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Letter to the Editor

CEREBROVASCULAR DAMAGE PREVENTION: SURGICAL ASPECTS

D. Lauritano[1*] and F. Carinci[2]

[1] Department of Translational Medicine, University of Ferrara, Italy;
[2] Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Italy.

**Correspondence to*:
Dr. Dorina Lauritano,
Department of Translational Medicine,
University of Ferrara,
44121 Ferrara, Italy.
e-mail: dorina.lauritano@gmail.com

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INTRODUCTION

Globally, life span continues to increase, and the World Health Organization (WHO) predicts that in 2050, two billion individuals will be over 65 years of age. This prolongation of life leads to the progressive deterioration of physical and mental health which occurs with ageing, and this leads to the requirement for greater social and medical care (1).

In past centuries, no one could anticipate that the surgical aspect in the field of cerebrovascular diseases would occupy such a large part of medical-scientific activity (2). However, today the prevention of cerebrovascular diseases must be considered not only in terms of pharmacological treatment, to which we were accustomed, but the surgical aspect must also be considered. In tackling the prevention of this important disorder, which currently represents the third leading cause of death and the most serious cause of disability, the risk factors must be studied, which is not straightforward, as it involves challenging epidemiological aspects.

DISCUSSION

There are two prevention methods for cerebrovascular damage: the pharmacological method and the surgical method, and these can be considered antithetical. Both require a preliminary diagnosis of stenosis or obstruction of an artery which vascularizes the brain, that is, if the obstruction affects the large vessels of the neck such as the carotid or vertebral arteries.

Considering a high-risk for developing cerebrovascular disease, the surgical approach will be indicated (3). If it is a stenosis or an obstruction of several small vessels at the level of the brain, the subject of medical prevention will arise. Therefore, close collaboration between the neurologist and the vascular surgeon is important for diagnosis and therapy.

In any case, however, the situation needs to be carefully evaluated and it is currently possible to make use of instrumental noninvasive and repeatable techniques. In recent years, there has been a notable development of techniques that offer good reliability and prediction ability. Using these techniques when faced with a cerebrovascular pathology, it is possible to avoid trauma and risks to the patient that other tests would inevitably entail.

The diagnostic approach involves the use of the well-known Doppler ultrasound method (4). A further improvement of the ultrasound technique consists of the Doppler examination called “Eco-flow” which allows, with the reconstruction

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of the reflection of ultrasonic waves, the visual highlighting of the vessel. The image provided by this completely safe and noninvasive technique reproduces, with excellent reliability, results superimposable to those of an angiography, an invasive examination which is not completely risk-free, allowing the surgeon to confront any obstructive lesion.

This technique is followed by another one that is used with considerable frequency, called angioscintigraphy, a method that involves the intravenous injection of an isotope, such as technetium, and to following its progression with suitable instruments at the level of the neck arteries. The different concentration of the isotope at the level of the vascular structures translates into the reconstructed image on the display, which is portrayed in different intensities on a defined chromatic scale. For example, obstruction of a carotid artery will result in a reduction in the quantity of isotope in the ipsilateral hemisphere, which will be evident in comparison with the opposite hemisphere. This method also allows medical professionals to reconstruct the transit curves of the tracer in the two hemispheres and in the different vessel segments (middle cerebral carotid artery, etc.), indicating the perfusion speed but not of the blood flow. Remaining with the example of an obstructive lesion of the carotid artery, in this case, a slowing of transit will be observed in the damaged vessel compared to the contralateral one, indicated by a reduced increase in the ascending phase of the curve. This possibility of analyzing the speed of transit can also be applied to the study of the middle cerebral arteries of which similar curves will be highlighted.

The task that then arises is to evaluate the functionality of the cerebral structures, which can be an indication for considering a surgical approach. If there is stabilized damage to the nerve cells, an increase in perfusion which is obtainable with unblocking or other surgical techniques (bypass), will not result in a clear functional recovery. Noninvasive techniques such as Computerized Axial Tomography (CAT) have provided a precise anatomical description of the brain structures but not of their functionality (5).

Today, it is possible to use techniques that are similar to CAT scans, which utilize both gamma and positron emitting isotopes. If a non-fuse tracer, such as technetium, is injected during a tomoscintigraphic examination (gamma CAT), any areas of different uptake will be observed in a series of "slices" of the brain structure starting from the vertex. In an infarct area, the alteration of the blood-brain barrier (BBB) will cause diffusion of the tracer. It is clear that, in such a case, it is necessary to carefully determine whether there is the need for increased blood flow to the area in question or whether this would do more harm than good.

The current perspectives in the field of non-traumatic diagnostics also offer other much more precise possibilities. In fact, the use of C11-labeled glucose allows the distribution of the tracer to be visualized and is therefore able to provide an indicator of the metabolism in the central nervous system (CNS) (6). Similarly, techniques that use O_2-15, a positron emitter, allow the evaluation of both perfusion and cerebral consumption of oxygen (7).

These methods allow for the evaluation, not only of the distribution of the flow, but also for the ability of brain tissue metabolism. This information should be considered for evaluating the functionality of the brain tissue and the prospect of any surgical intervention aimed at restoring blood flow to injured areas. From this perspective of correlations between flow and metabolism, and with the continued collaboration of vascular surgeons, it is believed that in the not-too-distant future it will be possible to prevent and treat cerebrovascular pathology more effectively.

CONCLUSIONS

The ageing of the global population will increase the number of people affected by cerebrovascular diseases in the coming decades. It is important to focus on the prevention and treatment of these disorders, in order to ensure a higher quality of life for the ageing population. In recent decades, cardiovascular diseases, strokes, and obstruction of the cerebral vessels often require surgical interventions, which today have assumed fundamental importance. In recent years, there has been a notable development of surgical techniques that offer good reliability and predictive ability. The diagnosis of cerebrovascular diseases involves the use of Doppler ultrasound and "Eco-flow" which allow for visualization of the vessels and are very useful diagnostic techniques for the surgeon. Additionally, angioscintigraphy involves the intravenous injection of technetium, and highlights the different concentrations of the isotope at the level of the vascular structures. The utilization of CAT for investigating vascular pathologies provides a satisfactory anatomical description of brain structures. Other diagnostic methods are gamma CAT and the use of glucose labelled with C11. These methods are useful for describing the morphology of tissue, but not for the functionality of cerebral structures. These techniques assist neurologists and surgeons in the evaluation of the flow distribution and in deciding whether to carry out a possible surgical intervention aimed at restoring blood flow.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

BETA2-ADRENERGIC AGONISTS ARE SYMPATHOMIMETIC DRUGS WITH A MYOLYTIC-SPASMOGENIC ACTION

A. Coppola*

Private practice, Studio Armando Coppola, Naples, Italy.

