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IN THE BRAIN, VARIOUS INFLAMMATORY MEDIATORS CAN BE RELEASED THROUGH THE ACTIVATION OF MAST CELLS

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ABSTRACT

In humans, mast cells (MCs) are ubiquitous in tissues and express numerous surface receptors that allow them to respond to various stimuli and participate in many diseases, including allergies, inflammation, infections, and autoimmune and brain diseases. The activation of MCs in the brain can induce neuroinflammation with release of proinflammatory cytokines and chemokines and activates other compounds such as histamine and serotonin (5-HT), which play an important role in the central nervous system (CNS). The immediate degranulation of MCs leads to the production of histamine and 5-HT which contributes to the inflammatory process. Activated MCs release numerous neuroinflammatory molecules such as the cytokines tumor necrosis factor (TNF), IL-1, IL-6, vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ), and CXCL8, amongst others. The inflammatory effect of MCs can overlap with that of peripheral circulating monocytes, amplifying neuroinflammation and neurodegeneration.

KEYWORDS: *mast cell, neuroinflammation, brain, neurodegeneration, cytokine, chemokine*

INTRODUCTION

The immune system plays an important role in brain diseases. Immune cells are ubiquitous and therefore also reside in the meninges where they act as guardians to protect the body against microorganisms (1). In trying to defend the body, immune cells produce inflammatory molecules such as cytokines, metalloproteinases, arachidonic acid products, and other compounds, that mediate brain pathology (2). Mast cells (MCs) are immune cells that mediate innate immunity and acquired immunity. They are proinflammatory effector cells, that reside in high numbers within the central nervous system (CNS) and can play critical roles in the development of inflammation in many disorders (3). MCs are found throughout the body, including the brain. When they are activated in the brain, MCs release biological mediators such as cytokines/chemokines, leukotrienes, prostaglandins, and stored enzymes, all which play an important role in brain disorders (3,4).

Neuroinflammation is associated with neurological and cognitive effects with mechanisms that are still unclear. MCs can mediate CNS immune responses and play a role in neuroinflammation and in several neurological diseases such as Alzheimer's disease (AD) (5), multiple sclerosis (6), and Parkinson's disease (7).

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DISCUSSION

MCs are immune cells of bone marrow origin that are involved in the pathophysiology of many allergic and non-allergic diseases. Moreover, they participate in many pathological processes, including brain diseases and autoimmune diseases. MCs mediate brain damage in stress and neuropsychiatric disorders by releasing inflammatory mediators which can be of two types: those secreted immediately, such as proteases, and those secreted after a few hours, such as cytokines and chemokines (8).

MCs contribute to almost all aspects of neuroinflammation by releasing inflammatory mediators (9). The cytokines released by MCs that are the most reported to induce neuroinflammation are tumor necrosis factor (TNF), IL-1, IL-6, vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGFβ) (10). The chemokines CXCL8 and CCL2, 3, and 4 also participate in neuroinflammation (11). Some cytokines, such as IL-1, can have an autocrine effect by activating microglia through toll like receptor (TLR) 4 which amplifies neuroinflammation (12). Pro-inflammatory cytokines induce capillary permeability and leak, and vascular dilation in brain tissue, and activate several inflammatory genes. In diseases such as AD, MCs react to plaque formations by producing various cytokines and chemokines, facilitating the permeability of the blood-brain barrier (BBB) (13).

TNF is the only cytokine stored in the granules of MCs which can be released by degranulation immediately upon activation. In addition, TNF can be produced and secreted after several hours of protein synthesis. MC-derived TNF potently mediates the inflammatory reaction and sensitization of meningeal nociceptive receptors (14).

Microglia are immune cells that are similar to macrophages and are located in the CNS. Microglial cells are phagocytic immune cells that release a series of pro-inflammatory molecules, such as IL-1, TNF, and IL-6, when they are activated from endogenous or exogenous stimulus (15). Neuroinflammation and neurodegeneration can be amplified when the inflammatory effect of microglia overlaps with that of peripheral circulating monocytes.

