Intraneuronal amyloid-β accumulation in basal forebrain cholinergic neurons: a marker of vulnerability, yet inversely related to neurodegeneration

This scientific commentary refers to ‘Neuronal amyloid-β accumulation within cholinergic basal forebrain in ageing and Alzheimer’s disease’, by Baker-Nigh et al. (doi: 10.1093/brain/awv024).

Abnormal accumulation of intracellular hyperphosphorylated tau as neurofibrillary tangles and amyloid-β protein as extracellular senile plaques are two of the principal neuropathological features of Alzheimer’s disease. While most research in Alzheimer’s disease has focused on amyloid-β that accumulates in the extracellular space of brain parenchyma or in blood vessels of the brain, evidence from transgenic mouse models and autopsy studies of humans supports the hypothesis that amyloid-β may also accumulate within the cytoplasm of neurons (Gouras et al., 2012). How this occurs remains uncertain given that amyloid precursor protein (APP) is cleaved to generate amyloid-β at the plasma membrane and within endosomes, with subsequent release of amyloid-β into the extracellular space or accumulation within the lumen of endosomes either directly from endosomal cleavage or after reuptake from the extracellular space. Evidence is mounting that the neuronal cytosolic signal detected with immunohistochemistry is actually amyloid-β and not antibody binding to another protein, most notably APP. The evidence particularly favours amyloid-β in studies where attention has been paid to experimental design, such as that of Baker-Nigh et al. in this issue of Brain. While some amyloid-β antibodies clearly cross-react with APP, the ones used in this study, including an oligomer-specific antibody (Lambert et al., 2007), do not. That and complementary biochemical studies suggest that the reported cytosolic signals might well reflect amyloid-β, and in particular oligomeric amyloid-β.

Many of the previous studies of intraneuronal amyloid-β have focused on the neocortex or hippocampus, areas considered intrinsically vulnerable to neurodegeneration in Alzheimer’s disease, while less attention has been paid to subcortical neurons that project to the cortex, such as the cholinergic neurons of the basal nucleus of Meynert. Neurodegeneration in Alzheimer’s disease often, but not always (Murray et al., 2011), follows a stereotypical pattern that was recognized and conceptualized by Braak and coworkers as a staging scheme based upon the progressive accumulation of abnormally phosphorylated tau protein within topographically distinct neuronal populations (Braak and Braak, 1991). The Braak staging scheme has been validated in a number of clinicopathological studies of well-characterized patients across a span of cognitive functioning (Nelson et al., 2012). Recently, Braak and coworkers have drawn attention to early tau pathology in subcortical neurons, in particular those of the locus coeruleus, which project to vulnerable neurons in the allocortex, suggesting that these subcortical neurons may be affected before cortical neurons (Braak et al., 2011). These studies were presaged by those of Mesulam and co-workers who noted the presence of basal nucleus neuronal tau pathology before allocortical neurodegeneration (Mesulam et al., 2004).

In the present study, Baker-Nigh et al. (2013) do not address how intraneuronal amyloid-β accumulation relates to tau pathology in basal nucleus neurons, but instead focus on the possible contribution of amyloid-β to synaptic dysfunction, given that amyloid-β is hypothetically transported to presynaptic terminals via anterograde axonal transport. If this is true, one might predict that amyloid-β would accumulate at sites of axonal injury resulting from trauma or other acute white matter pathologies. However, it is APP and not amyloid-β that accumulates at axonal swellings following acute axonal injury. Gouras et al. (2010) proposed that intraneuronal amyloid-β plays its most important role in pathogenesis in the presynaptic cell and that it is locally generated in the synapse from APP. This would fit...
better with the large body of evidence showing that APP not amyloid-β is a cargo of axonal transport.

Neurodegeneration of basal forebrain cholinergic neurons is of great interest in Alzheimer’s disease, since cholinergic deficiency provides a viable, albeit symptomatic, therapeutic target. On the other hand, evidence would suggest that neuronal loss and significant cholinergic deficiencies in Alzheimer’s disease occur relatively late in the disease course (Davis et al., 1999), in contrast to their earlier involvement in other neurodegenerative disorders, such as dementia with Lewy bodies. The underlying mechanism of neurodegeneration of basal forebrain cholinergic neurons in Alzheimer’s disease is not known, although they are clearly vulnerable to neurofibrillary tangles. Baker-Nigh et al. (2015) also detected intraneuronal amyloid-β42 using immunohistochemistry and quantified amyloid-β42 in the cytoplasm by measuring optical density. They showed intraneuronal amyloid-β42 in young adults, as well as in elderly controls and patients with Alzheimer’s disease. Although it did not reach statistical significance, intraneuronal amyloid-β42 showed a trend for decreasing from young to old controls, and from old controls to Alzheimer’s disease. Oligomeric amyloid-β was also detected in young adults with biochemical methods, but it is not possible to know what proportion of this is derived from intraneuronal oligomeric amyloid-β. How intraneuronal amyloid-β of the basal forebrain might link to abnormal increases in phospho-tau and eventual neurofibrillary degeneration and neuronal loss requires further investigation.

The specificity of observed changes to large neurons of the basal forebrain was addressed by comparison with magnocellular neurons in the globus pallidus, which could be studied in the same sections, assuring that experimental conditions were identical in both neuronal populations. Baker-Nigh et al. (2015) argue that the long projections of basal forebrain cholinergic neurons make them intrinsically vulnerable to intraneuronal amyloid-β accumulation. Further anatomical studies addressing this issue would be of interest. For example, does intraneuronal amyloid-β differentially accumulate in other large neurons with long cortical projections, such as the magnocellular neurons of the lateral geniculate nucleus, which send long projecting axons to the primary visual cortex?

A curious finding in this study was that two individuals in their nineties, who performed in the superior range on neuropsychological tests (‘SuperAged’), had some of the lowest levels of intraneuronal amyloid-β in basal nucleus neurons (One case, Subject S2, had the lowest values of all those studied), comparable to those seen in Alzheimer’s disease and much lower than in healthier younger controls. These individuals seem to be resistant to possible detrimental effects associated with loss of oligomeric amyloid-β, and it would be of great interest to know if the SuperAged were individuals with extensive cortical amyloid deposits, similar to those seen in Alzheimer’s disease and much lower than in healthier younger controls. Unfortunately, information about the degree of amyloid deposition and neurofibrillary pathology was not included in the report for the SuperAged, or for that matter, for the patients with Alzheimer’s disease or the young controls.

Dennis W. Dickson and Melissa E. Murray
Department of Neuroscience, Mayo Clinic,
4500 San Pablo Road, Jacksonville,
FL 32224, USA

Correspondence to: Dennis W. Dickson,
E-mail: dickson.dennis@mayo.edu
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