**Correspondence to*:
Dr. Armando Coppola,
Private practice, Studio Armando Coppola,
Corso Garibaldi 246,
Naples 80141, Italy.
e-mail: armandocoppola70@gmail.com

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INTRODUCTION

Selective β2-adrenergic agonists are very important sympathomimetic drugs which have been used for thousands of years and today, remain the one of the first-line treatments for asthma and chronic obstructive pulmonary disease (1). In addition to being the most powerful bronchodilator drugs (with myolytic action) currently available, these compounds can prevent bronchospasm (anti-spasmogenic action) induced by various types of agents. Another favorable prerogative is constituted by the notable flexibility of use of these drugs, due to the availability of short-acting and long-acting compounds that can be used respectively for the symptomatic treatment of asthma episodes and the prolonged control of the bronchospasm (2).

DISCUSSION

Three β receptors have been identified, called β1, β2, and β3, which are located respectively in the heart, in the smooth muscle of the airways, and in adipose tissue (3). Upper airway smooth muscles contain mostly β2 adrenergic receptors, while in the terminal respiratory tracts and alveoli, β1 and β2 receptors are both present. Additionally, the bronchial epithelia and mucous glands contain β2 receptors which are vital for regulating secretions. In the airways, inflammatory cells such as alveolar macrophages have β2 receptors (4).

β2-adrenergic receptors are membrane receptors coupled to stimulatory G proteins and consist of a single polypeptide chain having an extracellular N terminus and an intracytoplasmatic C terminus (5).

β2-agonists bind to their specific receptors, causing a conformational modification at the level of the fifth and sixth transmembrane domain, after which there is the activation of stimulatory G proteins made up of three α β γ subunits, which can directly activate the Ca^{2+} positive dependent potassium flux or stimulate adenylate cyclase by increasing the concentration of intracellular cAMP (6). Intracellular cAMP determines the activation of protein kinase A (PKA) and protein kinase G (PKG), and the subsequent phosphorylation of numerous substrates which initiate or modulate various cellular responses that are responsible for the myolytic and anti-spasmogenic action (7).

Three fundamental mechanisms for cellular responses can occur: (i) there can be a reduction in the cytosolic free Ca^{2+} concentration which can occur due to the extrusion of Ca^{2+} outside the cell due to activation of the ATP-dependent Ca^{2+} pump, (ii) an increase in Ca^{2+} uptake within intracellular stores; or (iii) an inhibition of Ca^{2+} release from intracellular stores sensitive to the second messenger inositol 1,4,5-triphosphate (IP3). There can be a hyperpolarization of the cell

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membrane or a decrease in the efficiency of the contractile apparatus through direct inhibition of the kinase at the level of the myosin light chain.

Therefore, β2-agonists act as functional antagonists causing bronchodilation independently of the contracting agent (Table I). β2-agonists can also cause bronchodilation indirectly by inhibiting the release of bronchoconstriction mediators, such as histamine and leukotrienes, that are generated by specific antigen-activated mast cells (MCs).

Table I. *Positive features of β2-agonists.*

- Powerful and rapid onset of the bronchodilation effect.
- Action on large and small caliber airways.
- High efficacy by inhalation with consequent selective activity on the target organ.
- Stimulation of mucociliary clearance.
- Inhibition of cholinergic and non-cholinergic neurotransmission.

However, it should be noted that while disodium cromoglicate, which is less powerful in inhibiting the release of histamine from MCs compared to β2-agonists, also prevents the late inflammatory phase of the response, and a pre-treatment with β2-agonists only prevents the immediate phase without any effect on macrophages.

β2-agonist activation also stimulates surfactant secretion by type II alveolar cells (8). The increase in surfactant secretion reduces the adhesiveness of bronchial secretions, which is increased in the case of bronchial asthma, and improves the transport of mucus through the lumen of the airways. This effect is also related to an improvement in mucous clearance, resulting in both improved ciliary function and the transport of ions and water across the epithelium. Finally, it is important to remember the modulatory effect of β2 receptor activation on cholinergic transmission. The activation of β2-receptors located on the post-ganglionic cholinergic nerves at a prejunctional level reduces the release of acetylcholine and may contribute to the bronchodilator effect by reducing reflex bronchoconstriction.

Pharmacological action of β2-agonists

the β2-agonists currently in use derive from chemical manipulations made to the structure of natural catecholamines, with the dual purpose of obtaining increasingly selective molecules and minimizing unwanted side effects, especially at a cardiovascular level (9).

Adrenaline, the precursor of β2-agonist drugs, stimulates both α and β receptors (2). The short half-life of the molecule, which is taken up by the terminal nerves, and the metabolization by catechol-O-methyltransferases distributed throughout the body, make adrenaline administered orally ineffective. Furthermore, its therapeutic interest, even when administered by aerosol, is limited by the non-negligible side effects deriving from α and β stimulation.

The β2-agonist research process began in the 1940s with the development of isoproterenol, the first compound with exclusive activity on β receptors, obtained by replacing the terminal methyl group of the adrenaline side chain with an isopropyl group. Despite the advantage due to the lack of α-adrenergic activity (vasoconstriction), isoproterenol, however, retains the β1/β2 activity of adrenaline and the bronchodilation effect profile characterized by a powerful and rapid, but extremely fleeting action.

Subsequent modifications of the catechol nucleus and/or the side chain of isoproterenol led to the synthesis of resorcinol derivatives (orciprenaline, terbutaline, fenoterol) and saligenin derivatives (salbutamol, carbuterol) with a longer duration of action as they are resistant to degradation operated by catechol-O-methyltransferases and of greater selectivity for the β2-receptor (10).

In resorcinol derivatives, the hydroxyl groups of the aromatic ring, compared to the catechol derivatives, are located in positions 3 and 5, instead of 3 and 4. This modification has made these compounds resistant to catechol-O-methyltransferases, prolonging the duration of the broncho-dilating effect. Metaproterenol, the first synthetic resorcinol derivative, retains the side chain of isoproterenol, while in fenoterol, the latter was modified by adding a hydroxyphenyl group. The β2 selectivity of resorcinol is not very high.

The salbutamol prototype of saligenin was obtained through a dual chemical manipulation with the addition of a methyl radical to the hydroxide group in position 3 of the catechol ring and the addition of a tertiary butyl group to the ethanolamine side chain (11). These modifications have allowed the acquisition of notable resistance against catechol-O-methyltransferases and greater selectivity for the β2 receptor subtype, respectively.

