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NEUROTENSIN AFFECTS METABOLISM, INFLAMMATION, AND NEUROLOGICAL PATHOLOGIES INVOLVING MAST CELLS

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ABSTRACT

Neurotensin (NTS) is a neurotransmitter and neuromodulator with 13 amino acids that has paracranial and endocrine effects on various organs. NTS can have a stimulating effect on both normal and cancer cells. Additionally, it stimulates the anterior pituitary gland to produce hormones that reduce pain. At the brain level, NTS is closely associated with the effects of dopamine and is therefore involved in neurological disorders. NTS is derived from the pro-NTS precursor and is transcribed via mRNA involving the c-Fos and AP-1 genes. NTS acts through three receptors: NTSR-1, 2, and 3; NTSR-1 and NTSR-2 belong to a class of G-coupled proteins and have several similarities, while NTSR-3 seems to be slightly different from the other two and has yet to be defined. NTS is a modulator of the digestive tract and cardiovascular system, and participates in fat absorption and regulation of energy homeostasis. In rodent experiments, NTS mediates inflammation and metabolic diseases associated with obesity, and its level is high in hepatic steatosis. In addition, NTS activates MCs to produce inflammatory mediators that can affect the central nervous system (CNS). However, more studies are needed to clarify the exact function of NTS and whether this protein could be a therapeutic target.

KEYWORDS: *neurotensin, neurotensin receptor, metabolism, inflammation, neurological pathology, mast cell*

INTRODUCTION

Neurotensin (NTS) is a peptide of 13 amino acids that functions as a brain neurotransmitter and neuromodulator and was isolated by Carraway and Leeman in 1973 (1). In the brain, NTS modulates dopaminergic transmission, while at the peripheral level, it is a paracrine and endocrine modulator of the cardiovascular and digestive systems (2). It has been noted that NTS can also have a stimulating action on the growth of normal and tumor cells (3) (Fig.1).

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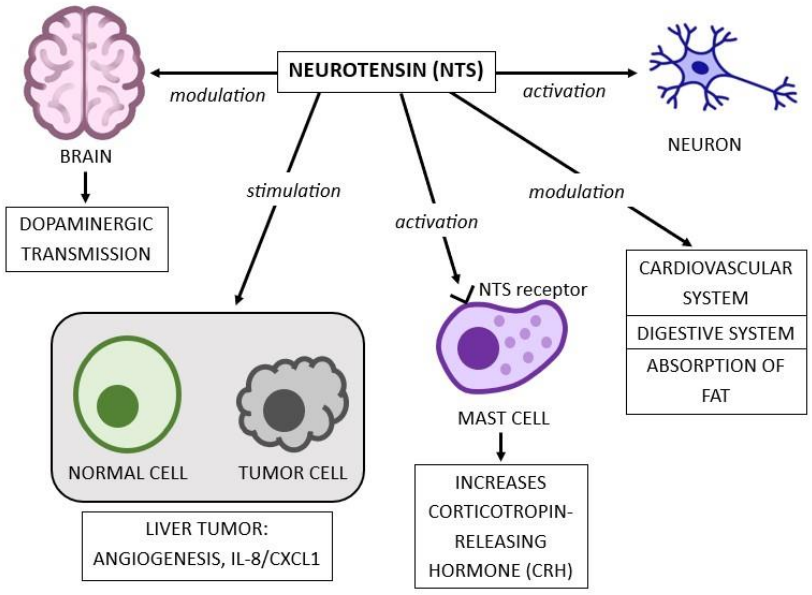

Fig. 1. *Neurotensin (NTS) activates neurons and modulates cerebral activity, causing dopaminergic transmission. NTS also influences normal and tumor cells and can cause angiogenesis and IL-8/CXCL1 activation, modulates the cardiovascular system, the digestive system, and the absorption of fat, and by binding to its receptor, activates mast cells (MCs) to release corticotropin-releasing hormone (CRH).*

DISCUSSION

NTS is a neuromodulator, with powerful effects on hypothermia stimulation, on the secretion of hormones by the anterior pituitary gland, and on the physiological mechanisms within the body that are capable of blocking or attenuating pain (4). In the central nervous system (CNS), neurotensin is a neuromodulator, particularly concerning dopaminergic transmission, and to a lesser extent, serotonergic and noradrenergic transmission (5). Preventive *in vivo* treatment with anti-opioid drugs does not abolish the pain-relieving effect induced by NTS, demonstrating that the two pathways of antinociceptive inhibition are different (6).

