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Ageing of the brain

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Abstract

The brains of individuals who are cognitively normal show age-related changes that include an overall reduction in the brain volume and weight and enlargement of the brain ventricles. These changes are partly the result of nerve cell loss but accurate estimates of neuronal loss are notoriously difficult to make. There is loss of synapses and dendritic pruning in the aged brain but in selected areas rather than globally. Neurofibrillary tangles and senile plaques are the neuropathological hallmark of Alzheimer's disease in which they are more abundant and widespread than in the brains of intellectually intact elderly people. Alzheimer's disease has, therefore, been regarded as accelerated brain ageing, however, since there is a strong genetic contribution to developing the disease it implies that it may not be the inevitable, even if frequent, consequence of old age. The interplay between genetic and environmental factors probably determines the degree of pathological brain ageing and whether or not individuals develop dementia.

Keywords: Alzheimer's disease; Ageing; Neurofibrillary tangles; Senile plaques; Amyloid

1. Cognitive performance in ageing

Cognitive performance declines with increasing age in the elderly and a question that has taxed numerous neuroscientists is to what extent the decline is the consequence of 'normal' or non-pathological ageing as opposed to neurodegenerative disease, of which Alzheimer's disease is the most common. A recent study has re-examined this issue and also investigated if possession of apolipoprotein E4 (ApoE4) is a contributory factor since ApoE4, as opposed to ApoE2 or ApoE3, is a genetic risk factor for Alzheimer's disease (Mayeux et al., 2001). According to this study, memory declined over time in a large sample of healthy elderly but there was no significant loss of visuospatial/cognitive function or language, both of which are affected in Alzheimer's disease. Possession of an ApoE4 allele, however, resulted in a more rapid decline, which implies that ApoE is important for maintenance of normal brain function in addition to any specific role in Alzheimer pathogenesis. Mice in which the endogenous ApoE gene has been knocked-out but transgenic for human ApoE4 have also been shown to perform worse in several behavioural tests than those transgenic for ApoE3 (Raber et al., 1998). This confirms that genetic factors probably play a role in non-pathological functional decline of the brain and it is likely that other genes influencing age-dependent cognitive decline will be identified. Envi-

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ronment too seems to be a factor since poor education has been reported to result in accelerated memory decline and dementia (Schmand et al., 1997).

2. Anatomical changes in the brain associated with non-pathological ageing

Autopsy studies and more recently magnetic resonance imaging have shown that at a gross level, there is a decrease in brain volume and weight in individuals over the age of 60 years. The volume loss is accompanied by increases in ventricular volume and other cerebrospinal fluid (CSF) spaces. The brain regions most affected are the hippocampus and frontal lobes. Over the age range of 30–90 years, the volume losses are 14% in the cerebral cortex, 35% in the hippocampus and 26% cerebral white matter, there being relatively greater loss of white matter over the age of 50 (Esiri et al., 1997; Jernigan et al., 2001).

Numerous studies of neuronal numbers in the ageing brain have been conducted. There is still controversy over whether there is neuronal loss. This is partly due to a variety of technical problems, as well as shrinkage of neuronal cell bodies such that they may not be counted within a particular class of neurones but, nevertheless, are still present (reviewed in Esiri et al. (Esiri et al., 1997)). Improved stereological methodology has shown a 10% loss of neurons in the human cerebral cortex (Pakkenberg and Gundersen, 1997). Nevertheless, there is generally a consensus that neurones in certain brain regions are lost with age, including those in the hippocampus, cerebral cortex, and amygdala. Other neurones show shrinkage without loss and other brain regions seem to be spared of shrinkage and neuronal loss. The latter includes the nucleus basalis, an area that becomes involved in Alzheimer's disease in which the neurones do show disease-related signs of shrinkage and loss (Chiu et al., 1984).

