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STRESS, DEPRESSION, AND DEMENTIA CONTRIBUTE TO NEURODEGENERATION

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ABSTRACT

Stress, depression, and dementia are disorders that affect one another and can lead to neurodegeneration. Chronic stress is often linked to chronic inflammatory diseases (sterile inflammation) such as cardiovascular disease, autoimmune diseases, and diabetes. Neurodegenerative diseases, caused by a dysregulation of the immune system, are mediated by inflammatory proteins, including cytokines and chemokines. Mast cells (MCs) are immune cells involved in inflammation and the mediation of stress through the secretion of chemical mediators and pro-inflammatory cytokines. Depression often occurs in adulthood and accompanies stress, leads to mood disorders, and involves the affective and cognitive spheres. Deficiency of brain-derived neurotrophic factor (BDNF), which affects neurons, is often responsible for depression. Depression and decline in cognitive function in the elderly lead to memory loss and dementia. In these brain diseases of advanced age, an inflammatory state often arises due to the activation of microglia and other innate immune cells, which release pro-inflammatory cytokines. The use of antidepressants could have a therapeutic effect by inhibiting inflammatory proteins. Further studies on these important topics related to the brain system will help clarify many aspects that are still obscure today.

KEYWORDS: *neurodegeneration, dementia, depression, stress, brain*

INTRODUCTION

Stress, depression, and dementia are contributing factors for neurodegeneration. In many clinical studies, it has been observed that stress is often implicated in neurodegenerative diseases, with the involvement of some hormone receptors showing an increase in the phosphorylation of abnormal proteins such as amyloid beta (Aβ) in Alzheimer's disease (AD), and activation of the kinase, resulting in inflammation (1, 2). With increasing age, 90 years or more, about 30% of people present senile dementia (3), and each year there are almost 10 million new cases worldwide (4). In the elderly, AD is the most common cause of dementia and has been estimated to account for roughly half the cases of dementia (3). Various risk factors such as social aspects, illnesses, genetic predisposition, malnutrition, and psychiatric factors can be involved in neurodegeneration (Table I). In this article, we will discuss the influences of stress, depression, and dementia on one another, and their contribution to the process of neurodegeneration.

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Table 1. *Important neurodegenerative disease risk factors.*

• Poor social class	• Hypertension
• Low level of education	• High blood cholesterol
• Low birth weight	• Sedentary lifestyle
• Brain damage and/or trauma	• Diet lacking in essential vitamins and minerals
• Cerebral vascular disorders	• Continuous contact with a polluted environment
• Hormonal dysfunction	• Depression
• Stress	• Dementia

Stress

Stress is the psychophysical response to excessive emotional, physical, and mental factors. The body responds to stress with psychological and physiological responses, which affect the body in different ways and levels of severity and can alter homeostasis (5). Chronic stress is a debilitating pathological state, and often manifests after trauma, leading to hyperexcitation, cognitive disorders, and mood and memory alterations. It can affect memory and has been correlated with reduced executive functioning (6), and in the elderly, chronic stress is often linked to senile dementia, a debilitating pathological state accompanied by hyperexcitation, cognitive disorders, and alterations of humor.

Long-term stress negatively affects the innate and adaptive immune systems and can result in chronic low-grade inflammation. Chronic stress is a risk factor for disorders such as metabolic dysfunction, chronic hepatitis, cardiovascular disease, autoimmune disease, diabetes, and obesity (7), diseases which impact the immune system, causing dysregulation and "sterile inflammation" (not induced by microorganisms) in which neuroinflammation contributes to neurodegenerative pathology (8). A better understanding of the immune and inflammatory pathogenetic mechanisms linked to stress should be of help in the search for new therapeutic strategies.

Often individuals with chronic stress have high levels of inflammatory markers, such as C-reactive protein (CRP), IL-6, TNFα, IL-1β, and the transcription factor nuclear factor kappa B (NF-κB) (9), and possibly, acute phase Aβ. In addition, pro-inflammatory cytokines such as TNF, IL-1β, and IL-6 can also be elevated in both peripheral blood and cerebrospinal fluid, leading to depression and other mental disorders (10-12). The cytokine IL-6 appears to be the one most involved in chronic stress, with a higher incidence in the serum of women with this pathology compared to men (11). IL-4, an anti-inflammatory cytokine produced by T lymphocytes that helps B cells to produce antibodies, appears to be decreased in chronic stress (13,14), and therefore unable to counteract the effect of pro-inflammatory cytokines.

Therefore, considering these observations above, we can deduce that inflammation constitutes a predisposing factor for chronic stress, and above all, involves innate immunity. The activation of inflammation occurs through danger-associated molecular patterns (DAMPs). These endogenous non-microbial molecules increase in chronic stress and mediate inflammation (15), whether it involves inflammasome or not (Fig.1). Acute and chronic inflammation can mediate neurodegenerative processes and therefore should be treated.