MCs expose the TLR on their cell surface, which is capable of binding microorganisms with consequent cellular activation and an inflammatory response. Activated MCs immediately release (in seconds) preformed mediators such as histamine, protease, and TNF, and later (after hours) they secrete inflammatory cytokines and chemokines by protein synthesis (8) (Fig.1). Furthermore, MCs can also release arachidonic acid compounds, such as prostaglandin D2 (PGD2) and the leukotrienes C4, D4, and E4, which induce the slow reaction of anaphylaxis (SRS-A) (16). The microbial activation of the TLR on MCs leads to a series of cascading reactions, with the formation of NF-kB and the synthesis of pro-inflammatory cytokines such as IL-1 (17). MCs produce numerous vasoactive mediators and other molecules that induce inflammation. Many of these molecules can disrupt the BBB by promoting the passage of toxic molecules into the CNS (9). The release of inflammatory mediators from MC granules, such as histamine and serotonin (5-HT) (in rodents), occurs immediately after activation (18).

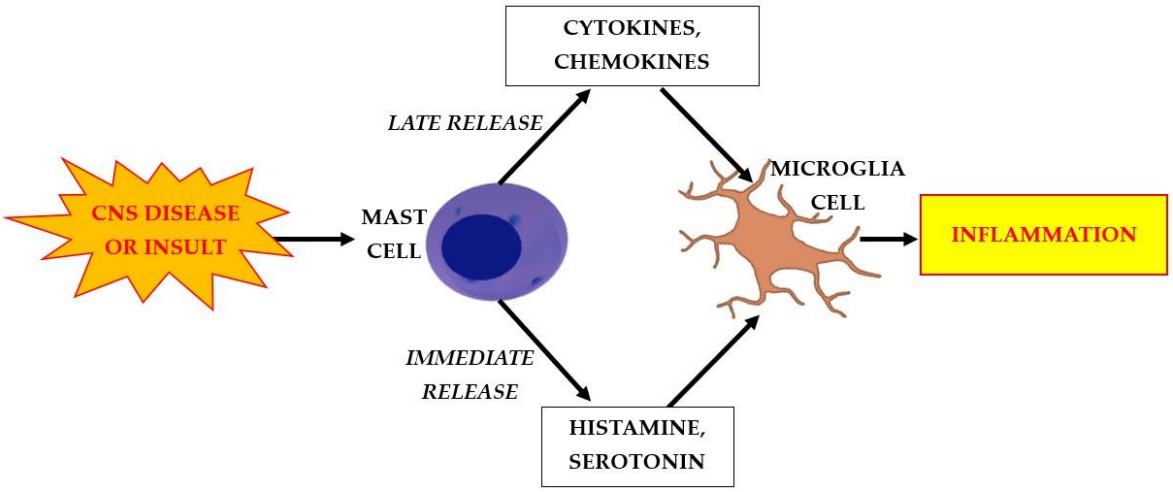

Fig. 1. *Disease or insult in the central nervous system (CNS) activates mast cells (MCs) to rapidly release (after seconds) preformed mediators such as histamine and serotonin (5-HT), and later (after hours), to secrete inflammatory cytokines and chemokines. This process results in a cascade of further reactions that activates microglia cells and results in inflammation.*

Histamine

Histamine is a biogenic amine that was first discovered by Windaus and Vogt in 1907 and is linked to the anaphylactic reaction. It is responsible for energy homeostasis, smooth muscle constriction, vasodilation, immunoregulation, and other functions (19). Histamine is ubiquitous in tissues and is contained in basophils, dendritic cells, T cells, platelets, neurons, and glial cells, and has important effects on the immune response and blood cells (20).

In MCs, histamine is rapidly synthesized and stored in specific granules from which it is subsequently released. Histamine is synthesized more slowly by immune cells such as T cells and is synthesized from the amino acid L-histidine via the carboxylation reaction (21). It is inactivated by histamine-N-methyltransferase or diamine oxidase, which is not found in the brain.

In the CNS, histamine is produced only in histaminergic neurons, has a half-life of approximately 25 minutes, and circulates in the body as a hormone that mediates diverse functions including vascular activity, cellular maintenance, metabolism, and inflammation (22). At the microglial level, histamine can be pro- or anti-inflammatory, depending on the homeostatic state. Histamine acts through four G-protein-coupled receptors: H1R, H2R, H3R, and H4R that are found in immune cells (23).