The issue of whether synapse number is affected in ageing is also a controversial matter. Loss of synapses (up to 20%) has been reported to occur in some cortical regions (Masliah et al., 1993). It has been suggested that, because of an apparent progressive loss of synapses, then even without concomitant Alzheimer's disease, by the age of 130 years the critical point of 60% loss observed in Alzheimer's disease would be reached. Hence dementia would be inevitable if human life span is thus extended in the future (Terry and Katzman, 2001). However, there is evidence that hippocampal synaptic density is not reduced with normal ageing in areas that receive input from layer II neurones of the entorhinal cortex where neuronal loss occurs (Lippa et al., 1992). This was suggested to be the consequence of sprouting by the remaining neurones, again as a compensatory reaction to neuronal loss. Others have also found that synapses in lamina III and V of the human frontal cortex show no age-related changes (Scheff et al., 2001). Loss of dendritic arbour has been found to increase with but it is also region specific and may also be compensated by regenerative changes (Coleman and Flood, 1987; Flood et al., 1987a,b).

Studies of specific brain regions in aged animals have been proposed as a means to resolve some of these discrepancies since they usually do not develop Alzheimer-type changes to confound the picture (Morrison, 2001). Even here though there is the caveat that amyloid deposition and senile plaques are observed in elderly individuals of some non-primate species (Cummings et al., 1996). However, studies of the senescence-accelerated mouse (SAM) have shown a correlation between cognitive impairment and a decrease in hippocampal dendritic spine density as well as changes in blood brain barrier (Kawaguchi et al., 1995; Ueno et al., 2001). Animal studies do have the advantage that various experimental manipulations, such as transgenesis are possible and specific environmental stimuli can be used, as well as probe more readily for molecular correlates of age-dependent changes in synapse numbers.

3. Changes in gene and protein expression in the ageing brain

Profiling of gene expression in ageing mouse

brain have shown that around 2% of the 6347 genes surveyed show either increases or decreases in expression of up to 2.1-fold in magnitude (Lee et al., 2000). In a preliminary proteome analysis using two-dimensional gel electrophoresis, a similar proportion of proteins has also been shown to vary during the course of ageing (Tsugita et al., 2000). Genes identified by array analysis could be assigned to sets of functional classes that by inference implicate these systems in neuronal ageing. There were increases in genes involved in inflammation, stress responses and decreases in genes for trophic activities, protein metabolism and DNA repair. Most alterations were mitigated by caloric restriction. Another study of hypothalamus and cerebral cortex of aged mice found partially similar changes but also that there were increases in proteases potentially important in processing the amyloid precursor protein (APP) and decreases in protein phosphatase 2A which is a tau phosphatase (Jiang et al., 2001). Although intriguing, these are only tentative indicators that age-dependent changes in gene expression may precipitate Alzheimer-type neurodegeneration since we are still far from understanding the molecular pathogenesis of Alzheimer's disease.

4. Genetics and the ageing brain

Genetic factors clearly affect the ageing of the brain. This is apparent from the contribution of the ApoE allotype to age-dependent cognitive decline discussed above and studies of SAM mice. Inbred strains of mice may prove to be an additional powerful tool in the dissection of the genetic contribution to the ageing brain. Recent studies have shown that gene loci can be identified in mice that influence hippocampal structure (Lu et al., 2001). A large difference in the extent of age-related neuritic dystrophy has been reported between C57BL6 and DBA/2J mice, the progenitors of sets of inbred strains, which is encouraging for the identification of the responsible genes (Schmidt et al., 1998).

5. Cellular changes

5.1. Introduction

All of the pathological features diagnostic of Alzheimer's disease also are present in the brain of the intellectually intact elderly but in much smaller numbers than are found in Alzheimer's disease (previously reviewed in Anderton, 1997). This is one of the arguments used in support of the possibility that Alzheimer's disease is the relatively early, but inevitable consequence of ageing. However, since genetic factors, such as ApoE4 and other unidentified genes, contribute risk for developing Alzheimer's disease (Myers et al., 2000), it is perhaps more likely that the combination of genetic and environmental factors will determine whether individuals succumb to this disease or escape, no matter to what age they live.

