

Impact of the metabolic syndrome on the evolution of neurodegenerative diseases

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Metabolic syndrome (MetS) might be defined as the simultaneous accumulation of several functional changes that frequently occur in adults over 60 years of age (Gomez et al., 2018). The diagnosis of MetS requires the presence of three or more factors such as high body mass, type-2 diabetes mellitus (T2DM), dyslipidemia, and arterial hypertension, which increase the risk of cardiovascular diseases as well as neurological complications, as stroke and dementia (Dyken and Lacoste, 2018). Usually, these functional changes coincide and result in insensitivity for example hormones as leptin, adiponectin, and insulin (Dyken and Lacoste, 2018).

Insulin resistance is the critical piece in the appearance of metabolic dysfunctions, which stands out T2DM, in addition to relating to numerous injuries and pathologies in target organs (Taylor, 2012). Therefore, the sedentary lifestyle, genetic predispositions, alcohol abuse, bad eating habits, in addition to other environmental factors, increase the risk for obesity, favoring the appearance of MetS (Barazzoni et al., 2018).

Obese individuals have pictures of adipocyte hypertrophy and hyperplasia (Boleti et al.,

2020). Hyperplasia of adipose tissue leads to an increase in the differentiation of pre-adipocytes into adipocytes (adipogenesis) in which pro-inflammatory mediators or adipokines are generated (Boleti et al., 2020). The excess of free fatty acids in the blood plasma from adipocytes or the high intestinal inflow of fat from the diet activates a potent transcription factor, the nuclear factor kappa B (NF-κB), which is involved in the expression of several related genes the inflammatory response in adipose tissue and liver. Thus, it results in increased expression of pro-inflammatory cytokines, as tumor necrosis factor-α, interleukin (IL)-1β and IL-6, chemokines, prostaglandins, and adhesion molecules, acting on specific targets, which cause macrophage infiltration, promoting systemic inflammation and insulin resistance (Miller and Spencer, 2014).

Systemic inflammation associated with a high-fat diet increases the levels of circulating pro-inflammatory cytokines, resulting in central inflammation (Figure 1) (Boleti et al., 2020). These circulating pro-inflammatory cytokines migrate and cross the blood-brain barrier to the brain and hypothalamus, also resulting in the activation of the NF-κB in the glial cells and

hypothalamus and consequently leading to hypothalamic inflammation and leptin resistance. MetS can lead through risk factors for symptoms of depression, brain lesions of the white matter and cognitive dysfunction in the elderly (Boleti et al., 2020).

Alarmingly, the number of older adults with dementia is increasing worldwide (Blossom et al., 2018), and this pathology may affect mainly those with MetS (Ng et al., 2016). Additionally, individuals with dementia are at risk for cardiovascular disease (Blossom et al., 2017). Therefore, it becomes necessary to understand the interaction of the diseases that make up the MetS condition and how it causes the advancement in the neurodegenerative disorders, as well as strategies that can be taken to mitigate this painful process.

In addition to dementia, diseases such as depression and strokes, are recognized as clinical complications due to metabolic diseases, such as T2DM (Van Sloten et al., 2020). Although the process of neurological disorders related to T2DM is complex and multifactorial, microvascular dysfunction must be taken into consideration, which directly affects the brain, promoting mental disorders (Van Sloten et al., 2020). Moreover, arterial hypertension increases arterial stiffness, which raises blood flow and worsens lesions in target organs. However, arterial stiffness affects the microvasculature, which directly influences the brain diseases. Consequently, the chronic effects of AH can trigger encephalopathies due to global cerebral hypoperfusion, cerebral infarction with microinfarctions, among other deleterious conditions resulting from pressure overload. However, the individual with MetS suffers from all the pathological conditions mentioned above in an integrated manner, presenting a well-established inflammation.

Recent evidence shows that dysfunction in insulin signaling accompanied by chronic neuroinflammation are factors for cognitive decline and other brain disorders (Boleti et al., 2020). In this context, adiponectin, which is an anti-inflammatory cytokine produced by adipocytes, with actions to improve insulin sensitivity. In the brain, the action of adiponectin has been documented as an essential regulator of brain physiology, preserving and improving cognitive functions.