The newer generation of long-acting selective β2 agonists includes salmeterol and formoterol. Both drugs are potent and highly selective β2-agonists and salmeterol may be a partial agonist at β receptors in some tissues. Their long duration of action (about 12 hours) appears to be due to their lipid solubility rather than resistance to metabolic inactivation. Their remarkable lipid solubility allows these drugs to dissolve in high concentrations in the smooth muscle cell membrane. It is assumed that when they are dissolved in this way, they act as a slow-release depot that supplies active ingredients to the adjacent β receptors for a prolonged period.

β2-agonist drugs are classified based on their pharmacodynamic and pharmacokinetic characteristics: β2-agonists as background drugs, including long-acting inhaled β2-agonists and long-acting oral β2-agonists, and β2-agonist symptomatic drugs, including inhaled β2-agonists with rapid onset of action and short-acting oral β2-agonists (which are recommended for patients who are unable to use inhaled drugs). Inhaled β2-agonists with a rapid onset of action result in a prompt and immediate improvement in symptoms, and include salbutamol (albuterol), terbutaline, fenoterol, reproterol, and pirbuterol. Formoterol has both rapid onset and a long duration of action.

The dose administered and the dose of drug present systemically determines the frequency and importance of unwanted side effects. The main side effects are cardiovascular stimulation (tachycardia, extrasystoles), muscle tremors, and hypokalemia. However, the inhalation route of β2-agonists is the most advantageous method of administration, as it enhances the efficacy of bronchodilation while limiting unwanted side effects.

CONCLUSIONS

β2-agonists are historical bronchodilators which have an anti-spasmogenic and myolytic action, and today, still remain the first-line treatment for asthma and chronic obstructive pulmonary disease. Compared to other drugs, β2-agonists have the advantage of acting quickly and being highly effective. The biological action of these drugs is exerted after binding to their β1, β2, and β3 receptors located on the cells of the target tissue, such as smooth and cardiac muscles. Despite the widespread use of these drugs, their side effects must be considered, which include hypokalemia, tachycardia, extrasystoles, and muscle tremors.

Conflict of interest

The author declares that they have no conflict of interest.

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

R. Pellegrino*

Physiatrist and Pain Therapist, Lecce-Castromediano/Cavallino, Via S. Pelico, Lecce, Italy.

**Correspondence to*:
Dr. R. Pellegrino,
Physiatrist and Pain Therapist,
Lecce-Castromediano/Cavallino,
Via S. Pelico 34,
73100 Lecce, Italy.
e-mail: drpellegrino@yahoo.it

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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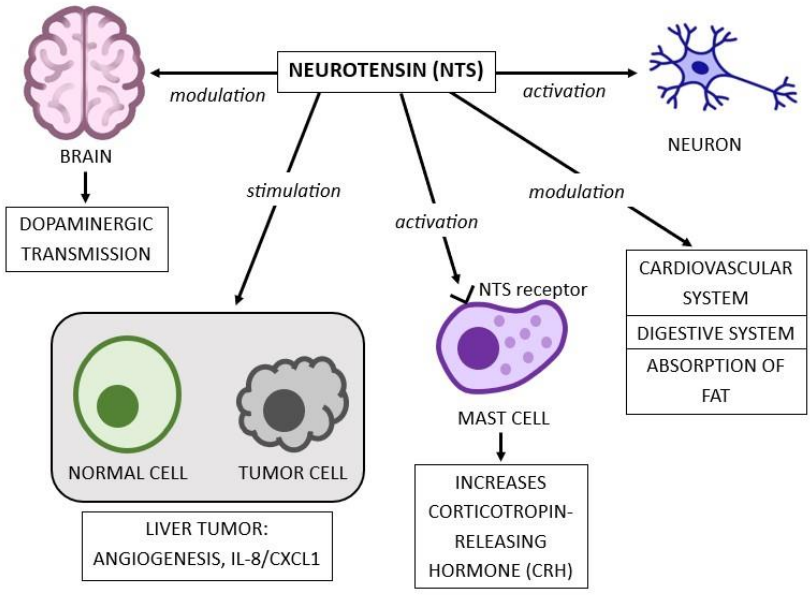

Fig. 1. *Neurotensin (NTS) activates neurons and modulates cerebral activity, causing dopaminergic transmission. NTS also influences normal and tumor cells and can cause angiogenesis and IL-8/CXCL1 activation, modulates the cardiovascular system, the digestive system, and the absorption of fat, and by 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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PHYSICAL ACTIVITY AND BRAIN HEALTH: "MENS SANA IN CORPORE SANO"

F. Pandolfi[1*] and R. Padula[2]

[1] Allergy and Clinical Immunology, Fondazione Policlinico Universitario A, Gemelli IRCCS, Catholic University, Rome, Italy;
[2] Clinical and experimental biology, University of Foggia, Italy.

Correspondence to:
Franco Pandolfi,
Allergy and Clinical Immunology,
Fondazione Policlinico Universitario A. Gemelli IRCCS,
Catholic University,
00168 Rome, Italy.
e-mail: franco.pandolfi@unicatt.it

ABSTRACT

Physical activity has beneficial effects for the health of the entire body, including the central nervous system (CNS). Periodic physical exercises and consistent physical activity leads to increased cardiovascular endurance and capacity, enhanced muscular tone, increased muscular strength, improved metabolism, decreased adiposity, and additionally, strengthens the immune system, making the body less vulnerable to certain diseases. Recently, it was noticed that in physically trained subjects, the number of leukocytes was increased; this contributed to greater resistance to infections by microorganisms. An important immune protein that increases in individuals who are physically active is interleukin-1 (IL-1), which is responsible for the feverish effect, and is primarily produced by monocytic cells and lymphocytes.

KEYWORDS: *physical activity, sport, immunity, IL-1, neurodegenerative, health, CNS*

INTRODUCTION

It is well known that physical activity is good for the health of the entire body (1). Periodic physical exercises and consistent physical activity has benefits for our health by positively affecting cardiovascular and muscular strength and metabolism, by decreasing adiposity, and additionally, by strengthening the immune system, making the body less vulnerable to certain diseases (2).

During physical activity, fatigue can occur with activation of the sympathetic system and the hypothalamus, resulting in the release of catabolic products and inflammatory molecules, including cytokines (3). Athletes who engage in intense and prolonged physical exercise have altered neuropsychological conditions and experience the loss of bodily fluids with sweating. Intense exercise can cause the release of cortisol which is an immunosuppressive molecule, and this effect can be damaging. On the other hand, it is known that physical activity improves cognitive and brain functions and moderate exercise can strengthen the immune system (4).