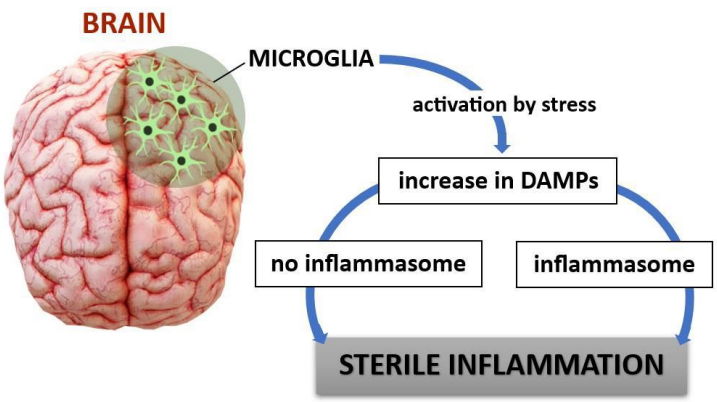

Fig. 1. *When activated by stress, microglia increase danger-associated molecular patterns (DAMPs), which can act with or without inflammasome to generate "sterile inflammation" in the brain.*

Several immune cells are involved in mediating stress, including mast cells (MCs). Allergic diseases, asthma, and dermatitis worsen with stress (Table II), so it is pertinent to think that MCs involved in these pathologies can mediate inflammation.

Table II. *Some symptoms which can aggravate stress.*

• Allergy	• Fatigue	• Itching	• Palpitations
• Anxiety	• Headache	• Myalgia	• Weakness
• Asthma	• Hypotension	• Pain	• Wheezing

In stress, neuropeptides are released and activate MCs to secrete both chemical mediators and pro-inflammatory cytokines. Neuropeptides such as substance P, neurotensin, and corticotropin, together with IL-33 released by MCs and macrophages, generate a stronger inflammatory state than these compounds alone (16,17). The inflammatory effects can be inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) which act by blocking the enzyme cyclooxygenase 2 (COX-2) induced by IL-β and/or TNF (18). Glucocorticoids are powerful anti-inflammatory and immunosuppressive agents that work by blocking inflammatory cytokines and can have a therapeutic effect in stress where cortisol levels have been shown to be below the physiological concentration (19).

Depression

Depression is defined as a sustained state of low mood accompanied by sadness and irritability, with altered brain physiology that can lead to bipolar disorder. Depression is a psychiatric illness that occurs in 10-15% of the population worldwide (29). It can be very serious and is associated with a higher number of suicides. The highest incidence of depression is seen between the ages of 18 and 25 and women appear to be the most vulnerable (21,22). There is no satisfactory cure for this disease and anti-depressant drugs are non-specific and come with unwanted side effects. There are various degrees of clinical depression, including endogenous, unipolar, and recurrent depression, which leads to mood disorders involving the affective and cognitive spheres.

Neurotransmitters such as serotonin (5-HT), norepinephrine, and dopamine are often used as therapeutic drugs with poor results. 5-HT is a neurotransmitter that derives from L-tryptophan and acts on synapses, and its deficiency can lead to depression (23). Psychosocial stress, such as social isolation, has also been linked to defective 5-HT functioning and can contribute to depression and anxiety disorders (24,25). Brain-derived neurotrophic factor (BDNF) is known to have effects on the nervous system and belongs to the neurotrophin family. BDNF affects memory by acting on synaptic connectivity, growth, and repair of neurons. Its deficiency at the hippocampal level causes effects of depression, which can be restored by raising BDNF levels through therapeutic interventions (26). BDNF injected into the rat brain increases 5-HT, dopamine, and norepinephrine levels by acting biologically on tyrosine kinase receptors (27).

Low-grade inflammatory processes, as well as immune system dysfunction, are involved in the pathogenesis of depression. The primary brain immune response induces microglia to produce inflammatory cytokines, such as IL-1, which raises body temperature and stimulates liver cells to produce CRP and other inflammatory mediators (9).

Dementia

Dementia is characterized by a decline in many cognitive functions such as memory loss, inability to carry out daily activities, inability to judge and criticize, decline in language, loss of autonomy, and behavioral disorders. It can be caused by brain disorders, such as AD and Huntington's Disease, and it increases exponentially with age. The activation of microglia leads to an increase in inflammatory cytokines that participate in this pathology. Both innate immune cells such as microglia and macrophages, and adaptive immune cells such as T and B lymphocytes, participate in chronic brain inflammation that may lead to dementia (28). The inflammatory state leads to deterioration of cerebral white matter and neuronal and glial damage, resulting in memory loss (29). Anti-inflammatory therapies can be used if the pathological state is not severe and may improve the state of dementia (30).

Depression is a risk factor for dementia and cognitive impairment (31). In fact, one study highlighted that after a diagnosis of depression, the risk of developing dementia within six months is 15 times greater (32). Experiments on rodent models have highlighted that therapeutic treatment with antidepressants can improve both anxiety and cognitive status (33,34). The improvement in depression after taking antidepressants could be attributed to an inhibition of the glia and/or a high neurotrophic function (35,36). The exact mechanisms of action of antidepressants are not yet clear, and some

authors have reported that these drugs, which target monoamines, are associated with increased rates of dementia (37,38). These contradictions probably occur because states of dementia can have different origins. Considering what is reported above in this paper, the number of researchers who recommend the use of antidepressants is greater than those who advise against it. Therefore, the use of antidepressants can reduce depression and related dementia.

CONCLUSIONS

In conclusion, depression, stress, and dementia are frequent in the global population and contribute to cognitive impairment and neurodegeneration. Psychological distress can occur in depression, anxiety, and chronic stress, and its symptoms can lead to dementia and predict neurodegeneration. The pharmacological therapies adopted today have unwanted side effects and are unsatisfactory. It is therefore necessary to increase clinical research to more effectively combat mental disorders that affect both social relationships and productivity, and lead to lower quality of life for sufferers.

Conflict of interest

The author declares that they have no conflict of interest.

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