

Figure 3: Sympathetic neuronal activity and NGF-mediated stimulation of the adrenal glands and HPA axis play a role in lipolysis, adipocyte proliferation, hypertrophy and hyperinsulinemia, which are signs of metabolic syndrome. The NGF source of mast cells and eosinophils maintains these processes and is involved in the development of neurogenic inflammation, pain, angiogenesis and Th2 dominance.

NGF: nerve growth factor;
HPA axis: hypothalamic- pituitary-adrenal axis;
SP: substance P;
CGRP: calcitonin gene-related peptide;
MCP1: monocyte chemoattractant protein-1;
TNFα: tumor necrosis factor α;
TGFβ: transforming growth factor β;
IL: interleukin;
Th2: T-helper 2 lymphocyte.

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