Thus, strategies that reduce the inflammatory profile of individuals with MetS appear to be efficient in metabolism control. The reduction of body weight is one of the effective strategies, which is associated with

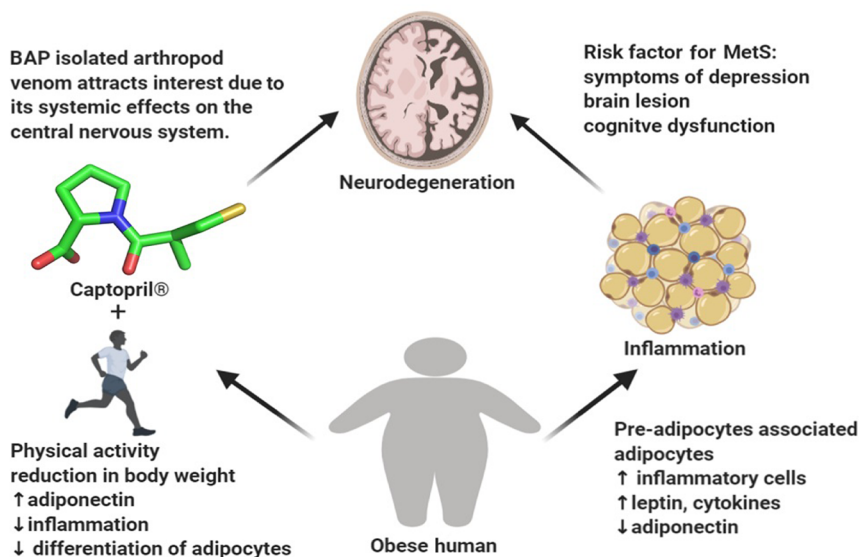


Figure 1 | Probable actions resulting from MetS.

Inflammation due to the accumulation of adipose tissue can cause dysfunctions in the nervous system. Otherwise, the use of medication and the adoption of a healthy lifestyle can reduce and even prevent neurodegeneration. BAP: Biologically active peptides; MetS: metabolic syndrome. This figure was created with Biorender.

the reduction of all risk factors, including the risk for T2DM. However, the reduction in body weight is better accompanied by changes in eating habits, such as reduced caloric intake and increased levels of physical activity, thus increasing energy expenditure. Other strategies, such as drugs to reduce body weight or control obesity, do not seem to achieve the same success in long-term treatment. Interestingly, regular physical exercise has numerous benefits for MetS, as glycemic control, reduced blood pressure, body weight control, and improved lipid profile. Additionally, exercise plays a vital role in preventing and reducing the progression of neuronal disorders, such as Alzheimer's disease. Thus, the regular practice of exercise training increases the process of neurogenesis and synaptogenesis, as it allows an increase in blood flow, improves insulin sensitivity, reduces the inflammatory profile, increases the concentrations of brain-derived neurotrophic factor, insulin-like growth factor, and adiponectin, as well as other hormones and second messengers. However, the practice of exercise, due to the beneficial effects, cannot suspend the prescription of drugs to control diseases related to MetS, but acting in a complementary manner according to the clinical picture.

Biologically active peptides (BAP) are molecules composed of amino acids with a molecular mass of up to 5 kDa found in several organisms demonstrating activity against bacteria, fungi, viruses, protozoa, cancer cells, and immunomodulatory. BAP therapy has shown promising results *in vitro* and *in vivo* for inflammatory and neurodegenerative diseases treatment, both presented the capacity antiinflammatory activity, as for presenting activity against pathogens resistant to drugs used in the clinical environment (Carniglia et al., 2017).

Given this aspect, the methodology denominated rational design optimizes through planning and organic synthesis, the construction of peptides analogous to bioactive molecules. For example, bioinspired in neurotoxins that lead to the development of drugs with high anti-inflammatory activity, but without the characteristic cytotoxic effect demonstrated by parental peptides (Groß et al., 2016).

The therapeutic areas that stand out in the use of peptides are areas related to metabolic and oncological diseases. The first stands out for the epidemic growth of obesity and T2DM, and the latter due to the increase in mortality and the need for new treatment options for chemotherapy. There is a movement in the pharmaceutical

industry towards rare diseases using isolated medicines, including peptides. A classic example of a drug developed based on the observation of the triggering of the systemic effect caused by pairing is Captopril® (capoten), one of the best selling drugs in the world and effective in controlling hypertension. This medicine has an oligopeptide as active ingredient - 10- (piroglutamil) rich in proline isolated from *Bothrops jararaca* snake venom (Hayashi and Camargo, 2005). Captopril inhibits competitively the angiotensin converting enzyme acting on angiotensin I to angiotensin II conversion producing peripheral vasodilation and lowering blood.

The BAP efficiency from isolated arthropod venom attracts interest due to their wide range of systemic effects on the central nervous system, acting to inhibit or stimulate specific structures, such as ion channels, receptors, and transporters of neurotransmitter. These actions induced analgesics, anxiolytics, anti-epileptics, or neuroprotectors, allowing treatment of numerous diseases (Boleti et al., 2020).

Because of this scenario, we believe that shortly, the rational planning of peptides with immunomodulatory activity will be an alternative in the development of a biotechnological tool with effectiveness in combating neurodegenerative diseases, further improving the chance of success in the treatment combined with exercise training.

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