Inflammation & Cell Signaling 2014; 1: e182. doi: 10.14800/ics.182; © 2014 by Rocío M. de Pablos, *et al.*
http://www.smartscitech.com/index.php/ics

REVIEW

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

Rocío M. de Pablos[1], Ana M. Espinosa-Oliva[1], Manuel Sarmiento[2], José L. Venero[1]

[1]*Departamento de Bioquímicay Biología Molecular, Facultad de Farmacia, Universidad de Sevilla. c/ Profesor García González, 2. 41012-Sevilla, Spain. Instituto de Biomedicina de Sevilla (IBiS)-Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla 41013, Spain*
[2]*Present address: Gray Institute for Radiation Oncology and Biology. Department of Oncology. University of Oxford, Oxford OX3 7LJ, UK*

Correspondence: Rocío M. de Pablos
E-mail: depablos@us.es
Received: May 19, 2014
Published online: August 14, 2014

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

To cite this article: Rocío M. de Pablos, *et al*. Stress and inflammation: a detrimental combination in the development of neurodegenerative disease. Inflamm Cell Signal 2014; 1: e182. doi: 10.14800/ics.182.

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 to two classes of receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) [7]. MR and GR have different affinity for corticosterone, whilst MR have great affinity GR show less attraction with the endogenous hormone. They also differ in their distribution; MR are located mainly within limbic regions (eg. 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 coacting 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 HC and the amygdala. AD involves a disruption in the synaptic transmissions which involve a decrease over time to a global impairment, characterized by the deposition [10-12] of amyloid-β (Aβ)-40 and -42 proteins into extracellular plaques (β-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

psychological stress in midlife and the development of late-life dementia in a population-based sample of females followed for 35 years [24]. The interest of these works lies in the fact that they indicated the possible relationship between long-term life stress (psychological stress) and the onset of dementia late in life. The conclusion is that there is a clear correlation between psychological stress in adult women and subsequent development of mental diseases, especially AD. All these epidemiological studies clearly show a direct link between chronic stress and the commencement of AD.

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 telegram 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 [40]. 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 primingoccurs 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.

Acknowledgements

This work was supported by grant SAF-2012-39029 from the Spanish Ministry of Economy and Competitiveness and P10-CTS-6494 (Proyecto de Excelenciaof Junta de Andalucia).

References

1. McEwen BS. Protective and damaging effects of stress mediators. New Engl J Med 1998; 338:171-179.
2. Miller DB, O'Callaghan JP. Neuroendocrine aspects of the response to stress. Metabolism 2002; 51:5-10.
3. Smith AD, Castro SL, Zigmond MJ. Stress-induced Parkinson's disease: a working hypothesis. Physiol Behav 2002; 77:527-531.
4. Lupien SJ, Fiocco A, Wan N, Maheu F, Lord C, Schramek T, *et al*. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 2005; 30:225-242.
5. Espinosa-Oliva AM, de Pablos RM, Villarán RF, Sarmiento M, Herrera AJ, Machado A. Proaging effects of stress: a review. Approaches to aging control 2010; 14: 33-54.
6. de Kloet ER, Joles M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci 2005; 6:463-475.
7. Joels M, Krugers H, Karst H. Stress-induced changes in hippocampal function. Prog Brain Res 2008; 167:3-15.
8. Masters CL, Beyreuther K. Alzheimer's disease. BMJ 1998; 316:446-448.
9. Iqbal K, Grundke-Iqbal I. Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention. J Cell Mol Med 2008; 12:38-55.
10. Mesulam MM. Neuroplasticity failure in Alzheimer's disease: bridging the gap between plaques and tangles. Neuron 1999; 24:521-529.
11. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science 2002; 298:789-791.
12. Rowan MJ, Klyubin I, Cullen WK, Anwyl R. Synaptic plasticity in animal models of early Alzheimer's disease. Philos Trans R Soc Lond B Biol Sci 2003; 358:821-828.
13. Kim JJ, Foy MR, Thompson RF. Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. Proc Natl Acad Sci USA 1996; 93:4750-4753.
14. Nitta A, Fukuta T, Hasegawa T, Nabeshima T. Continuous infusion of beta-amyloid protein into the rat cerebral ventricle induces learning impairment and neuronal and morphological degeneration. Jpn J Pharmacol 1997; 73:51-57.
15. Tanzi RE. The synaptic Abeta hypothesis of Alzheimer disease. Nat. Neurosci. 2005; 8:977-979.
16. Wilson RS, Evans DA, Bienias JL, Mendes de Leon CF, Schneider JA, Bennett DA. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology 2003; 61:1468-1469.
17. Wilson RS, Barnes LL, Bennett DA, Li Y, Bienias JL, Mendes de Leon CF, *et al*. Proneness to psychological distress and risk of Alzheimer disease in a biracial community. Neurology 2005; 64:380-382.
18. Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. Neuroepidemiology 2006; 27:143-53.
19. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, *et al*. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry 2006; 163:2164-2169.
20. Tsolaki M. Post-traumatic stress dementia: a new target for cholinesterase inhibitors. Neurobiol Aging 2004; 25:26-27.