5.2. Accumulation of pigment

Lipofuscin is a pigment that accumulates in some neurones with increasing age. Lipofuscin contains peroxidised protein and lipids and may represent increasing failure of cells to eliminate these products of peroxidation-induced cell damage.

5.3. Neurofibrillary tangles neuropil threads

Neurofibrillary tangles and senile plaques (see below) are regarded as the histopathological hallmarks of Alzheimer's disease. However, they are both present in the brains of non-demented individuals as, indeed, are Hirano bodies and granulovacuolar degenerative changes; the distinguishing feature of Alzheimer's disease being that the numbers of all four features are greater and more widespread. In normal ageing, the numbers of tangles, which occupy the cell body of affected neurones, is therefore, relatively low and restricted to the hippocampus, amygdala and entorhinal cortex. However, in a series of brains from demented and non-demented individuals in middle to late life, it has been shown that when minimal neurofibrillary tangles are present, they are found in the transentorhinal region. In brains

with increasing neurofibrillary change, the entorhinal cortex is also affected and further pathology includes the hippocampus, with associated cognitive impairment (Braak and Braak, 1991). Severely demented individuals are found to have widespread cortical neurofibrillary changes. These observations have led to the proposal that neurofibrillary changes can be staged, with the early stages (I and II) not being associated with dementia.

Ultrastructurally, neurofibrillary tangles are composed of paired helical filaments (PHF) and occasional straight filaments, and studies with biopsy specimens from Alzheimer patients has shown that in neurones severely affected by PHF, the normal cytoskeleton of microtubules and neurofilaments is totally lost (Flament-Durand and Couck, 1979; Gray et al., 1987). Thus, some neuronal loss is probably the consequence of the lack of a functional cytoskeleton.

Neuropil threads are thread-like structures in the neuropil of the grey matter (Braak et al., 1986). Ultrastructurally and immunocytochemically, they have been shown to be essentially the same as the PHF found in neurofibrillary tangles and in the dystrophic neurites of neuritic plaques and are, therefore, another aspect of neurofibrillary degeneration. In normal ageing they are restricted mainly to the entorhinal cortex, hippocampus and amygdala, but are more widespread in Alzheimer's disease.

5.4. Senile plaques

Senile plaques are areas of grey matter up to 200 μm across consisting of a central extracellular core of amyloid surrounded by swollen abnormal neurites, these plaques are also known as neuritic plaques. The central core contains numerous proteins but the principal protein is a small peptide 39–43 amino acids long known as amyloid β-peptide (Aβ), that is aggregated into fibrils. Small numbers of neuritic plaques are present in the normal aged brain and in Alzheimer's disease their numbers are greatly increased. Individuals with Down's syndrome develop all of the typical changes of Alzheimer's disease by the fourth decade of life but in younger Down's cases, the first signs of Alzheimer change is the appearance of 'diffuse deposits' of Aβ (Mann and Esiri, 1989). It is only later that neurofibrillary tangles and neuritic plaques appear and this observation has given strong support to the idea that amyloid deposition is the trigger for other changes in Alzheimer brain. However, large amounts of 'diffuse Aβ deposits' are found without a neuritic involvement in some brains from individuals who were intellectually intact, although some studies claim that there is a correlation between cognitive decline and total Aβ load in the brain (reviewed in Dickson, 1996). The abnormal neurites surrounding the Aβ core contain numerous PHF and lack normal cytoskeletal structures.

5.5. Granulovacuolar degeneration

As the description implies, the lesion is of one or more apparently empty vacuoles other than for a central granule, which are found in the cell bodies usually of pyramidal cells in the hippocampus. The extent of this lesion increases with age and is more extensive in Alzheimer's disease (Xu et al., 1992). Little is known about the biochemical contents of granulovacuoles other than that the granules react with antibodies to cytoskeletal and other proteins found in tangles (Stadelmann et al., 1999; Dickson et al., 1993; Kahn et al., 1985).

