Can neurodegeneration be separated from neuropathological hallmarks of chronic idiopathic human neurodegenerative disease? A perspective from modelling!

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Abstract

Chronic neurodegenerative disease is characterized by extensive regional loss of neurons in the brain and neuropathological hallmarks in surviving neurones. Genetic modelling by overexpression of hallmark proteins does not produce extensive neurodegeneration, whereas genetic deletion of neuronal 26S proteasomes does, as well as some hallmarks of human disease.

Chronic neurodegenerative diseases including Alzheimer’s disease, dementia with Lewy bodies and Parkinson’s disease are characterized by the neuropathological features of deposits of so-called amyloidogenic proteins, including intraneuronal inclusions containing proteins such as hyperphosphorylated tau and α-synuclein and extraneuronal deposits of fragments of the Alzheimer precursor protein. Additionally, there is extensive regional neurodegeneration-neuronal death in all the diseases [1,2].

It is a curious fact that some 14 years of genetic modelling of chronic neurodegenerative disease by overexpression of normal or mutated versions of human amyloidogenic proteins has not produced widespread regional neurodegeneration, in spite of producing amyloid plaques and intraneuronal deposits of proteins, but not the intraneuronal inclusions characteristic of human disease! Most attempts at modelling disease have relied on mouse [3–5] or fruitfly [6] transgenesis. In the mouse there is scant evidence of neurodegeneration in regions afflicted in man: in the fruitfly there is evidence [6] transgenesis. Additionally, there is extensive regional neurodegeneration-neuronal death in all the diseases [1,2].

In humans, there is little knowledge of the relationship between regional neuronal death and the biogenesis of intraneuronal and extraneuronal amyloid deposits. Molecular neuropathological approaches are limited because of the obvious limitations of autopsy material. Since multiple biopsies are generally ethically not permitted, disease progression in the individual brain cannot be followed. Therefore it is not clear as to whether plaques and tangles trigger neuronal death and accompanying gliosis or whether neurons dying for other molecular reasons generate the neuropathological hallmarks of disease. The neuropathological investigations describe the situation in the brain that remains at death and does not show what happened to the neurons that have died; these cells are gone. The relationship between gliosis and neuronal death is similarly not clear. Gliosis may be a morphological response to neuronal demise or glial cells may proliferate to produce trophic factors that either promote neuronal death or protect neurons from death processes as well as triggering remodelling of neuronal connections to preserve vestiges of neuronal networks to preserve cognition and memory. In amyotrophic lateral sclerosis, non-motor neuronal autonomous contributions to cell death are supported by experimental evidence [7]. In this condition, evidence also exists that muscle cells can exert molecular cell survival influences on innervating motor neurons [8].

One difficulty is that the mechanism(s) of neuronal death are not well established. Although evidence for apoptopic processes have been documented, the precise events in the death of human brain neurons are not known [9]. For example, whether neuronal death is preceded by extensive dye-back of neuritic processes is unclear. The time taken for neurons to die is not known or whether neurons devoid of extensive connections can survive for prolonged periods. The clearance of dead neurons by glial cells is not fully characterized. There are also immunological and inflammatory responses involved in the elimination of dying neurons. The extent of compensatory neuronal reconnections involving synaptic plasticity to slow or preserve memory is not understood. The degree to which memory can be preserved by such compensations before the onset of clinical symptoms is also not known.

Neuronal survival is almost certainly orchestrated by complex intercellular neuron–neuron and neuron–glial...
trophy and cause cell death. Neurons may respond by tipping the balance between survival and death mechanisms, favoring neuronal death.

The diversity of the functions of protein ubiquitination in the cell, to rival protein phosphorylation, suggests that ubiquitin-based signaling responses and ubiquitin-dependent protein degradation by the 26S proteasome and selective autophagic systems are central to neuronal homeostasis [13]. Age-related malfunction of these systems, in predominately non-dividing neurons, may cause the formation of inclusions containing ubiquitylated proteins and trigger neurodegeneration. Experimentally, genetic ablation of a 26S proteasome regulatory ATPase gene and autophagy genes in the brain causes neurodegeneration [14–16]. While it would be inadvisable to claim that protein catabolic deficiencies are the only cause of human neurodegeneration, it is clear from mammalian genetic models that the inability to degrade proteins in brain neurons causes cell death (and inclusions resembling human Lewy bodies with 26S proteasome depletion) in contrast with the overexpression of so-called amyloidogenic proteins.

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### References


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