The impacts of physical activity and exercise on the immune system

Starting from the general concept that white blood cells defend the body and immunize it from infectious diseases, it is easy to understand that a physiological increase of these cells can strengthen the immune system (5). It has been seen that the number of leukocytes was increased in physically trained subjects; this contributes to a greater resistance to

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infections by microorganisms (6). The reason for the increase in leukocytes is not clear, but there are some possible hypotheses: a) physical exercise causes a loss of extracellular fluids, resulting in a greater concentration of blood cells, and therefore, a greater number of both leukocytes and red blood cells; b) after physical exercise, there is an increase in the levels of catecholamines and adrenaline, which regulate the number of leukocytes in the blood circulation; c) the production of some hormones during physical activity can affect the pool of leukocytes in circulation (7).

The increase in white blood cells plays an important role in the body's defense against infections, although apparently the leukocytes of athletes do not appear functionally indistinguishable from those of sedentary individuals (8). The increase in leukocytes seems to affect T lymphocytes (anti-viral and anti-tumor) more than B lymphocytes, which protect from bacterial infections (9). Another important immune element that increases in individuals who are physically active is interleukin-1 (IL-1), a protein produced by some leukocytes that is responsible for mediating fever and the inflammatory response (10).

IL-1 causes fever in humans and is responsible for producing heat in cold-blooded animals (11). Human fever is an immune reaction that serves to protect the body from insults, such as bacterial and viral infections. During the inflammatory reaction, IL-1 is produced by macrophagic cells and increases inflammation, which is detrimental to the body (12). Elevated levels of IL-1 produce fever, and a subsequent drop in blood iron levels, a reaction that protects the body from microbial invasion (13). IL-1 activates leukocytes such as lymphocytes and macrophages, which are responsible for the immune reaction.

The increase in temperature due to exercise stimulates the production of IL-1 which mediates the immune response (14). Hyperthermia after exercise depends on both the metabolic activity of the muscles and the production of IL-1 (15). In general, when the leukocytes of athletes are stimulated *in vitro*, they produce more IL-1 than those who do not participate in sports, and athletes are less likely to experience states of depression (16). Again, in the laboratory, by bringing the peripheral blood leukocytes of sedentary individuals into contact with the serum of athletes, cellular stimulation and greater reactivity against microorganisms were obtained (17).

IL-1 is an endogenous mediator of fever and belongs to the cytokine family composed of pleiotropic molecules that are involved in many pathological processes (18). Animals treated with IL-1 were seen to develop hypotension caused by the induction of nitric oxide (NO) and decreased systolic blood pressure (19). The cytokine IL-2 (or T cell growth factor) also causes fever with an indirect mechanism on the hypothalamus, unlike IL-1 (20). IL-2 induces IL-1, tumor necrosis factor (TNF), and interferon gamma (IFN-γ), but not the marker C-reactive protein which is induced by IL-1 (21).

Physical training with an immune stimulus can be part of anti-tumor therapy without harmful effects on the body compared to conventional anti-tumor therapies which cause inflammation and immunodepression. Physical exercises reduce pro-inflammatory markers such as C-reactive protein and TNF, a potent inducer of inflammation and mediator of neuroinflammation, without inhibiting natural killer (NK) cells and cytotoxic T lymphocytes (22). However, this data still needs to be confirmed by future studies.

Different studies highlight the stimulus, albeit mild, of physical activity on NK cells, which are important for the immune response against malignant tumor diseases (23). NK cells are circulating lymphocytes that increase after physical exercise and are involved in the anti-tumor immune response with a cytotoxic effect (24). In addition, it was noted that individuals (not professional athletes) who practiced periodic exercises had a longer life expectancy than those who did not partake in physical activity (25).

The cytokines and chemokines that are involved in inflammation and could be regulated by physical activity are shown below (26) (Table I).

Table I. *Cytokines and chemokines mediating inflammation that could be regulated by physical activity.*

Cytokines:	Interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor (TNF), interferon gamma (IFN-γ)
Chemokines:	monocyte chemoattractant protein (MCP)-1 and MCP-3

The belief that exposing the body to cold can lower its resistance to infections finds a scientific explanation in the fact that certain viruses and bacteria that habitually and harmlessly live in the organism become pathogenic when body temperature is lowered (27). Experiments and studies have clearly demonstrated that recurring physical exercises reduce the risk of cardiovascular disease and contribute to longevity. But not only that, exercise helps to keep body weight under control, increase energy, and reduce stress (28).

If adrenaline is injected into a resting individual in quantities equal to those produced by an athlete after effective physical exercise, the increase in the number of leukocytes will be the same as that of the athlete (29). This means that

adrenaline, which is also one of the compounds responsible for growth (GH), is stimulated by physical activity (30). This, as is known, is co-responsible, together with other compounds, for the production of antibodies, rejection reactions, and the increase in neutrophils (31).

To date, there is no clinical evidence to demonstrate that physical exercise has anti-tumor effects, but what is certain is that physical activity increases NK cells which are capable of killing tumor cells. When the NK cells of an athlete are collected after intense physical exercise and put into contact with tumor cells *in vitro*, there is a greater degree of killing by the leukocytes compared to NK cells derived from individuals who do not practice sport (32). Several expert scientists, specializing in sport and immunity, have stated that vigorous and periodic physical activity provides the body with a natural defense, protecting individuals against ageing and cardiac ischemia and its consequences (33).

The impacts of physical activity and exercise on brain health

Physical activity has beneficial effects for the brain and the central nervous system (CNS) (34). Research has shown that exercise positively affects cognition, and that lack of physical activity is a risk factor for many diseases, including cardiovascular pathologies and neurodegenerative disorders (35). The immune-modifying properties of physical activity and exercise have anti-inflammatory effects throughout the entire body, including the CNS (36).

Reactive oxygen species (ROS) are produced by muscles during physical exercise and stimulate the transport of glucose necessary for an increase in metabolism (37). In the brain, there is an increase in metabolic activity as blood flow increases and ROS are produced by neuronal cells (38). The production of ROS occurs mainly in the mitochondria, and their increase could contribute to ageing (39).

A sedentary lifestyle is damaging for bodily health and cognitive and brain functions. Studies on physical activity in the elderly have shown that neurocognitive activity is enhanced by daily exercise (40). The benefits of physical activity are undeniable and clear, however, the exact mechanisms by which it benefits brain health are not completely understood.

The neurological effects of physical activity have been evaluated with magnetic resonance imaging (MRI) and neurocognitive measures (41). It seems that physical activity leads to an increase in neurotrophic factor, which helps to maintain brain volume and provide protection for neurons, and affects lipid transport and amyloid load, which can lower the risk of dementia and prevent the development of neurodegenerative diseases (42). However, it is still unclear if physical activity affects amyloid and tau protein metabolism that occurs in Alzheimer's disease.

