Molecular pathology of Alzheimer’s disease

The impact of molecular biology on neurological disease in the last five years has been dramatic, albeit anticipated, and Alzheimer’s disease is no exception. However, the advances in Alzheimer’s disease are remarkable for the accompanying change in attitude from the view that it is an inexorable degenerative condition which overlaps with ageing, to the view that it is a disease which may have an identifiable, and by inference potentially treatable, molecular pathology. These advances awaited the biochemical studies on the two key neuropathological features of Alzheimer’s disease, namely neurofibrillary tangles and senile plaques.

Neurofibrillary tangles are perikaryal silver-stained inclusions found particularly in pyramidal cortical neurons and the diffuse subcortical projection system. Electron microscopy shows neurofibrillary tangles to consist of paired helical filaments and recent isolation and purification of the central core of the paired helical filament permitted partial amino acid sequencing and subsequent identification of the encoding gene. This was found to be the microtubule associated protein tau. The abnormality that leads to the aggregation of tau to form neurofibrillary tangles may be a consequence of abnormal hyperphosphorylation, although it is still not clear whether this molecular event is merely a late consequence of neuronal metabolic disturbance, since neurofibrillary tangles can be found in a variety of diseases. The same approach of protein sequencing and gene cloning has been applied to the other neuropathological marker, the senile plaque. This consists of a rim of dystrophic neurites around a central core of an amyloid protein, classified on the basis of insolubility, Congo red staining with birefringence and fibril formation, a feature shared with other amyloid proteins and believed to be related to a cross linked beta pleated structure. The insolubility of the senile plaque amyloid delayed chemical isolation, but once achieved it was shown to be a 39 to 42 amino acid protein referred to as amyloid beta protein, A4 protein or \( \beta A4 \) peptide. This was shown to be the same protein that is deposited in blood vessels to cause the congophilic angioapathy of Alzheimer’s disease. From the primary amino acid sequence the cDNA clone was isolated and was shown to encode for a much larger 770 amino acid protein, of which the \( \beta A4 \) peptide was only a small component. This amyloid precursor protein (APP) molecule is a transmembrane protein of which the majority is extracellular. The \( \beta A4 \) component is partially embedded within the membrane (fig). There are at least six different APP transcripts due to differential splicing, of which four contain the \( \beta A4 \) moiety. The three major transcripts, APP 695, 751 and 770, all contain the \( \beta A4 \) sequence and APP 751 and 770 also contain a conserved sequence found in the Kunitz family of protease inhibitors, the best-studied member of which is bovine pancreatic trypsin inhibitor or aprotinin. Cell proliferation and differentiation require a series of surface-related proteolytic events which may be regulated by such protease inhibitors. The inclusion of a Kunitz domain in the APP molecule suggests a physiological role for the protein in protease activity regulation and certainly one secreted form of APP, resulting from cleavage of the extracellular component, is identical to the protease inhibitor, pro tease nixin-II. APP 770 is the main transcript in most tissues, but in brain APP 695, which lacks the protease inhibitor domain, predominates.

The physiological role of APP in the brain is unclear, but currently the subject of intense research. It is synthesised in the cell bodies and then undergoes fast anterograde axonal transport to the synaptic endings where it is colocalised with synaptophysin and is believed to be involved in the maintenance of synaptic contact. The homology to pro tease nixin-II also suggests a role as a growth regulating factor. Much speculation, however, has centred on the increase in APP expression in response to a variety of neuronal stresses which include head injury. This response is mediated by interleukin I and so is similar to the stress response of the heat shock protein family, a set of evolutionary-conserved proteins which are expressed in response to cell stress.