In the brain, H1R and H2R receptors are located on neurons and glia, while the H3R receptor is exposed only by neurons. H1R and H2R are found in numerous quantities in inflammatory cells such as MCs. The H2R mediates the inhibition of basophil degranulation, the innate immune response, and the generation of cytotoxic T lymphocytes (19). In addition, the stimulation of H2R in neutrophils and eosinophils inhibits the release of lysosomal enzymes and modulates the migration of these cells (24). The cytokines IL-1, IL-3, IL-8, and GM-CSF activate MCs to produce low quantities of histamine (25). After stimulation of H2R in lymphocytes, the release of histamine causes a lack of maturation and antibody production in B cells and plasma cells. The stimulation of H2R on T cells leads to the production of inflammatory cytokines.

Through the activation of the H1 receptor, histamine is responsible for 50% of prostaglandin generation. PGD2 is a potent vasoconstrictor which is completely released 5 minutes after MC activation of anti-IgE (26). Antihistamines, such as the anti-H2R, act as analgesics, likely by blocking 5-HT through Ca^{2+} channels (27).

Serotonin (5-HT)

5-HT is a neurotransmitter involved in many pathophysiological functions of the organism. It is contained in the granules of rodent MCs, but not in those of humans. 5-HT is involved in the gut-brain axis, a two-way interaction that leads to inflammation and other symptoms.

5-HT is related to the cellular immune system; In fact, drugs used to treat the effects of 5-HT also affect the immune system. Activated immune cells in the brain can mediate neuroinflammation and psychiatric diseases and 5-HT modulates the immune system through the regulation of immune cells, such as T cells, macrophages, dendritic cells, platelets, and MCs (28). The noradrenergic system is mediated by norepinephrine, which controls brain functions related to negative emotions. Norepinephrine can modulate the function of the peripheral immune system through 5-HT (29). In fact, the 5-HT 5-HT1A receptor promotes the proliferation of T lymphocytes, and blocking this receptor leads to an inhibition of cellular immunity and the synthesis of cytokines produced by T cells (30).

5-HT is found in many cells, including neurons, and the reduced expression of this neurotransmitter in the brain can lead to depression and other pathologies. 5-HT inhibitors can reduce the proliferation of CD4+ T lymphocytes and increase CD8+ suppressor cells, resulting in immunosuppression (28). These methods are useful in transplant rejection and autoimmunity. Furthermore, 5-HT is involved in the degranulation and migration of MCs, resulting in the secretion of pro-inflammatory cytokines. Thus, 5-HT mediates the immune response and inflammation, as well as CNS functions, mood, depression, food intake, anxiety, learning disorders, and other behavioral characteristics.

CONCLUSIONS

The activation of brain MCs can induce neuroinflammation with the release of proinflammatory cytokines and chemokines and can also activate chemical mediators such as histamine and 5-HT which play an important role in the CNS. However, these concepts reported here require further studies to clarify the mechanisms of action for the reactions involved. The inhibition of MC activation could represent an important therapeutic strategy for several neuroinflammatory diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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IDEAL ASSIMILABLE AND BIOAVAILABLE PROTEIN COMPOUND: SUPPLEMENTARY DIETARY PROTEIN HELPS CANCER PATIENTS

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ABSTRACT

Proteins are the building blocks of organisms that are essential for carrying out daily cellular biological functions and for leading a healthy life. They are composed of a series of amino acids linked together, and have various metabolic defence functions for the organism. In some pathological states, such as cancer, anorexia, bulimia, dysmetabolism, malabsorption, vomiting, etc., there may be a protein deficiency. In subjects affected by cancer who are undergoing therapy, altered metabolism and progressive weight loss are common complications associated with protein deficiency. The loss of protein in tissues results from hepatic dysfunction which compromises the body's ability to synthesize proteins. A high-protein compound containing essential amino acids, which is free of fat and sodium, could be indicated to compensate for protein deficiency, and can be useful for improving the quality of life for cancer patients.

KEYWORDS: *nutrition, protein, amino acid, metabolism, health*

INTRODUCTION

Proteins are composed of amino acids and are the basic building blocks of organisms that serve many purposes for the human body. They have various metabolic defense functions for the organism and act as structural support, catalysts, enzymes, hormones, and initiators of cell death. Due to their many functions, proteins are vital for the daily biological functioning of cells and for maintaining proper health.