The benefits of exercise were also found to be relevant in children, where physical activity has been correlated with improvements in attention and cognition (43). Regular physical activity in children has positive effects on brain structure and function, enhancing attention, learning, and memory.

Furthermore, physical activity is important to prevent obesity, which is associated with an increased risk of chronic diseases, including neurological disorders, such as dementia (44). Evidence shows that obesity is associated with cognitive deficits and functional and structural changes in the brain, as well as being a risk factor for the development of Alzheimer's disease (45).

CONCLUSIONS

When practiced regularly, moderate physical activity has many beneficial effects for the body and can help prevent the onset of vascular, inflammatory and autoimmune, and neurological diseases. In modern times, life is often sedentary which can be harmful to health, and exercise should be stressed as an important habit to maintain health of the entire body, including the brain. Further studies should continue to clarify the mechanisms by which physical activity affects the immune and neurological systems.

Conflict of interest

The authors declare that they have no conflict of interest.

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CARDIAC AND CIRCULATORY PARAMETERS IN THE TREATMENT OF CEREBRAL EDEMA WITH OSMOTIC DIURETICS

A. Pellati*

Department of Translational Medicine, University of Ferrara, Ferrara, Italy.

Correspondence to:
Dr. Agnese Pellati,
Department of Translational Medicine,
University of Ferrara,
44121 Ferrara, Italy.
e-mail: agnese.pellati@unife.it

ABSTRACT

Cerebral edema can occur following harmful insults to the brain such as hemorrhage, stroke, and mechanical trauma, and can lead to a state of coma. The infusion of osmotic diuretics is considered a valid method of therapeutic treatment. These treatments are intended to reduce intracranial pressure. Mannitol is one of the osmotic substances which is often used in the treatment of edema, although the side effects must be taken into account. This article reports the effect of mannitol in patients in coma due to acute cerebrovascular insufficiency and any cardiovascular and renal alterations.

KEYWORDS: *stroke, hemorrhage, edema, mannitol, trauma, cardiovascular*

INTRODUCTION

Cerebral edema can occur in conditions of traumatic brain injury, cerebral hemorrhage, subarachnoid hemorrhage, brain tumor, and ischemic stroke, and can be relieved with an infusion of various hypotonic solutions (1). For many years, the use of osmotic diuretics has been considered one of the most valid methods for the treatment of cerebral edema (2). The objective of the administration of these drugs is to quickly, and for a short period, create an effective osmotic gradient between the vascular compartment and the edematous brain tissue. This allows for the movement of interstitial and glial fluids towards the vascular district, with a consequent reduction in intracranial pressure.

Among osmotic diuretics, mannitol is the most frequently used (3). In cerebral edema, mannitol may be helpful as a diuretic in the treatment of patients with untreatable edema and to increase urine flow by clearing debris from the renal tubules (4). The administration method currently considered most suitable consists of a venous perfusion of 20% mannitol solution at a dosage of 1g/kg of body weight to be carried out over a time span of 10-20 minutes.

While recognizing the validity and usefulness of this drug, we must remember a series of side effects resulting from its administration that have been described in the literature (5). Although allergic reactions have been reported to occur with mannitol treatment, they do not seem to occur more frequently than with the infusion of other macromolecular solutions (6). However, the most prominent side effects seem to be those affecting the cardiovascular system and among these, the most severe is undoubtedly circulatory overload, which can result in pulmonary edema (7). However, this danger was considered negligible given that the administration of mannitol in serious cardiac patients was not seen to lead to a single case of pulmonary edema in a large study (8). Experimental research demonstrated an increase in cardiac output that was presumably linked to a direct positive inotropic action on the myocardial fiber and/or to an indirect action

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mediated by the sympathetic nervous system, or to increased left ventricular end-diastolic volume (8). Furthermore, continuous, or sub-continuous infusion of mannitol appears to be able to cause metabolic acidosis and renal failure (9). These complications certainly occur when plasma osmolarity is very high. However, the circulatory and the renal side effects would require more careful investigation, given the important clinical implications that may be linked to them (10). Both one and the other can be promptly treated and/or partially prevented, provided that their onset is known with certainty. With this study, we attempted to clarify whether the administration of 20% mannitol in comatose patients due to acute cerebrovascular insufficiency could cause dangerous cardiovascular changes or could give rise to hyperosmolarity, which is harmful to the renal system.

METHODS

Osmotic diuresis with mannitol was used to treat cerebral edema in 45 patients in coma due to acute cardiovascular failure. 27 patients were female and 18 were male, with an average age of 62 years. The anamnesis showed 26 patients were affected by arterial hypertension, 7 were affected by diabetes mellitus, and 6 patients had experienced an episode of transient ischemic attack (TIA) in the previous years. 2 patients had electrocardiographic signs of previous myocardial infarction. The study was approved by the institutions' local committee and patients gave their informed consent.

All patients came experienced problems of ventilatory failure. After providing immediate ventilatory assistance, we proceeded with cannulation of the subclavian vein via the subclavicular route, with monitorization of the central venous pressure (CVP), the electrocardiogram (ECG), and blood pressure (BP).

In 9 patients, upon admission it was necessary to rapidly administer diazoxide venously, in order to reduce dangerous levels of blood pressure. The degree of coma was assessed according to the Plum and Posner method. The cerebrospinal fluid (CSF) pressure was monitored in only 6 patients by positioning an intrathecal catheter. In these 6 patients, mannitol administrations were carried out coinciding with increases in CSF pressure. In the other cases, the criterion followed was purely clinical based mainly on repeated neurological examinations and observations of the ocular fundus.

Before initiating the mannitol infusion, a blood sample was taken to determine the parameters reported in the table below (Table I). These samples were repeated 5/10/15/20/30/60 and 90 minutes after the start of the infusion. Urine was also collected to control both the water balance and to study the parameters expressed in Table I. The 20% mannitol solution was administered by venous infusion at a dose of 1 g/kg of body weight. The duration of administration was 10 minutes in 16 patients (group 1) and 20 minutes in the other 29 patients (group 2). It should be noted that the mannitol infusion was started after at least 15 minutes of stable blood pressure values.

Table I. *Blood and urinary parameters studied.*

Blood parameters:	Plasma osmolarity, Na, K, Ca^{2+}, Blood sugar, Cytometric blood count, Hematocrit, Arterial gas analysis
Urinary parameters:	Electrolyte balance (24 hours), Na, K, Ca^{2+}, Osmolarity

RESULTS

Blood pressure significantly decreased in all patients during the rapid infusion of mannitol. The mean arterial pressure (MAP) in the first group of patients decreased on average by 19 +/- 2 mmHg and by 16 +/- 5 mmHg in the second group (+/- SE). Diastolic blood pressure had a greater percentage reduction than systolic blood pressure. The greatest reduction in almost all patients occurred on average after 6 +/- 2 minutes from the start of the infusion of the osmotic diuretic in the first group and after 9 +/- 3 minutes in the second group.