21. Tsolaki M, Kounti F, Karamavrou S. Severe psychological stress in elderly individuals: a proposed model of neurodegeneration and its implications. Am J Alzheimers Dis Other Demen 2009; 24:85-94.
22. Tsolaki M, Pantazi C, Stiliou F, Aminta M, Diudi P, Karasoulas Kazis A, *et al*. Prevalence of dementia in Greek Orthodox Monasteries: the role of diet poor in lipids. Brain Aging 2003; 3:13-17.
23. Tsolaki M, Papaliagkas V, Kounti F, Messini C, Boziki M, Anogianakis G, *et al*. Severely stressful events and dementia: a study of an elderly Greek demented population. Psychiatry Res 2010; 176:51-54.
24. Johansson L, Guo X, Waern M, Ostling S, Gustafson D, Bengtsson C, *et al*. Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. Brain 2010; 133:2217-2224.
25. Ahima RS, Harlan RE. Charting of Type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. Neurosci 1990; 39:579-604.
26. Ahima RS, Tagoe CNB, Harlan RE. Type II corticosteroid receptor-like immunoreactivity in the rat cerebellar cortex: differential regulation by corticosterone. Neuroendocrinol 1991; 55:683-694.
27. Maki BE, McIlroy WE. Influence of arousal and attention on the control of postural sway. J Vest Res 1995; 6:53-59.
28. Metz GAS, Schwab ME, Welzl H. The effects of acute and chronic stress on motor and sensory performance in male Lewis rats. Physiol Behav 2001; 72:29-35.
29. Metz GA, Jadavji NM, Smith LK. Modulation of motor function by stress: a novel concept of the effects of stress on behavior. Eur J Neurosci 2005; 22:1190-1200.
30. Charlett A, Dobbs RJ, Purkies AG, Wright DJ, Peterson DW, Weller C, *et al*. Cortisol is higher in parkinsonism and associated with gait deficit. Acta Neurol Scand 1998; 97:77-85.
31. Schwab RS, Zieper I. Effects of mood, motivation, stress, and alertnesson the performance in Parkinson's disease. Psychiatr Neurol 1965;150:345-357.
32. Schwab RS, England Jr AC. Parkinson syndromes due to various specific causes. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology: disease of the basal ganglia. New York: Wiley; 1966:227-247.
33. Zigmond MJ, Abercrombie ED, Berger TW, Grace AA, Stricker EM. Compensatory responses to partial loss of dopaminergic neurons: studies with 6-hydroxydopamine. In Current concepts in Parkinson's disease research. Edited by Schneider JS, Gupta M. Toronto: Hogrefe & Huber; 1993:99-140.
34. Stein-Behrens BA, Elliot EM, Miller CA, Schilling JW, Newcombe R, Sapolsky RM. Glucocorticoids exacerbate kainic acid-induced extracellular accumulation of excitatory amino acids in the rat hippocampus. J Neurochem 1992, 58:1730-1735.
35. Smith J. Stress and aging: theoretical and empirical challenges for interdisciplinary research. Neurobiol Aging 2003; 24:77-80.
36. McGeer EG, McGeer PL. The importance of inflammatory mechanisms in Alzheimer disease. Exp Gerontol 1998; 33:371-378.
37. Guo JT, Yu J, Grass D, de Beer FC, Kindy MS. Inflammation-dependent cerebral deposition of serum amyloid a protein in a mouse model of amyloidosis. J Neurosci 2002; 22:5900-5909.
38. Buxbaum JD, Oishi M, Chen HI, Pinkas-Kramarski R, Jaffe EA, Gandy SE, *et al*. Cholinergic agonists and interleukin 1 regulate processing and secretion of the Alzheimer beta/A4 amyloid protein precursor. Proc Natl Acad Sci USA 1992; 89:10075-10078.
39. Hirose Y, Imai Y, Nakajima K, Takemoto N, Toya S, Kohsaka S. Glial conditioned medium alters the expression of amyloid precursor protein in SH-SY5Y neuroblastoma cells. Biochem Biophys Res Commun 1994; 198:504-509.
40. Blasko I, Marx F, Steiner E, Hartmann T, Grubeck-Loebenstein B. TNFalpha plus IFNgamma induce the production of Alzheimer beta-amyloid peptides and decrease the secretion of APPs. FASEB J 1999; 13:63-68.
41. Vassar R. The beta-secretase, BACE: a prime drug target for Alzheimer's disease. J Mol Neurosci 2001; 17:157-170.
42. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci 2005; 25:8843-8853.
43. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 1988; 38:1285-1291.
44. McGeer PL, McGeer EG. Glial reactions in Parkinson's disease. Mov Disord 2008; 23:474-483.
45. Klegeris A, McGeer EG, McGeer PL. Therapeutic approaches to inflammation in neurodegenerative disease. Curr Opin Neurol 2007; 20:351-357.
46. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 2009; 8:382-397.
47. Tansey MG, McCoy MK, Frank-Cannon TC. Neuroinflammatory mechanisms in Parkinson's disease: potential environmental triggers, pathways, and targets for early therapeutic intervention. Exp Neurol 2007; 208:1-25.
48. Cicchetti F, Brownell AL, Williams K, Chen YI, Livni E, Isacson O. Neuroinflammation of the nigrostriatal pathway during progressive 6-OHDA dopamine degeneration in rats monitored by immunohistochemistry and PET imaging. Eur J Neurosci 2002; 15:991-998.
49. Gao HM, Jiang J, Wilson B, Zhang W, Hong JS, Liu B. Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. J Neurochem 2002; 81:1285-1297.
50. Liberatore GT, Jackson-Lewis V, Vukosavic S, Mandir AS, Vila M, McAuliffe WG, *et al*. Inducible nitric oxide synthase stimulates dopaminergic neurodegeneration in the MPTP model of Parkinson disease. Nat Med 1999; 5:1403-1409.
51. Miklossy J, Doudet DD, Schwab C, Yu S, McGeer EG, McGeer PL. Role of ICAM-1 in persisting inflammation in Parkinson disease and MPTP monkeys. Exp Neurol 2006; 197:275-283.
52. Hernández-Romero MC, Delgado-Cortés MJ, Sarmiento M, de Pablos RM, Espinosa-Oliva AM, Argüelles S, *et al*. Peripheral inflammation increases the deleterious effect of CNS inflammation on the nigrostriatal dopaminergic system. Neurotoxicology 2012; 33:347-360.
53. Holst O, Ulmer AJ, Brade H, Flad HD, Rietschel ET. Biochemistry and cell biology of bacterial endotoxins. FEMS Immunol Med Microbiol 1996; 16:83-104.