The function of NTS in the brain is in close association with the action and biological effects of dopamine, whose pathological variations are found in many neurological disorders, such as Parkinson's disease (7). The biological effects of NTS include psychostimulant and anti-psychotic effects (8).

NTS derives from a larger pro-NTS/neuromedin precursor molecule (pro-NTS/NN), a complex processed and cleaved by endopeptidases that belong to protein convertases (9). The precursor process is tissue-specific and therefore, may be different in various organs (10). For example, the pro-NTS/NN precursor in the brain is processed to form NTS and NN, while in the intestine, there is NTS and a large-NN (11). The inactivation of NN occurs promptly by aminopeptidase, while NTS is inactivated by metalloendopeptidases (12). It appears that NN is a neuropeptide that is mostly localized in the brain, while large NN is produced in the intestine and functions as a hormone that is transported by the peripheral blood (13). At the genetic level, NTS appears to be transcribed through precursor mRNA involving c-Fos and AP-1 (14).

The NTS receptors (NTSR) are NTSR-1, NTSR-2, and NTSR-3 (15). NTSR-1 and NTSR-2 belong to a class of G-coupled proteins and have several similarities, while NTSR-3 seems to be slightly different from the other two and has yet to be defined (15). The best-known and first-synthesized NTS receptors are NTSR-1 and NTSR-2 (16).

NTS binds to NTSR-1 with high affinity, while the NTSR-2 receptor has low activity for this neurotransmitter. These receptors are distributed differently in the CNS; for example, NTSR-1 seems to be expressed predominantly in neurons, while NTSR-2 is expressed more greatly in glia (17). In humans, NTSR-1 is composed of 418 amino acids located on chromosome 20q13 and its activation with NTS involves the increase in calcium ions (Ca^{2+}), IP3, and the activation of phospholipase C (PLC) at the intracellular level (18). Receptor internalization appears to be temperature-dependent and is translated in neurons (19). The human NTSR-2 has 401 amino acids and appears to be an antagonist of NTSR-1 (20). The activation of NTSR-2 stimulates mitogen-activated protein kinases (MAPKs), increases the concentration of intracellular Ca^{2+}, and activates IP3 and cAMP, although these processes still need to be confirmed (21).

The mRNA encoding NTSR-2 resides in brain tissue and especially in the cortex, hippocampus, and hypothalamus, and appears to be exclusive to neurons. The NTSR-2 receptor seems to be more involved in analgesia, while NTSR-1 seems to be responsible for the central effects of NTS (22).

Effects of Neurotensin (NTS) on metabolism and inflammation

Among the biological effects of NTS, its participation in the absorption of fats and in the regulation of energy homeostasis should be highlighted (23). NTS is a modulator of the digestive tract and cardiovascular system of mammals and also acts as a growth factor for normal and tumor cells (24). Pro-NTS is associated with obesity and type 2 diabetes mellitus (25). In animal models, NTS has been observed to mediate inflammation of abdominal fat and is a potential cause of type 2 diabetes mellitus, obesity-associated metabolic diseases, and hepatic steatosis (26) NTS is considered a biomarker for hepatic steatosis and obesity and represents a potential therapeutic target (27).