Gradually and progressively, the MAP values reached the baseline values after 25 +/- 5 min from the moment coinciding with the lowest value of the MAP in the first group, and after 20 +/- 7 min in the second group. In patients treated with diazoxide (a molecule structurally related to thiazide diuretics and characterized by the ability to activate potassium channels) before the start of mannitol infusion, the variations in MAP were completely comparable to those of the other patients.

No statistically significant changes in heart rate were observed. During the second half of the mannitol infusion, CVP increased, although not significantly. Electrocardiographic alterations were recorded in 23 patients (electrocardiogram: long QT; flattened diphasic T; above sub-level St; supraventricular extrasystoles). These alterations were already present before the start of treatment in 60% of patients. The highest peak of plasma osmolarity behavior was always recorded after the first half of the infusion (5 min in the 1st group and 10 min in the 2nd group). The blood gas variations were not significant in the two groups of patients.

It is interesting to underline a slight reduction in PO_2 values in over half of the patients during and immediately after the infusion. The variations in Na, K, and Ca^{2+} in the blood (although not important for our study) had a statistically significant duration in relation to the infusion period of the osmotic diuretic. The hematocrit value underwent a progressive reduction during the infusion which was slightly delayed compared to the increase in osmolarity.

DISCUSSION

Although the initial values of BP and CVP were at the upper limits of normal, neither an increase in blood pressure nor signs of cardiovascular overload were observed, except in two anesthetized hypertensive patients. The rapid infusion of mannitol through a rapid increase in blood volume could have caused the feared circulatory overload, the most striking manifestation of which is pulmonary edema.

Instead, a reduction in arterial BP was documented in almost all patients and a non-significant increase in CVP after the second half of the infusion. The lowest MAP values preceded, albeit slightly in almost all patients, the moment in which the plasma osmolarity values progressively increased until reaching the highest levels, always after half the infusion time, in both the first and second groups. Subsequently, the osmolarity curve progressively returned towards lower values as water was drawn into the vascular district.

The decrease in systolic blood pressure could be explained by the vasodilatory action of mannitol (11). In fact, it has been experimentally demonstrated that mannitol directly, and/or through the effects of increasing plasma osmolarity, would cause significant vasodilation, especially in the vascular district of skeletal muscles (12). The decrease in peripheral vascular resistance of venous return and blood viscosity would be the main factors contributing to the reduction in BP (13). It is interesting to note that the lowest values of MAP and diastolic pressure precede the moment of the highest degree of plasma osmolarity (12). The high plasma osmolarity would probably lead to a release of chemical mediators capable of inducing district vasodilation responsible for the decrease in peripheral vascular resistance (14). The documented increase in cardiac output, secondary to the positive inotropic action of mannitol, would therefore not be sufficient to cancel the opposite effect of the reduction in peripheral vascular resistance, at least initially. Subsequently, the pressure gradually returns to baseline values thanks to a reflex vasoconstriction with the participation of some receptors located in the skeletal muscles and central nervous system (CNS) (15).

The feared circulatory overload was not observed in any case. However, in 50% of patients, although mechanical ventilation was kept constant, the PO_2 curve underwent a momentary and slight reduction. This could be justified by an alteration of gas exchange at the alveolar-capillary level caused by an increase in interstitial fluid (16).

The electrocardiographic alterations that were observed did not appear to be caused by mannitol as these appeared in more than half of the cases before the infusion of the osmotic diuretic (17). Furthermore, they appear to be due to the brain lesion responsible for the coma state (18).

CONCLUSIONS

In conclusion, we report that blood pressure significantly decreased in all patients of this study during the rapid infusion of mannitol. In fact, more specifically, the diastolic blood pressure had a greater percentage reduction than systolic blood pressure. Mannitol infusion caused cardiovascular side effects with electrocardiographic alterations in almost half of the patients treated.

Conflict of interest

The author declares that they have no conflict of interest.

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THE EFFECT OF EPIDERMAL GROWTH FACTOR ON RNA, DNA, ACID PHOSPHATASE, AND LACTIC-DEHYDROGENASE IN NEWBORN RAT SKIN

I. Simeonidou[1] and G. Caccianiga[2*]

[1] Department of Parasitology, School of Veterinary Medicine, Aristotle University, Thessaloniki, Greece;
[2] School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy.

Correspondence to:
Gianluigi Caccianiga,
School of Medicine and Surgery,
University of Milano-Bicocca,
Monza, Italy.
e-mail: gianluigi.caccianiga@unimib.it

ABSTRACT

Epidermal Growth Factor (EGF) works by binding with high affinity to its EGF receptor (EGFR) on the cell membrane. EGF stimulates intracellular calcium levels, and increases glycolysis and DNA and protein synthesis through the action of intrinsic tyrosine kinase activity of the receptor that initiates a signal transduction cascade. Injection of minute amounts of EGF into newborn rats produces hyperplasia of the epidermis with a marked increase in the protein and nucleic acid content per unit, along with phosphatase and lactic dehydrogenase in the injection area. The activity of a number of epidermal enzymes is also increased by EGF. In this study, the biological effect of EGF with a growth-stimulating activity on epidermal cells was investigated.

KEYWORDS: *epidermal growth factor, skin, hyperplasia, DNA, RNA, lactic dehydrogenase, acid phosphatase*

INTRODUCTION

Neutrophins (NTs) are protein molecules that regulate the organism at both the central nervous system (CNS) and peripheral levels (1). NTs include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4).

NT-3 is involved in CNS development by regulating the activity of synapses and the growth of nerve fibers and neurons. NT-3 belongs to the nerve growth factor (NGF) family and is encoded by the NTF3 gene. It has a similar amino acid sequence as NT-4 (2). BDNF is the most abundant NT in the CNS that can cross the blood-brain barrier (BBB) and can be delivered throughout the body. It has long been reported that the growth and differentiation of some cell types are directly influenced and regulated by specific growth factors.

Similar to NGF, Epidermal Growth Factor (EGF) is found in high concentrations in the salivary gland of the male mouse from where it can be extracted, purified, and cloned. EGF was discovered by Stanley Cohen in 1965, when he showed the first biological effect of this protein on newborn mice (3). EGF is a 6.045 Kd protein that is composed of 53 amino acid residues and three intramolecular disulfide bonds, which plays an important role in regulating cellular growth, proliferation, and differentiation. EGF stimulates the intrinsic tyrosine kinase activity through its receptor, initiating a signal transduction cascade with a series of cellular biochemical changes, such as increases in intracellular calcium levels,

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glycolysis, and DNA and protein synthesis, followed by cell proliferation (4). EGF also causes an increase in the expression of some genes, including the one coding for the EGF receptor (EGFR) (5).

