Stress and inflammation: a detrimental combination in the development of neurodegenerative disease

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Chronic stress accelerates the appearance of some neurodegenerative disorders, such as Alzheimer’s disease and Parkinson’s disease. On this review we firstly, describe some human epidemiological studies that highlight the possibility that chronic stress could increase the incidence or the rate of incidence of Alzheimer’s disease and Parkinson’s disease. Secondly, we discuss the important role of inflammation in the progression and development of these neurodegenerative diseases. Finally, we try to justify the relationship between stress and inflammation with some experimental data. This work strongly suggests that chronic stress could be considered a key factor for the development of neurodegenerative diseases through microglial activation.

Keywords: stress; inflammation; neurodegenerative diseases


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Introduction

Stress could be simply defined as any disruption of homeostasis, whereas ‘stressor’ would be any of the myriads of internal or external challenges that cause this disruption [1-4]. Disturbed homeostasis initiates a series of events called the stress response or cascade; this well-choreographed response will involve the hypothalamic pituitary adrenal (HPA) axis that is in charge to restore homeostasis. Stress is a condition of human experience and an important factor in the onset of various diseases [5]. In general, it is considered that stress is not reduced only to the dramatic stressful events in our lives but rather to all those little daily problems that are capable of raising the activity of physiological systems sufficiently to cause a wear.

Exposure to stressful situations triggers the activation of two systems: the sympatho-adreno-medullary system and the HPA system [6]. The first leads to raise the levels of circulating adrenaline whereas the second run the release of corticosteroid hormones from the adrenal cortex. Corticosteroid hormones have the ability to cross the blood brain barrier owing to their lipophilic properties and
interact with two classes of receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) [7]. MR and GR have different affinity for corticosterone, whilst MR have greater affinity. GR show less attraction with the endogenous hormone. They also differ in their distribution; MR are located mainly within limbic regions (e.g. amygdala and hippocampus). On the other hand, GR are distributed throughout neurons and glia. Although stress can be beneficial in its acute phase, repeated and severe stressful stimuli produce adverse effects on neuronal functions, especially in those structures involved in stress response, such as hypothalamus, prefrontal cortex (PFC) and hippocampus (HC).

There are numerous studies showing how stress can accelerate cell aging, immune senescence and some age-related diseases, such as neurodegenerative diseases and osteoporosis among others [5].

Inflammation could be associated with the onset of some neurodegenerative disorders which involve different levels of inflammation. However, the response to inflammation is not equivalent in all brain structures; therefore, a direct relationship might not be well discerned. In this review we try to elucidate the possible relationship between stress and certain neurodegenerative diseases focusing on the coating effect of inflammation and stress as a key event in this process.

**Chronic stress is a risk factor for the development of neurodegenerative diseases**

Neurodegenerative diseases are a heterogeneous group of disorders that are chronic and progressive among other features. Most of these diseases, including Alzheimer’s disease (AD) and Parkinson’s disease (PD), represent a continuous challenge for medical research. They have increasing prevalence among population, generally characterised by a poor prognosis leading to a higher morbidity rate. There are very few effective treatments against them and none have shown the ability to completely remove the disease. Therefore, this group of neurological issues that represent a significant input of the human suffering, still remains as one of the most challenges in the clinic.

AD is the most common source of dementia among the population over 85, affecting 50% of people within this age [8, 9]. The brain of AD patients after death reveal evident cerebral atrophy affecting several learning and memory processing brain areas such as temporal, parietal and frontal cortex along with the hippocampus. AD involves a disruption in the synaptic transmissions which involve a decrease over time to a global impairment, characterized by the deposition of amyloid-β (Aβ) protein which forms extracellular plaques (amyloidosis), synaptic dysfunction and neuronal death [13, 14]. Many theories have been proposed to discern these mechanisms, including amyloid cascade, mitochondrial impairment, oxidative stress, inflammation, mutations in specific proteins, maintained response to injury or infection, and problems to keep regular brain maintenance along with the correct clearance of abnormal proteins. Taking into account the heterogeneity of the initial factors and the poor correlation between β-amyloidosis along with the degree of cognitive impairment in early stages of AD [15], it is highly unlikely to discern what are the most determinant factors involved in the onset and progression of the disease; in the 95 to 98% of patients with late AD development, this is particularly true. Furthermore, risk factors for increased Aβ deposition are also established AD risk factors (such risk factors include mutations in presenilins 1 and 2 as well as APP missense mutations and non-genetic factors such as old age). Moreover, chronic stress and other environmental factors may also be involved in accelerated AD pathogenesis [16-19]. It is interesting to mention among the first clinical cases describing a possible relationship between stress and AD, the case of a 60-year-old woman diagnosed with a progressive aphasia after severe psychological stress who finally developed dementia. Similarly, a 49-year-old woman was diagnosed with cognitive deficit after the loss of her father, whereas the cognitive abilities of a man began to deteriorate after losing all his properties. These cases enabled the association between a severe psychological stress event and the onset of cognitive deficit [20, 21]. Since then, many epidemiological studies have been carried out to study the relationship between distressing episodes and the clinical mental prognosis.