54. Kielian TL, Blecha F. CD14 and other recognition molecules for lipopolysaccharide: a review. Immunopharmacology 1995; 29:187-205.
55. Godoy M, Tarelli R, Ferrari CC, Sarchi MI, Pitossi FJ. Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. Brain 2008, 131:1880-1894.
56. Chen H, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, *et al*. Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Ann Neurol 2005; 58:963-967.
57. Chen H, Zhang S, Hernán MA, Schwarzschild MA, Willett WC, Colditz GA, *et al*. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 2003; 60:1059-1064.
58. Esposito E, Di Matteo V, Benigno A, Pierucci M, Crescimanno G, Di Giovanni G. Non-steroidal anti-inflammatory drugs in Parkinson's disease. Exp Neurol 2007; 205:295-312.
59. Castaño A, Herrera AJ, Cano J, Machado A. The degenerative effect of a single intranigral injection of LPS on the dopaminergic system is prevented by dexamethasone, and not mimicked by rh-TNF-alpha, IL-1beta and IFN-gamma. J Neurochem 2002; 81:150-157.
60. Herrera AJ, Castaño A, Venero JL, Cano J, Machado A. The single intranigral injection of LPS as a new model for studying the selective effects of inflammatory reactions on dopaminergic system. Neurobiol Dis 2000; 7:429-447.
61. Kim WG, Mohney RP, Wilson B, Jeohn GH, Liu B, Hong JS. Regional difference in susceptibility to lipopolysaccharide-induced neurotoxicity in the rat brain: role of microglia. J Neurosci 2000; 20:6309-6316.
62. de Pablos RM, Villarán RF, Arguelles S, Herrera AJ, Venero JL, Ayala A, *et al*. Stress increases vulnerability to inflammation in the rat prefrontal cortex. J Neurosci 2006; 26:5709-5719.
63. Espinosa-Oliva AM, de Pablos RM, Villarán RF, Arguelles S, Venero JL, Machado A, *et al*. Stress is critical for LPS-induced activation of microglia and damage in the rat hippocampus. Neurobiol 2011; 32:85-102.
64. Herrera AJ, de Pablos RM, Carreño-Müller E, Villarán RF, Venero JL, Tomás-Camardiel M, *et al*. The intrastriatal injection of thrombin in rat induced a retrograde apoptotic degeneration of nigral dopaminergic neurons through synaptic elimination. J Neurochem 2008; 105:750-762.
65. Herrera AJ, Tomás-Camardiel M, Venero JL, Cano J, Machado A. Inflammatory process as a determinant factor for the degeneration of substantia nigra dopaminergic neurons. J Neural Transm 2005; 112:111-119.
66. Carreño-Müller E, Herrera AJ, de Pablos RM, Tomás-Camardiel M, Venero JL, Cano J, *et al*. Thrombin induces in vivo degeneration of nigral dopaminergic neurones along with the activation of microglia. J Neurochem 2003; 84:1201-1214.
67. de Pablos RM, Herrera AJ, Espinosa-Oliva AM, Sarmiento M, Muñoz MF, Machado A, *et al*. Chronic stress enhances microglia activation and exacerbates death of nigral dopaminergic neurons under conditions of inflammation. J Neuroinflammation 2014; 24:11-34.
68. Tomás-Camardiel M, Rite I, Herrera AJ, de Pablos RM, Cano J, Machado A, *et al*. Minocycline reduces the lipopolysaccharide-induced inflammatory reaction, peroxynitrite-mediated nitration of proteins, disruption of the blood-brain barrier, and damage in the nigral dopaminergic system. Neurobiol Dis 2004; 16:190-201.