EGF is one of the first growth factor protein families to be identified and characterized by its structure. It is a transmembrane protein tyrosine kinase composed of two units that is involved in the development of the epidermis in mammals, including humans (6). EGF plays an important role in regulating cell growth, proliferation, and differentiation, and acts by specifically stimulating the growth of skin epithelia and keratinization processes (7).

It has been reported that EGF injections in newborn animals caused precocious eyelid opening (after 6 days instead of 14 days) due to an enhancement of epidermal growth and keratinization (8). Subsequently, the same authors also demonstrated a direct growth-stimulating effect on epidermal cells (8).

Acute ischemic kidney injury induced in rodents can also cause the release of EGF after 24 hours, due to the serine protease that cleaves the EGF precursor. Furthermore, EGF is present in platelets, macrophages, urine, saliva, milk, and plasma, and is capable of stimulating the metabolic effects of the body. The injection of small quantities of EGF produces the rapid growth of all skin epithelium and marked thickening of the keratin state (9).

In this study, the effect of EGF on the synthesis of nucleic acids, proteins, and some enzymatic activities of the epidermis was studied.

MATERIALS AND METHODS

Newborn rats were injected subcutaneously every day with EGF in aqueous solution, in the amount of 2 μg per gram of body weight for a duration of 5 days. 8 animals from the same litter were used for each experiment; 4 were used as controls and the other 4 were subjected to EGF treatment.

At the end of the treatment, the animals were euthanized, and the skin was immediately removed and stretched on special surfaces that were kept constantly cooled to 3-4° centigrade. Circular areas with a diameter of 2 cm were then sectioned from the skin and stretched using a specially constructed circular blade. Then, the separation of the epidermis from the dermis was achieved by incubating the sections of skin in a diluted solution of 2% trypsin in a phosphate crepe buffer for approximately 30 minutes.

After this treatment, the epidermis was separated from the underlying layer of dermis, carefully washed in physiological solution, and the thin sections were used for the various chemical analyses for the determination of nucleic acids. Each piece of the epidermis was extracted with 5% trichloroacetic acid at zero degrees centigrade and washed three times with alcohol ether mixture, and finally, with ether.

The prepared samples were then left to dry at a temperature of 50°C and then extracted again with 5% TCA (2 mm for each sample) in a thermostatic bath at 90°C for 15 minutes. Ribonucleic acid was determined in 0.2 cm square aliquots of this extract using the orcinol reaction for pentoses according to the method of Volkin and Cohen, measuring the D.O. at 660 mμ in a Beckman DU spectrophotometer. For each experiment, a standard curve was made in parallel with pure RNA (Sigma).

When calculating the results, a correction factor for the color produced by the DNA in the reaction with orcinol was considered, after determining that 7.4 μg of DNA gave a reaction equivalent to that of 1 μg of RNA. For the determination of DNA, the phenylalanine reaction for desose-pentoses was used according to the Disch and Schwarz method, modified by Volkin and Cohen, using aliquots of 1 cm^3 of the TCA extract. The optical density of the samples was read at 540 mμ, in a Beckman DU. For each experiment, a standard curve was determined using a DNA stock solution (Sigma). For the determination of the enzymatic activity, the epidermis sections were homogenized in 0.9% NaCl (0.5ml for each 2cm diameter section of skin). The homogenates were centrifuged for 5 minutes at 3000 RPM, and the supernatant was used for analysis. The enzymes examined included acid phosphatase and lactic dehydrogenase. For the determination of acid phosphatase, the method of Bessey et al. was followed and the method of Kornaberg was followed for lactic dehydrogenase. For the determination of dry weight and total nitrogen, whole sections of the epidermis (2 cm diameter) were used, which were freed from the dermis by trypsinization, according to the Kjeldahl method.

RESULTS AND DISCUSSION

The injection of the growth factor EGF in the doses indicated above produced a rapid response of the skin epithelia as soon as the seventh day of treatment, due to the early eruption of the incisor teeth and the early opening of the eyelid fissures. Both these phenomena were due to the keratinization of the respective lining epithelia. At histological examination, the hyperplasia of the skin in the treated animals appeared evident and marked everywhere, as well as the hyperkeratosis. In the table, the results of RNA and DNA levels of the epidermis of the treated animals and the control

animals are reported. The values are expressed in terms of μg/unit of area, with area as a perfectly circular section 2 cm in diameter (Table I).

Table I. *Stimulation of RNA or DNA and acid phosphatase and lactic dehydrogenase in the newborn rat skin after EGF treatment.*

Control (untreated rats) (RNA μg/unit)	2.1 +/- 1.9
Control (DNA μg/unit)	1.0 +/- 0.8
Control (Acid Phosphatase U/ml/h)	4.5 +/- 2.4
Control Lactic-dehydrogenase (μM/ml/h)	7.3 +/- 4.2
RNA μg/unit of area (3.10 cm2) (EGF treated rats)	620 +/- 50
DNA μg/unit of area (EGF treated rats)	340 +/- 30
Acid Phosphatase U/ml/h (EGF treated rats)	19.5 +/- 2.5
Lactic-dehydrogenase μM/ml/h	32.5 +/- 3.1

As can be seen, treatment with EGF causes a significant increase in both RNA and DNA, and the ratio between the experimental mean value and the average control value is 1.33 for DNA and 1.31 for RNA. The increase in the dry weight appears to be even more significant. The ratio between experimental and control groups appears to be 1.65 while the percentage of nitrogen content remains unchanged.

Finally, the table shows the values of some enzymatic activities. It was observed that in the epidermis of the experimental animals, acid phosphatase and lactic dehydrogenase are constantly and markedly increased. The results of the present work demonstrate that the injection of EGF selectively stimulates the growth of the epidermis, confirming previous morphological observations (10). Therefore, when EGF (2 μg/g) is injected into the rat, there is a keratinization of the skin after 5 days, compared to the control group. The effect of EGF is reflected in a significant increase in the content of proteins and nucleic acids in the skin of the treated animals. This increase appears particularly marked when the values relating to the dry weight per unit area are considered. This is due to the abundant keratinization observed in the animals.

CONCLUSIONS

In conclusion, the subcutaneous injection of small doses of EGF strongly stimulates the processes of synthesis and growth of the epithelial cells of the skin. The mechanism through which this effect occurs remains unclear, and clarification could help contribute to the understanding of processes that regulate cellular growth and differentiation (11).

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

POLLEN ALLERGY AND THE CNS

M. Di Gioacchino*

Center of Advanced Science and Technology (CAST), G. D'Annunzio University, 66100 Chieti, Italy.