If amyloid deposition is a key process in Alzheimer’s disease then clearly \( \beta A4 \) has to be released via processing of the APP molecule. There are two main pathways. The first is the so called secretase pathway which results in a cleavage near to the membrane surface before Leucine 688 and releases the extracellular component; the secretase enzyme appears to recognise an \( \alpha \)-helix confirmation some 12-13 residues from the membrane. The second pathway, the endosomal-lysosomal pathway, involves internalisation of the APP molecule and subsequent degradation which produces potentially amyloidogenic carboxy-terminal fragments, some of which contain intact the \( \beta A4 \) sequence. Moreover, soluble \( \beta A4 \) peptide, as opposed to fibrillar amyloid, can be produced by healthy cells in culture and can be measured in human CSF.

Much of the intense research into the structure and function of APP has been driven by the discovery of mutations in the APP gene associated with familial Alzheimer’s disease (FAD). The realisation of the hereditary significance of Alzheimer’s disease has been rela-
ed with congophilic angiopathy at APP 692 and 693 are near to the secretase cleavage site (fig). A direct link between an APP mutation and βA4 deposition has been established in cultured cells which have been transfected with APP 670/671 mutation cDNA and which produce 6–8-fold more βA4 peptide than cells expressing normal APP.40

If it is accepted that APP mutations in these families cause the disease then amyloid deposition from the APP molecule is seen to be the essential pathological process and the “amyloid cascade hypothesis” has been generalised to other familial and sporadic cases.31 Although APP mismetabolism would appear to be established as the cause in these few families, the generalisation of this hypothesis remains speculative. A number of questions remain unanswered, not the least of which is how amyloid deposition itself leads to cell death and tangle formation. βA4 peptide has been reported to be directly toxic to neurons in culture32 and APP cDNA-transfected P19 cells show spontaneous degeneration when induced to transform into post-mitotic neurons.44 Alternatively, there is evidence that βA4 peptide may have an indirect, rather than direct toxic effect, to enhance glutamate toxicity via disruption of internal calcium homeostasis. This would also provide an explanation for tangle formation since tau hyperphosphorylation is calcium dependent.46 However, the changes which would render normal soluble β-A4 peptide toxic are at present unknown.26

Where do these advances in APP biochemistry and molecular genetics leave the clinician? How important are APP mutation families and what is the relationship between FAD and sporadic Alzheimer’s disease in general? First, APP mutation families appear to be extremely rare; to date eight APP 717 Val → Ile, one Val → Gly, one Val → Phe and two probably related APP 670–671 families have been reported. This represents less than 5% of the young onset FAD cases. In general, the families are similar to other cases of FAD and sporadic Alzheimer’s disease with early memory impairment and a generalised cognitive decline.28 The APP 717 Val → Ile families share with other FAD pedigrees features of prominent myoclonus47 and in the original APP 717 Val → Ile pedigree prominent extra pyramidal features were seen in some cases, which could be related to the presence of Lewy bodies in a single necropsied case.48 Only single APP 717 Val → Phe49 and APP 717 Val → Gly families have been reported. These show similar features to the APP 717 Val → Ile cases, but seizures in the APP 717 Val → Gly pedigree were an additional prominent clinical feature.50 Of interest is the fact that all APP mutation families have a broadly similar age of onset at around 50 years. Neuropathologically they have identical features of plaques and tangles and the cytoskeletal pathology with hyperphosphorylated tau is the same as that of sporadic Alzheimer’s disease.42 One unusual feature of the index APP 717 Val → Ile family was the presence of Lewy bodies46 but this has not been a consistent feature of this particular mutation.

Although the APP mutation families are rare, demonstration of the mutation does allow a definitive diagnosis in life without need for biopsy and, together with the prion dementia mutations51 justifies, screening in all young onset dementias with a family history. Moreover, this now allows predictive testing as with the prion dementias.53 The constant age at onset in APP mutation FAD suggests that a considerable degree of accuracy of predictive testing might be possible. Considerable caution however, needs to be exercised, since although the mutations appear to be fully penetrant, the ascertainment

Table 1

<table>
<thead>
<tr>
<th>Chromosome 21 linked</th>
<th>APP 717 Val-Ile34</th>
<th>APP 670 Lys-Asn44</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP 671 Met-Leu34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APP 693 Gly-Glu51</td>
<td>associated with</td>
<td></td>
</tr>
<tr>
<td>APP 692 Ala-Gly55</td>
<td>membranous</td>
<td></td>
</tr>
<tr>
<td>Chromosome 14-linked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>young onset46,57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome 19-linked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>late onset46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-chromosome 14,19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APP = amyloid precursor protein. Numbers refer to references.
of families for linkage analysis tends to self select such pedigrees. A clinical consortium is now being formed to establish guidelines for the interpretation of these mutations in terms of diagnostic testing and counseling.