In 2003 Wilson and colleagues [16] carried out a study on the cognitive function of elderly members of the Priesthood in Chicago, examining the association of distress disposition with AD, cognitive impairment and analysis of AD pathology. During an average follow-up of 4.9 years, 140 individuals developed AD. Those individuals with high distress environment (90%) had two fold the risk of developing AD than those with a low distress disposition (10%). The outcome of the study showed that proneness to psychological distress is clearly a key event in AD, showing separate correlation with AD signs such as amyloid plaques and neurofibrillary tangles. A similar study [22] on a small population of monks and nuns from Greek and Cypriot monasteries provided further data that explained how less stress might not prevent the onset of dementia, but it delayed the appearance of symptoms. Moreover, after examining a sample of 1271 patients with dementia during 7 years, Tsolaki’s group described that most patients reported a history of distressing events (life-threatening diseases and death of a loved one) before the onset of dementia [23]. Another very interesting work studied the possible relationship between self-reported
PD is associated with an extensive loss of dopamine (DA) neurons projecting from the substantia nigra (SN) to the caudate and putamen (known as the striatum in rodents). While in most instances the origin of the disease remains unknown, some cases of this disorder are attributed to specific causes such as viral infection, manganese poisoning or genetic mutation. Recently, herbicides and pesticides have been investigated as causal agents. There is no clear evidence of a causal relationship between stress (and stress hormones) and PD. Nevertheless, an increasing number of data suggest that they could be an important risk factor in the pathogenesis. GR density is not equal in all brain structures, and interestingly is higher in regions such as the motor cortex, basal ganglia and cerebellum, which are involved in motor control [25, 26]. This makes these areas more susceptible to the effects of stress in both human [27] and rat [28, 29]. This is also observed in PD patients with a positive association between cortisol and gait deficits [30]. Several studies discuss how the stress may deteriorate the symptoms of PD patients. These individuals usually experience a worsening in their tremor after anxious or anger episodes [31]. Therefore, stress may exacerbate parkinsonian symptoms, but it still remains unclear if it is the source of the disease or not. Schwab and England [32] considered in 1966 emotional trauma as an agent involved in the onset of the disease showing comparable conclusions. They cited two specific cases. In one, an individual learned via telegraph that his son had been in a plane that was shot down; in another, a woman witnessed her husband being killed in a car accident. In both instances, symptoms of PD emerged within hours, although such signs had never been previously detected.

On top of that, the main cause of PD appears to be age. Failure on the mechanisms in charge of cellular repairs seems to be more evident in people over 55 years old [33]. However, it is probable that another risk factor in the late onset of PD is the susceptibility of DA neurons to insult. It is vital to highlight that dysfunctions in the stress response increase during the aging process. For instance the response of the HPA axis to stress show less efficiency keeping homeostatic conditions and switch to a hyperactive, as an organism ages, thus exposing brain cells to higher levels of glucocorticoids (GCs) for longer period of time [34], generating and microenvironment which affect brain cells during the aging process.

All these data support the idea that chronic stress might be considered as one important risk factor in the outbreak of AD and PD-like diseases [35].

Inflammation plays a central role in the development of neurodegenerative diseases.