Protein deficiency may be present in some pathological conditions including cancer (1), anorexia and bulimia (2), malabsorption syndromes (3), dysmetabolism, and vomiting (4). Additionally, when various amino acids are transformed, proteins exert catabolic effects that can produce nitrogenous residues. For patients who have certain pathologies such as liver or kidney disease and neurological diseases, these nitrogenous residues are damaging (5,6). Furthermore, professional athletes may require an increased amount of protein due to the elevated demands of energy they are subjected to. For these reasons, a high-protein compound which includes essential amino acids, and that is free from fat and sodium, could be used in cases of protein deficiency.

DISCUSSION

Proteins are made up of the four fundamental elements carbon, hydrogen, oxygen, and nitrogen, and are composed of a set of amino acids linked by a peptide bond, forming chains that can be of varying lengths. Proteins are

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macromolecules (also called peptides) that are made up of chains of amino acids linked by an amine leg of an amino acid and a carboxyl group of another amino acid with the loss of a water molecule (Fig.1).

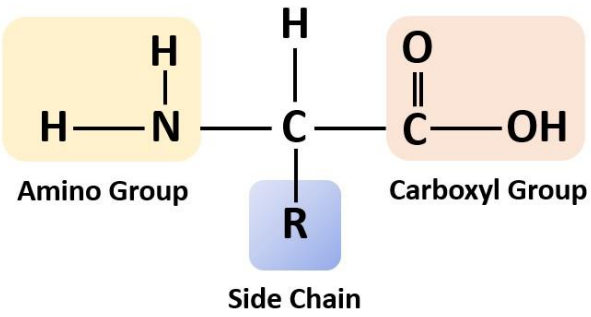

Fig. 1. *Formula of an amino acid, which is the functional unit that comprises proteins.*

Proteins participate in most functions of the organism including the transport of molecules, metabolic reactions, the synthesis and replication of DNA, and the response to stimuli (7). The different amino acid sequence characterizes the different proteins that fold and take on a specific structure which can be primary (the chain sequence of amino acids), secondary (α-helix shape), tertiary (three-dimensional unit of polypeptides), or quaternary (complex structure of polypeptide subunits). Fibrous structural proteins make up muscles, bones, and skin, defending the body from external insults, while globular proteins participate in cellular physiological functions and include enzymes, hormones, and antibodies.

Proper nutrition that is characterized by the correct consumption of nutrients in sufficient amounts, is the basis for maintaining the health of the body. Almost every food of animal or plant origin contains protein. However, the amino acid composition and the amount of protein varies amongst different foods (8). The highest levels of protein can be found in lean meats, fish, and legumes (9) (Table I).

Table I. *List of the main foods containing high levels of protein.*

- Lean meats such as beef, chicken, turkey, and lamb.
- Fish such as tuna, salmon, cod, sardines, mackerel, and mussels.
- Legumes such as lentils, chickpeas, beans, peas, edamame, and soy.

Essential amino acids are those which cannot be synthesized by metabolic intermediates in the human body, and therefore must be introduced into the body externally by diet. Proteins are very important in the diet because they participate in the development of immune defenses, the growth and renewal of tissues, allow digestion, and are fundamental for the transport of oxygen in the blood (10). Protein deficiency causes an energy deficit with fatigue and difficulty concentrating and learning, amongst other problems (8) (Table II).

Table II. *Some common dysfunctions related to protein deficiency.*

- reduced metabolic efficiency
- alterations in sleep and digestion
- accumulation of stress and anxiety
- fluctuations in body weight
- swollen ankles and feet
- dry and irritated skin with symptoms of premature aging (appearance of wrinkles)
- articular pains
- reduction in muscle volume
- hair loss
- bad mood
- muscle soreness
- ease of bleeding
- slow healing of wounds

In subjects affected by cancer, there is an alteration of the metabolism and progressive weight loss, with damage to organs and tissues and a decrease in energy (11). Anti-cancer therapies often do not improve the patient's weight recovery. Protein deficiency can lead to cachexia with loss of muscle tissue and nausea and vomiting (12), which can be aggravated by cancer therapies such as chemotherapy and radiotherapy (13).

