**Multi-author Review**
**Neuronal disorders**

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# Neuronal disorders: introduction

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Since the decade of the 50s of the previous century, medicine and surgery have improved in quality and quantity. As a consequence, the average lifespan of human beings has increased. Thus, a higher proportion of people over 70 are actually living in many countries, and a further increase of this senior population is expected in the future. Aging is the main risk factor for several neuronal disorders, and a high increase in the onset of some of these disorders, like Alzheimer's disease, senile dementia and Parkinson's disease, has taken place during the last 5 decades. This increase, too, appears set to continue in the future. On the other hand, there are other neurological disorders that appear at early ages that, thanks to improvements in medicine, now have a longer time from the beginning to the end of the disease. According to the World Health Organization, an estimated 37 million people worldwide currently have dementia, and Alzheimer's disease affects about 18 million of them [1]. Moreover, neurological disorders are not only a health problem, but also a familiar social and economic problem.

Some general theories suggest that neuronal disorders that appear in aged people could be the consequence of having aged neurons, since unlike other cells present in the human body, neurons of the central nervous system usually are as old as the human being in whom they are present. Other hypotheses suggest that independent of the nature of the neuronal disorder, many of these diseases could be initiated by common mechanisms involved in their pathological characteristics. For example, the disorders could be caused by loss of function of a protein due to mutation or to abnormal post-translational modifications, (phosphorylation, proteolysis, and so on). Later, an aberrant aggregation of those modified proteins could occur and promote a gain of a toxic function that may result in a lack of function (for example, synapsis loss) of the damaged neuron, followed by neuronal death. However, there is some discussion about how general this 'neurodegenerative hypothesis' is and about the effect of the aberrant aggregates (toxic or protective consequences) (see below) on neurons where they are present. On the other, different groups have suggested that oxidative damage could be one of the first steps in the development of disorders like Alzheimer's disease and Parkinson's disease.

In this multi-author review we will mainly comment on three neurodegenerative disorders: Parkinson's disease, Alzheimer's disease, and Huntington's disease, and on some disorders related to those diseases. In all of these disorders, some proteins are directly related to the pathology of the disease. These proteins are α-synuclein for Parkinson's disease; β amyloid precursor protein (APP) and tau protein in Alzheimer's disease; and huntingtin in Huntington's disease. Although more should be studied about the normal function of these proteins, it has been suggested that APP has a neuroprotective effect; that tau protein is a microtubule-associated protein that regulates the stability of neuronal (axonal) microtubules, and also may modulate axonal transport; that α-synuclein is a protein that can transiently bind to lipid membranes and can play a role in membrane-associated processes in the presynaptic terminal; and that huntingtin could act, among other functions, as a transcriptional cofactor. In pathological situations these proteins are modified. These modifications could involve mutations or post-translational modifications that will result in a conformational change of the proteins. In addition, in every case the modified proteins, or the

products resulting from their modification (like β amyloid peptide, which is a product of APP proteolysis), will polymerize. When that happens, they form aberrant aggregates, like Lewy bodies for α-synuclein polymers in Parkinson's disease; the two lesions found in Alzheimer's disease, senile plaques that are composed by aggregates of β amyloid peptides and neurofibrillary tangles, having as a major component phosphorylated tau; and finally the inclusion bodies formed by huntingtin aggregates in Huntington's disease. Depending on the pathology, these aggregates can be found in the extracellular space, in the cytoplasm, or in the nucleus. One question is whether the modifications in the proteins involved in the pathology of the disorders, or their aggregations could be involved in the neuronal dysfunction followed by neuronal death observed in these disorders. Indeed, it has become increasingly apparent that the morphological lesions long used by neuropathologists to confirm clinical diagnosis after death might provide an experimentally tractable handle for understanding causative pathways [2].

However, the fibrillar deposits that are found in postmortem diseased brains – for example, the amyloid plaques noted by Alzheimer, the Lewy bodies of Parkinson's disease and related diseases, and the nuclear inclusions of Huntington's disease – can be present in the brains of asymptomatic individuals and do not correlate to the severity of disease at time of death [3]. In fact, huntingtin aggregates appear to be neuroprotective during Huntington's disease development [4]. Another question is whether soluble monomers, oligomers, or larger aggregates are the most toxic species in the case of β amyloid pathology in Alzheimer's disease [5]. On the other hand, it cannot be excluded that in some cases aggregated misfolded proteins can be ubiquitinated and targeted for degradation by the proteasome, whereas in other cases, modified, unaggregated but misfolded proteins could be a bad substrate for the ubiquitin-proteasome pathway.

In any case, the study of the basic mechanism involved in the onset of neuronal disorders like Parkinson's disease, Alzheimer's disease and related tauopathies and Huntington's disease is of great interest for the development of therapeutical strategies for these disorders. In this multi-author review, we present articles on neuronal disorders such as Parkinson's disease (and other synucleopathies), on the analysis of the two main pathologies found in Alzheimer's disease, β amyloid pathology and tau pathology; on the analysis of other tauopathies, like Picks's disease, corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia with Parkinsonism linked to chromosome 17 [6]; on the description of some possible therapies for Alzheimer's disease; and on the characteristics of a less prevalent neuronal disorder such as Huntington's disease.

Tofaris and Spillantini describe the characteristics of α-synuclein, the main component of Lewy bodies, found in Parkinson's disease, and the effect of mutations in that protein that occur in some families with autosomal-dominant early-onset Parkinson's disease as well as the effect of post-translational modifications in the aberrant aggregation of α-synuclein. Among such post-translational modifications are those resulting from oxidative damage.

The article by Zhu et al. reviews the possible causes of oxidative stress in Alzheimer's disease. Oxygen radicals result in neuronal damage as a consequence of damage to mitochondria, or redox-active metals like iron and copper, or other factors. The review mainly focuses on damaged mitochondria, a characteristic of Alzheimer's disease, and deficiencies in several key enzymes of oxidative metabolism.

Tabaton and Tamagno deal with production of β amyloid peptide, the main component of the senile plaques found in Alzheimer's disease, through two sequential cleavages induced by β and γ secretases on APP. A possible molecular link between both secretases could be related to onset of oxidative stress. It is suggested that β amyloid peptide induces oxidative stress, which in turn increases the activities of β and γ secretases, which further enhances β amyloid production.

An article by Hernandez and this author describes alterations in tau, a cytoskeletal protein, that take place in Alzheimer's disease and in other dementias known as tauopathies. The tau pathology related to tau phosphorylation and aggregation, and their consequences in cell viability are reviewed.

After describing the characteristics of the components of the two major lesions found in the brain of Alzheimer's disease patients – beta amyloid peptide (a component of senile plaques) and tau protein (a component of neurofibrillary tangles) – Iqbal and Grundke-Iqbal review some developing pharmacological therapies for Alzheimer's disease, suggesting that inhibition of one of the aspects of tau pathology, its phosphorylation, could be a promising therapeutic strategy for treatment of the disease.

In the final article of this multi-author review, titled: 'Neuronal disorders', Ortega et al. discuss a possible mechanism for neuron toxicity that can occur in Huntington's disease. This mechanism may involve inhibition of proteasoma activity by intermediate aggregated forms of modified huntingtin, present in patients with Huntington's disease. Such a mechanism would impair the ubiquitin-proteasome system in Huntington's disease, which could promote neuronal dysfunction.

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