The relationship between inflammation and neurodegeneration has been widely described in the literature. It has been shown the presence of plaques and tangles of AD by immunohistochemistry techniques, and a clear infiltration of reactive immune cells such as microglia among them, displaying an inflammatory scenario [36]. Along with these observations, the amyloid deposition event has been assessed in different neuroinflammation animal models [37]. A cytokine array study was assessed in order to detect APP expression and interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α) or interferon (INF)-γ were found to increase the levels of APP. It was also shown that cytokines have a direct link in the upregulation of β-secretase [41] (the rate-limiting and necessary enzyme to synthetize Aβ deposits) and Aβ formation [42]. Kitazawa and colleagues described that microglia became activated in a progressive and age-dependent manner in the brain of a transgenic AD model (3xTg-AD) mice [42]. This activation correlated with the onset of fibrillar Aβ-peptide plaque accumulation and tau hyperphosphorylation. When these animals were treated i.p. with lipopolysaccharide (LPS, which is known to increase inflammation in the central nervous system, CNS), they found a significant induction of tau hyperphosphorylation. The authors also described that this effect seemed to be produced by the activation of cdk5. The same study also showed that the increase in inflammation (microglia activation) exacerbated key neuropathological features such as tangle formation.

After the report of microglial cell with an activated phenotype [43-45], the cell loss in PD patients due to inflammation has been widely demonstrated. In fact, the presence of reactive microglia is always related with high levels of pro-inflammatory cytokines [46, 47]. There are several animal models aimed to show neuroinflammation, including those using 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA) or rotenone [48-52]. LPS is an active compound in the cell wall of Gram-negative bacteria that is responsible for the initiation of the bacterial infection response in eukaryotic cells [53, 54]. Sub-toxic doses of LPS exacerbated disease progression in an animal model of PD [55], supporting that brain inflammation may play a significant role in PD progression. Recently was shown how chronic users of non-steroidal anti-inflammatory drugs or cyclo-
oxygenase inhibitors had 50% less probability to develop idiopathic PD [56-58].

**Chronic stress enhances the sensitivity to inflammatory processes of the brain**

There are certain areas of the CNS with different susceptibility to LPS-induced inflammation. Our group was the first in show the specific neuronal death within the nigrostriatal pathway after LPS injection [59, 60]. In turn, other structures, including those related to AD, such as the PFC and HC, were significantly less affected by LPS [61-63]. The fact of the existence of special sensitivity of the dopaminergic neurons together with these findings, enable us to highlight the inflammation as a key event in the onset of nigro-striatal dopaminergic system degeneration and its possible implication in PD [52, 59-62, 64-70]. Nevertheless, those areas of the CNS which poorly responded to inflammatory stimuli and are undoubtedly involved in AD, make us hypothesize that the trigger of the neurodegeneration might increase their death rate under others specific circumstances. Therefore, we studied how some of those areas (PFC and HC) responded to LPS under chronic stress. In these new case scenario, both areas showed a significant increase in the inflammatory response along with neurodegeneration [62, 63]. De Pablos [62] showed that risk factors such as chronic stress significantly increase the inflammatory process in the PFC caused by LPS injection. There are several changes after LPS injections induced by chronic stress: microglial activation and proliferation (OX-6 marker) along with a significant increase in the levels of the proinflammatory cytokines TNF-α, IL-1β and IL-6, and a reduction in the astrocytes population. This activated profile was seen in the neuronal population, showing a greater loss of neurons (NeuN, a specific neuronal nuclei marker) in the stressed animals along with the loss of cells expressing glutamic acid decarboxylase-67 and NMDA receptor 1A mRNAs, which coexpressed with/in PFC GABAergic neurons. This stress-induced neuronal loss after LPS injection suggests a synergistic effect between stress and inflammation. Espinosa-Oliva [63] showed that in spite of HC is insensitive to strong inflammatory stimuli such as LPS injection [61], a significant increase in inflammatory signals appear when LPS is injected into animals that have been exposed under chronic stress protocol for 9 days. This effect is shown by activated microglia together with astrogliosis and a greater increase in the expression of the proinflammatory cytokines IL-1β and TNF-α, and in the neuronal and inducible nitric oxide synthases (iNOS), which are also synergistically involved in the inflammatory processes. Moreover, immunohistochemistry against NeuN showed 50% of CA1 pyramidal neuronal loss under theses experimental conditions, whereas FluoroJade B staining demonstrated the presence of apoptotic cells the CA1 area.