Correspondence to:
Prof. Mario Di Gioacchino,
Center of Advanced Science and Technology (CAST),
G. D'Annunzio University,
66100 Chieti, Italy.
e-mail: digioacchino@me.com

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INTRODUCTION

The immune system defends the body from foreign substances (antigens). In atopic individuals, the immune system can overreact to exposure to certain substances such as allergens present in the environment (especially in spring) or in foods or in drugs, which are normally harmless to most people. In atopic subjects, antigens bind to their receptors and cause an allergic reaction. Allergens are molecules that can be identified by the immune system and stimulate an immune response. Some people are allergic to only one substance, while others are allergic to many. Today, about a third of the US population suffers from allergy. Pollen can cause an allergic reaction once in contact with the eyes or if inhaled. Allergies cause the production of inflammatory cytokines and chemokines in the nose and sinuses, which enter the bloodstream and can affect many organs, including the central nervous system (CNS) (1). The allergic phenomenon causes the release of inflammatory mediators that play a role in the activation of sensory nerves that produces psychological effects (2).

DISCUSSION

Inflammatory mediators act on endothelial cells causing vasodilation and increased vascular permeability with exudation of plasma exudate. These reactions can cause headaches, mood changes, fever, and tiredness. Antihistamine medications are a standard treatment to relieve seasonal allergies. If therapy with antihistamines does not produce any effect, an alternative may be the use of specific immunotherapy with a vaccine. However, the new antihistamine drugs, called second generation, do not cause effects on the mechanism of action of acetylcholine, which is released on parasympathetic nerve fibers. Some of these fibers are sympathetic and innervate the sweat glands, adrenal glands, and vasodilatory fibers (3). Interestingly, it appears that individuals who suffer from severe allergies also appear to have higher rates of anxiety and depression.

The myriad of pollen that is produced in the spring season can be excruciating for atopic individuals, i.e., those who are predisposed to the allergic phenomenon (Table I). Allergy is essentially an exaggerated reaction of the immune system and is due to specific activators called allergens, including pollen. In the case of the common spring allergy, pollen is the classic allergen. Pollen includes a set of male genetic information that is released into the air by plants, to be delivered to the female organs of other plants.

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Table I. *Primary symptoms presenting in allergy.*

- Itchy eyes
- Watery or red eyes
- Stuffy and irritated nose
- Cough
- Wheezing
- Runny nose
- Sneezing
- Sore or swollen throat
- Chest tightness

Thankfully, a new drug is due to be released on the market which is capable of combating allergy that afflicts approximately 8% of men and 12% of women. Researchers have found markers close to a gene located on chromosome 5 which is closely involved with allergy. The gene almost encodes a protein belonging to the cytokine family called interleukin-4 (IL-4), which is responsible for the production of IgE-type antibodies produced by immune cells, B lymphocytes, and plasma cells. Since this gene is fundamental for allergic induction, blocking it and inhibiting IL-4 could provide great benefits by utilizing a mechanism that is different from all other drugs that are currently available to treat allergy (4). However, blocking IL-4 can inhibit the production of all antibodies, which are important for B cell reactions.

Recently at the congress of the American Academy of Allergy and Immunology, some scientists described a new type of engineered vaccine against allergies in animal experiments, which, with some modifications, could also be valid for humans (5). Unlike antiviral vaccines or those against bacterial infection that stimulate the body's immune response, this vaccine works by helping only the immune organs to be more tolerant and less reactive.

In recent research, some scholars have used genetically modified mice lacking the receptor for the IgE antibodies that trigger allergy. The receptor is nothing more than a specific protein capable of binding, in this case, the IgE antibody. By blocking or eliminating the receptor, for example with a drug, the allergic phenomenon does not occur, even after stimulation of the cell.

In recent biotechnological research, molecules are being tested that do not allow the formation of IgE antibodies and this would also help against allergies. Other researchers have highlighted that mast cells (MCs), which release the molecules responsible for allergic symptoms, can be induced to commit suicide or apoptosis. If these cells lack growth factors such as interleukin-3 (which are responsible for the maturation of MCs) the allergic phenomenon is inhibited. This suggests that proteins responsible for MC growth are fundamental for the development of allergy. Studies on these issues are currently underway and the scientific community will certainly take advantage of this research for the treatment of allergies. Most of the drugs available today include the ABC theory: Avoiding allergens, blocking histamine, and correcting immune abnormalities.

Antihistamine drugs can have a moderate antiallergic effect, but they do not solve the problem because histamine mediates the allergic reaction for only approximately 30% of cases. The intake of antihistamines, which can also be sold without a medical prescription, causes drowsiness, difficulty urinating, dryness of the oral system, and dizziness, phenomena which are accentuated with the intake of alcohol and decongestants. Some medications that are not histamine blockers can be helpful in relieving nasal congestion and sneezing, but their side effects may also include insomnia. Many anti-allergic drugs that are available with medical prescription, can also block histamine without drowsiness, but they can cause cardiac arrhythmia in some people.

Doctors recommend using over-the-counter medications such as eyewashes and antihistamines, but some people often need prescription medications such as topical antihistamines that prevent the degranulation of MCs that contain allergic molecules that help mucus form (6). When the allergy is very strong and particularly tedious, steroid drugs such as cortisone are often used, which are administered in the form of nasal sprays, but also by other routes in order to reduce the inflammatory phenomenon.

Recently, some scholars in the USA have recommended that subjects suffering from chronic allergies take steroids and antihistamines also in preventive form, because allergy can often activate or accentuate asthmatic phenomena with narrowing and inflammation of the airways. Historically, long-term treatments have involved a series of graduated injections of allergens to induce tolerance to them, but this method has not given the desired results. Therefore, the use of allergens in graduated doses is falling into disuse and antihistamine and steroid drugs appear to be more effective and better tolerated to combat allergies which reach their peak incidence in spring.

Inflammatory substances that cause allergic reactions may also affect the CNS and are implicated in the development of anxiety and depression, as well as the exacerbation of these conditions that are already present in atopic individuals. For example, allergies and the symptoms that accompany them may lead to elevated levels of the stress hormone cortisol.

Allergy symptoms cause distress for sufferers, interfering with social interactions and the sleep cycle, which can worsen already existing mental health conditions or cause anxiety.

CONCLUSIONS

During allergic reactions, the immune system overreacts to exposure to allergens present in the environment or in foods or in drugs. Allergy affects approximately one third of the US population, and new therapeutic drugs are eagerly awaited to assist in the treatment of this often-seasonal affliction that can also produce negative psychological effects and lead to mood disorders.

Conflict of interest

The author declares that they have no conflict of interest.

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