Neuropeptides such as NTS interact with different cell types residing in the gut and play a key role in several aspects of intestinal pathophysiology. NTS is involved in many gastrointestinal pathologies with effects on the neurological, immune, and inflammatory systems (28). NTS directly activates neurons, epithelial, and immune cells with complex and still unclear mechanisms. NTS appears to play a protective role in immunity at the intestinal level, but on the other hand, it appears to activate the acute inflammatory and pathological response (29). Therefore, NTS can be both a pro-inflammatory and anti-inflammatory peptide. At a pro-inflammatory level, NTS participates in the brain-gut axis by activating visceral hypersensitivity, overgrowth of intestinal flora, intestinal inflammation, and hyperreactivity of mast cells (MCs) (30).

MCs are immune cells that mediate both primary and adaptive responses. They are located in tissues, where their maturation occurs through the stimulation by various cytokines such as IL-3, IL-6, and stem cell factor (SCF) (31). MCs are activated by various neuropeptides including substance P (SP), nerve growth factor (NGF) and NTS. When activated by NTS, MCs modulate and secrete numerous molecules such us heparin, nitric oxide (NO), transforming growth factor beta (TGF-β), tumor necrosis factor (TNF), and IL-10, which can have autocrine actions that can be either activating or inhibiting (32).

NTS increases the expression of the corticotropin releasing hormone 1 receptor (CRHR-1) on MCs. In addition, NTS stimulates the secretion of corticotropin releasing hormone (CRH) and VEGF from MCs activated by IgE or anti-IgE (33). NTS has been observed to be increased in the skin of rodents after acute stress, which stimulates MCs and increases vascular permeability (34). In addition, NTS stimulates MCs to produce increased levels of histamine through activation of NTSR (35). MCs located in the skin reside near the ends of sensory nerves and can be activated by neuropeptides including NTS produced by skin cells (36). Protease-producing MCs are capable of degrading NTS, highlighting the crosstalk between NTS and MCs. When activated by NTS, MCs residing in the skin can release chemical mediators of inflammation, making NTS a candidate for therapeutic targets of neuroinflammatory disorders (36).

Microglial cells express NTSR-3 which is involved in their cell proliferation (37) and also in neuroinflammation, after NTS binds to this receptor (38). In synergy with the neuropeptide CRH, NTS increases vascular permeability and causes the breakdown of the blood-brain barrier (BBB), exacerbating inflammatory reactions (39).

Neurotensin (NT) and neurological pathologies

NTS appears to mediate several neurological disorders including autism spectrum disorder (ASD), where this neuropeptide is elevated in the serum of children. In addition, it has been reported that NTS induces the expression of corticotropin-releasing factor-1 (CRF-1), increasing allergic disease mediated by human MCs (40). In an interesting study, NTS was reported to be elevated in the serum of young children with autistic disorder, compared to typically developing controls (41).

NTS could carry out its biological action in cooperation with other neuropeptides, such as CRH, and blocking its receptor NTSR-1 on MCs could be sufficient to improve some neurological diseases. (42). Moreover, there is a relationship between dopamine and NTS. In fact, it has been reported that dopamine receptor-2 signaling is capable of modulating the release of NTS (7). This data has been confirmed, as blocking the dopamine receptor-2 leads to a reduction in the secretion of NTS at an extracellular level (43).

These biological effects allow us to better understand the dopamine/NTS interaction in inflammatory neurological diseases where these neurotransmitters are involved. Theoharides reports in his experiments that young children affected by ASD present a neuroimmune dysfunction where NTS is increased and proposes that for this, NTS could constitute an interesting therapeutic target (44). By binding to its receptors, NTS stimulates MCs in rats to produce more histamine, increasing its plasma levels and vascular permeability (44). This author also reports that by stimulating the secretion of

MCs, NTS also increases endothelial growth factor (EGF) and plasma histamine levels (45). Taken together, these results indicate that NTS could stimulate the immune system in cooperation with MCs, with effects on CNS inflammation (41).

CONCLUSIONS

In conclusion, the secretion NTS activates MCs through the it's receptors to release pro-inflammatory compounds with consequent inflammation of the CNS. Therefore, NTS could be targeted as a new therapeutic option for treating neurological pathologies.

Conflict of interest

The author declares that they have no conflict of interest.

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