All these results support the idea of the importance of inflammation in both onset and progression in AD. Our contribution to this field is the addition of plaques and tangles formation as a first cause of inflammation, which could lead to the initiation of AD, and how this inflammation prolonged in time could turning into a main source of damage to the host tissue.

Moreover, in a recent study our group has shown that chronic stress enhances microglia activation along with the increase in mRNA expression of CD200, CX3CR1, monocyte chemoattractant protein-1 (MCP-1), IL-6, IL-1β, TNF-α and iNOS. These activated microglial cells have a pro-inflammatory phenotype since they colocalize with IKKβ, the inhibitor of the NF-κB.

These findings along with the fact that chronic stress also exacerbates death of nigral dopaminergic neurons after the injection of LPS [67], suggest a microglial priming state. When priming occurs in microglia or peripheral macrophages, these sensitized cells do not produce inflammatory or anti-inflammatory products, but if further stimulated they turn into a high inflammatory profile [71-77]. This priming effect is mediated by GC since the treatment with RU486, an antagonist of the GR, reversed all the parameters studied [62, 63, 67].

GCs are generally known as anti-inflammatory molecules, and indeed have wide variety of features that inhibit inflammation. Thus, it is hard to discuss that GCs increase inflammation under chronic stress, as has been perfectly made by Sapolsky’s group [78]. The outcome of GCs presence after treatment will be pro- or anti-inflammatory depending on their temporal exposition to immune challenges. Here, we try to summarize other results that also point out that chronic stress enhances or induces neuroinflammation. Stress and GCs (as dexamethasone) have been described to particularly disrupt the accumulation of glutamate, which seems to be produced through two different pathways: the increase of glutamate release and the decrease of clearance by the excitatory amino acid transporter in neurons and astroglia [79, 80]. These effects, along with others described on mitochondrial function [81], produced the overload of cellular calcium [82, 83] and could justify some of the harmful effects of GCs. Moreover, as we have described above, stress increases proinflammatory cytokines [84]. TNF-α increase produced by stress seems to be due to a direct effect through the activation of the TNF-α converting enzyme (TACE). Madrigal and colleagues [85] showed that the increase of TNF-α produced by immobilization stress was prevented by pretreatment with BB1101, an inhibitor of TACE activity. At the same time, the anti-inflammatory protective effect on dopaminergic neurons of the SN exerted by GCs through GR has been pointed out by Ros-Bernal and colleagues [86] who showed that GCs repressed the NF-κB
transcriptional activity essential for the inflammatory process that induces the degeneration of dopaminergic neurons. Conversely, the activation of NF-κB by stress has also been described [80]. In addition, we should not forget that chronic high levels of GCs compromise immune functions, in part by down regulating GR [87], suggesting that its protective effect could be compromised. In this case, the protective effect could turn out into a more inflammatory phenotype, with the final induction of apoptosis [88]. We suggest that GCs (i.e. dexamethasone) increase oxidative stress through the induction of MAO enzymes. Also, our group [69] has shown that dexamethasone -a potent synthetic member of the GC class of steroid hormones with anti-inflammatory properties- enhanced the dopaminergic neuronal death through the intranigral injection of thrombin -a serine protease with microglia-induced inflammatory features-; the damaging effect of dexamethasone was produced through the increased oxidative stress produced by the monoamine oxidase (MAO), since it was protected by MAO inhibition (tranylcypromine). The induction of MAO by GCs has been described [89, 90], and also the fact that this effect produced by dexamethasone in rat astrocytes was inhibited by the GC receptor inhibitor RU486 [91]. Moreover, dexamethasone was shown to produce reactive oxygen species that were directly involved in the toxic effects seen on different subset of brain cells [88]. This was counteracted by specific antioxidant compounds (as N-acetylcysteine and ascorbic acid) or enzymes (as superoxide dismutase and catalase), both in vitro and in vivo [92-94].

Conclusions

All this reviewed data remark that chronic stress must be considered as a crucial risk factor in the neurodegenerative processes and the development of AD and PD. This review also shows that chronic stress exacerbates microglial activation along with neuronal death after an inflammatory challenge in certain brain structures specifically involved in these neurodegenerative diseases. Therefore, new strategies to reduce the effect of stress on humans should be explored in order to get earlier prognosis and future targets for the treatment of some neurodegenerative conditions.

Conflicting interests

The authors declare that they have no conflicting interest.

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