69. Argüelles S, Herrera AJ, Carreño-Müller E, de Pablos RM, Villarán RF, Espinosa-Oliva AM, *et al*. Degeneration of dopaminergic neurons induced by thrombin injection in the substantia nigra of the rat is enhanced by dexamethasone: Role of monoamine oxidase enzyme. Neurotoxicology 2010; 31:55-66.
70. Villarán RF, de Pablos RM, Argüelles S, Espinosa-Oliva AM, Tomás-Camardiel M, Herrera AJ, *et al*. The intranigral injection of tissue plasminogen activator induced blood-brain barrier disruption, inflammatory process and degeneration of the dopaminergic system of the rat. Neurotoxicology 2009; 403-413.
71. Frank MG, Miguel ZD, Watkins L, Maier SF. Prior exposure to glucocorticoids sensitizes the neuroinflammatory and peripheral inflammatory responses to E. coli lipopolysaccharide. Brain Behav Immun 2010; 24:19-30.
72. Frank MG, Thompson BM, Watkins LR, Maier SF. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav Immun 2012; 26:337-345.
73. Frank MG, Watkins LR, Maie SF. Stress- and glucocorticoid-induced priming of neuroinflammatory responses: potential mechanisms of stress-induced vulnerability to drugs of abuse. Brain Behav Immun 2011; 25(Suppl 1):21-28.
74. Johnson JD, O'Connor KA, Deak T, Stark M, Watkins LR, Maier SF. Prior stressor exposure sensitizes LPS-induced cytokine production. Brain Behav Immun 2002; 16:461-476.
75. Perry VH. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain Behav Immun 2004; 18:407-413.
76. Smyth GP, Stapleton PP, Freeman TA, Concannon EM, Mestre JR, Duff M, *et al*. Glucocorticoid pretreatment induces cytokine overexpression and nuclear factor-kappaB activation in macrophages. J Surg Res 2004; 116:253-261.
77. Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun 2007; 21:259-272.
78. Sorrells SF, Caso JR, Munhoz CD, Sapolsky RM. The Stressed CNS: When Glucocorticoids Aggravate Inflammation. Neuron 2009; 64:33-39.
79. Leza JC, Salas E, Sawicki G, Russell JC, Radomski MW. The effects of stress on homeostasis in JCR-LA-cp rats: the role of nitric oxide. J Pharmacol Exp Ther 1998; 286:1397-1403.
80. Madrigal JL, Garcia-Bueno B, Caso JR, Perez-Nievas BG, Leza JC. Stress-induced oxidative changes in brain. CNS Neurol Disord Drug Targets 2006; 5:561-568.
81. Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, Falke C, *et al*. Dynamic regulation of mitochondrial function by glucocorticoids. Proc Natl Acad Sci USA 2009; 106:3543-3548.
82. Magarinos AM, McEwen BS. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement ofglucocorticoid secretion and excitatory amino acid receptors. Neuroscience 1995; 69:89-98.
83. Adachi N, Chen J, Liu K, Tsubota S, Arai T. Dexamethasone aggravates ischemia induced neuronal damage by facilitating the onset of anoxic depolarization and the increase in the intracellular Ca2+ concentration in gerbil hippocampus. J Cereb Blood Flow Metab 1998; 18:274-280.