Low protein plasma concentrations have been found in many disorders, including cancer (14). Tissue protein depletion appears to be common in patients with advanced cancer who have a loss of hepatic functions, including the ability to synthesize proteins (15). Therefore, administration of an oral supply of protein needs to and seems to be very effective in cancer patients. Ensuring nutritional requirements of protein in cancer patients is crucial to prevent and minimize negative health effects (16). The optimal intake of proteins and vitamins in cancer therapy can be of great help for the health and quality of life for patients.

In cancer patients with and without metastases, weight loss resulting as a consequence of low appetite must be counteracted. For this reason, the patient should consume foods with a high protein content. An effective therapy can include protein cocktails extracted from various foods such as meat, eggs, legumes, fish, and dried fruit, which is enriched with a set of multivitamins.

CONCLUSIONS

Therefore, we can conclude that in cancer patients and other pathologies that involve protein deficiency, the intake of protein from foods in combination with a high concentration protein supplement can be of great help in improving health and quality of life. A high-protein compound that contains essential amino acids and is free of fat and sodium could be indicated to compensate for protein deficiency.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

CANNABINOIDS FOR THE MANAGEMENT OF PAIN AND INFLAMMATION

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KEYWORDS: *cannabinoid, pain management, inflammation, opioid medication, CNS*

INTRODUCTION

The use of cannabinoids in the treatment of chronic pain is an important topic of discussion and research. Cannabis is effective in reducing chronic pain in many inflammatory diseases and improving quality of life. Patients with chronic pain often receive long-term opioid therapy, which places them at risk of opioid use disorder and overdose, and the use of medicinal cannabis in pain patients can reduce pharmacological treatment with opioids. Much scientific evidence reports that cannabidiol (CBD), a natural compound present in cannabis that is not addictive, reduces inflammation in patients with chronic pain mediated by microglia, which are more active in individuals suffering from pain (1,2). CBD could act on microglia by reducing cellular activity, which could lead to the inhibition of pain.

DISSCUSION

When inhaled through smoking, cannabis is effective in reducing chronic pain in many inflammatory diseases and improving quality of life. However, cannabinoids are not effective for all types of pain. The oral route of administration of cannabinoids appears to be more effective than smoking. The use of opioids to relieve pain can be ineffective and therefore new analgesic solutions must be sought. It is not exactly known how medical cannabis may affect opioid use in the state of chronic pain (3). Discovering how medical cannabis can influence opioid use and pain would have great scientific and social value. The question that arises is whether cannabinoids can help patients to reduce the opioid dosage and improve their health in acute and chronic pain. Interesting articles report that the use of medicinal cannabis in pain patients can reduce pharmacological treatment with opioids. This helps clarify the beneficial effect of medical cannabis on chronic pain in patients treated with opioids.

Much scientific evidence reports that CBD, a natural compound present in cannabis that is not addictive, reduces inflammation in patients with chronic pain mediated by microglia, which are more active in individuals suffering from pain (4). CBD acts as an immunomodulator and could act on microglia by reducing cellular activity and inflammatory compounds, which could inhibit pain. In fact, CBD has been shown to have anti-inflammatory properties such as IL-6 inhibition and the activation of anti-inflammatory pathways of microglia (5,6).

CBD acts through the endocannabinoid system and reacts, albeit with poor affinity, with a series of receptors involved in neuroinflammatory pathologies and epileptic seizures. By acting on other sites, CBD can regulate the activation of neuropeptides. Cannabis probably interacts with numerous molecular targets responsible for

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neuroinflammation and epilepsy, although it is still unclear how. This pain-relieving molecule attenuates excessive excitability. The TRPV1 cannabinoid receptor binds CBD, which results in the release of glutamate, increased calcium flux, and modulation of convulsions in epilepsy. The activation of CBD on its receptor leads to desensitization with an improvement of health. In addition, in neurons, CBD blocks calcium channels which play a key role in the release of neuropeptides. CBD can also block some opioid receptors involved in neuroinflammatory activities, including pain.

CONCLUSIONS

Cannabinoids are natural compounds that are a viable and safer alternative to the use of opioids and other synthetic pharmacological drugs in treating chronic pain and inflammation. CBD is a non-addictive compound that can reduce inflammation (including neuroinflammation) and pain by inhibiting the activity of activated microglia.

Conflict of interest

The author declares that they have no conflict of interest.

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