5.6. Hirano bodies

Hirano bodies are rod shaped structures up to 30 long and 8 μm wide that are found in or adjacent to hippocampal pyramidal cells. They increase in number with age and are also more abundant in Alzheimer's disease. Ultrastructurally, they appear as paracrystalline arrays of 60–100 nm filaments. Like PHF/straight filaments and granulovacuolar degeneration, Hirano bodies seem to be composed of cytoskeletal as well as other proteins found in tangles but principally those proteins associated with microfilaments, i.e. tropomyosin, α-actinin and vinculin (Schwab et al., 2000; Lee et al., 1999).

5.7. Congophilic angiopathy or cerebral amyloid angiopathy

This is a change in which there is extracellular deposition of Aβ in the walls of cerebral blood vessels. It is observed with increasing frequency with age and is extensive in Alzheimer's disease. Some rare families with a familial form, massive accumulation of Aβ occurs, resulting in fatal haemorrhage (Wattendorff et al., 1995).

6. Infarcts and leucoaraiosis

The accumulation of numerous small infarcts is another cause of dementia. Infarcts in small numbers are also found in brains from normal elderly individuals. Leucoaraiosis is a term used to describe a rarefaction of white matter usually close to the ventricles and can be visualised by CT scanning (Nencini, et al., 1993). The change tends to be diffuse and is more common in elderly brains and is present in Alzheimer's disease. The cause of the white matter changes is not known but may be the result of partial ischaemia.

7. Dementia-normal or pathological ageing

The brain is no different from other organs in that it is subject to increased incidence of disease as we age. The most common form of pathological ageing of the brain is the appearance of numerous plaques and tangles with concomitant Alzheimer dementia. The conundrum as to whether Alzheimer's disease is pathological in the sense that it is a disease or is just accelerated normal ageing is because the characteristic lesions are present in small numbers in the brains of intellectually normal old people. The issue is really whether indeed Alzheimer's disease is inevitable in everyone.

Apart from rare early onset Alzheimer's disease resulting from autosomal dominant mutations in the genes for the APP and presenilins 1 and 2, as discussed above, genetic factors influence risk of developing late-onset Alzheimer's disease. Possession of one or two alleles of ApoE4 is the strongest genetic factor for late onset Alzheimer's disease by being dose dependent (i.e. one or two copies of ApoE4) in increasing risk by two to three-fold (Corder et al., 1993). Perhaps, as many as 40 different candidate genes have been investigated and found in some studies to contribute some degree of increased risk (Prince et al., 2001) but recently in a genome wide scan a new locus on chromosome 10 has been identified (Myers et al., 2000).

Environmental factors are also believed to contribute to the development of Alzheimer's disease. Head injury has bee suggested to be a factor, although recent studies cast doubt on mild head injury (Plassman et al., 2000; Mehta et al., 1999). There is evidence that possession of ApoE4 gives rise to a poorer prognosis after severe head injury and that increased deposition of Aβ arises in those with ApoE4 following severe head injury (Horsburgh et al., 2000). Thus, there is some evidence that environmental factors interact with genetic factors in determining the risk of Alzheimer's disease. Healthy or pathological ageing, more generally, is likely to be determined by this interplay between genotype and environment, as indeed will perhaps many if not most diseases. Within the next decade it should be possible by association studies to identify which genes and their alleles contribute risk to disease and confer predisposition for healthy ageing.

8. The pathogenesis of senile plaques and neurofibrillary tangles

The study of the pathogenesis of Alzheimer's disease is a rapidly moving field and really beyond the scope of this review of the ageing brain. The reader is referred to some recent reviews on this topic (Esler and Wolfe, 2001; Lee et al., 2001; Selkoe 2001). Although knowledge of the biology of the key players such as APP and Aβ production, the function of presenilin-1 and the role of tau are all increasing, there is still much to be understood as to how these molecules contribute to the development of the lesions in the human brain. New treatments for Alzheimer's disease are likely to emerge and there are already promising

new results on preventing amyloid deposition and even removing it by the remarkable strategy of immunisation against the Aβ peptide (Morgan et al., 2000; Janus et al., 2000).

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