What of the other FAD cases? It is clear from the linkage data that FAD is genetically heterogeneous.32 Clinical heterogeneity in FAD has been assumed to reflect the underlying genetic heterogeneity.34 Recently chromosome 14 linkage has been reported in a number of young onset cases35-36 which show an earlier age at onset than those families with APP mutations. There are a number of candidate genes in this region of chromosome 14; the gene for a-1 antichymotrypsin which is found in association with senile plaques has been excluded46 but the gene for heat shock protein (HSP A2) is another interesting candidate because it shares stress induced up regulation with APP. It remains to be seen whether mutations on chromosome 14 will interact with APP metabolism and if so at what stage. The study by Schellenberg et al45 suggests that a substantial proportion of early onset cases can be explained by chromosome 14 linkage, although other cases are not linked, for example, the Volga German pedigrees. These are an ethnic group of Germans who emigrated to Russia in the late 18th century and subsequently to the USA and have a high prevalence of FAD.35 There is also the problem of late onset familial Alzheimer’s disease, which is considerably more difficult to analyse by molecular genetics, but in which chromosome 19 linkage has been reported.47

Increasingly, the term Alzheimer’s disease can be seen to be a rubric to cover a clinical and neuropathological entity which may be the end stage of many different disease processes and may or may not have amyloid deposition as the final common pathway. Alzheimer’s disease might thus be considered to resemble cirrhosis of the liver, a clinicopathological entity with a variety of causes. As with cirrhosis of the liver it also puts Alzheimer’s disease rightfully into the category of metabolic disorders, with the optimism for treatment and prevention that is associated with such diseases.

MN ROSSOR

The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1 3BG and St Mary’s Hospital, Praed Street, London W2 1NY, UK


Neurological stamp

John Coakley Lettsom (1744–1815)

Lettsom, an 18th century Quaker, physician and philanthropist, was one of the central medical figures of the period. His mother, Mary Coakley, bore seven sets of twins. The seventh and last pair were John Coakley Lettsom and his brother Edward—they were the only set of twins to survive.

Lettsom was a phenomenally successful practitioner. It is said that on his long rounds he wore out three pairs of horses each day. In London, he inaugurated a system of dispensaries which enabled poor people to be treated as outpatients. The system was then adopted by many towns throughout the country.

At the age of 28 Lettsom founded the Medical Society of London and in 1786 he described alcoholic polyneuritis to the Society. As well as the symptoms of neuritis he noted the mental symptoms associated with alcoholism. Lettsom knew nothing of the pathological process of the disease and it is not even clear whether he sensed its location. In spite of the fact that he did not use the term neuritis, he clearly recognised the disorder and its association with the “indulgence of drinking”.

During his lifetime a considerable number of verses were written around Lettsom. The most famous lines are those embodying his supposed inclination for bleeding all his patients. “When any sick to me apply, I physics, bleeds and sweats ’em; If after that they choose to die, What’s that to me, I. Lettsom”.

He was honoured by his country of birth, the British Virgin Islands, in 1973 (Stanley Gibbons 284, Scott 249).

L F HAAS
Molecular pathology of Alzheimer's disease.

M N Rossor

*J Neurol Neurosurg Psychiatry* 1993 56: 583-586
doi: 10.1136/jnnp.56.6.583

Updated information and services can be found at:
http://jnnp.bmj.com/content/56/6/583.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/