84. Dunn AJ, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. Adv Exp Med Biol 1999; 461:117-127.
85. Madrigal JL, Hurtado O, Moro MA, Lizasoain I, Lorenzo P, Castrillo A, *et al*. The increase in TNF-alpha levels is implicated in NF-kappaB activation and inducible nitric oxide synthase expression in brain cortex after immobilization stress. Neuropsychopharmacology 2002; 26:155-163.
86. Ros-Bernal F, Hunot S, Herrero MT, Parnadeau S, Corvol JC, Lu L, *et al*. Microglial glucocorticoid receptors play a pivotal role in regulating dopaminergic neurodegeneration in parkinsonism. Proc Natl Acad Sci USA 2011; 108:6632-6637.
87. Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun 2007; 21:9-19.
88. Baker AF, Briehl MM, Dorr R, Powis P. Decreased antioxidant defence and increased oxidant stress during dexamethasone-induced apoptosis: bcl-2 prevents the loss of antioxidant enzyme activity. Cell Death Diff 1996; 3:207-213.
89. Manoli I, Le H, Alesci S, McFann KK, Su YA, Kino T, *et al*. Monoamine oxidase-A is a major target gene for glucocorticoids in human skeletal muscle cells. FASEB J 2005; 19:1359-1361
90. Youdim MB, Banerjee DK, Kelner K, Offutt L, Pollard HB. Steroid regulation of monoamine oxidase activity in the adrenal medulla. FASEB J 1989; 3:1753-1759.
91. Carlo P, Violani E, Del Rio M, Olasmaa M, Santagati S, Maggi A, *et al*. Monoamine oxidase B expression is selectively regulated by dexamethasone in cultured rat astrocytes. Brain Res 1996; 711:175-183.
92. Orzechowski A, Jank M, Gajkowska B, Sadkowski T, Godlewski MM, Ostaszewski P. Delineation of signalling pathway leading to antioxidant-dependent inhibition of dexamethasone-mediated muscle cell death. J. Muscle Res. Cell Motil 2003; 24:33-53.
93. Oshima Y, Kuroda Y, Kunishige M, Matsumoto T, Mitsui T. (2004) Oxidative stress-associated mitochondrial dysfunction in corticosteroid-treated muscle cells. Muscle Nerve 2004; 30:49-54.
94. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, *et al*. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res 2003; 92:81-87.