Amyloid Precursor Protein Neurotrophic Properties As a Target to Cure Alzheimer's Disease

a report by

André Delacourte

Research Director, Research Center 815, National Institute for Health and Medical Research (Inserm)

André Delacourte is Research Director at Research Center 815 of the National Institute for Health and Medical Research (Inserm) in Lille, France. The aim of his team is to understand the natural and molecular history of sporadic Alzheimer's disease (SAD) so as to develop relevant diagnostic and therapeutic strategies. Among the discoveries of Dr Delacourte's team are: the concept of pathological tau proteins; the description of the bar-code of sporadic tauopathies – Alzheimer's disease (AD), dementia with parkinsonism (PSP, CBD), Pick's disease, myotonic dystrophy; the staging of tau and amyloid pathologies in SAD, showing that both processes are in synergy to provoke neuro-degeneration; the discovery that the seeds of amyloid plaques are pathological N-truncated Aβ peptides that are therapeutic targets for a vaccination approach; the demonstration that amyloid precursor protein (APP) intracellular products, potential neurotrophic factors, are decreased at an early stage in AD; the finding of a new family of APP-modulating drugs that have huge anti-Alzheimer potential; and the demonstration that APP is also a therapeutic target for Lewy body dementia. Dr Delacourte received his higher education and PhD from the University of Sciences in Lille.

Alzheimer's disease (AD) is a frequent brain pathology of the elderly, with a far more complicated aetiology than what was thought in the 1990s. The complexity particularly comes from the co-existence of two degenerating processes, tau aggregation and amyloid beta (Aβ) deposition, that affect polymodal association brain areas, a feature never observed in non-human primates and difficult to model.[1] Genetic studies have shown that Aβ precursor protein (PP) plays a central role in familial autosomic dominant AD.[2] Familial AD (FAD) and sporadic AD (SAD) have the same neuropathological phenotype, with Aβ accumulation in the gray matter of the neocortex.[3] Thus, there is a huge body of evidence that Aβ is the neurotoxic that causes both FAD and SAD.[4] The question is whether it is that simple. The National Institute for Health and Medical Research (Inserm) Research Center 815 have noted that the basic mechanisms are different in FAD and SAD, as there is a clear overproduction of Aβ species in FAD as well as a modification of the ratio of Aβ of 42 to 40.[5] This is not observed in SAD and it is assumed that the aetiology could be linked to a fibrillogenesis or clearance dysfunction of APP metabolites.

Furthermore, in most studies, the role of tau has been understated for a long time. To apprehend this role, the Inserm team has developed a spatio-temporal analysis of tauopathy in many brain areas of hundreds of non-demented and demented patients. This prospective multidisciplinary study showed that tauopathy always progresses in the brain along a precise and invariable pathway, from the entorhinal then hippocampal formation to polymodal association areas and ending in primary regions and many subcortical areas. The cognitive impairment follows the progression of the affected brain regions.[6] In strict parallelism, neocortical Aβ deposits increase in quantity and heterogeneity, suggesting a direct link between both neuro-degenerative processes.[1] Deciphering this link is the key to finding a relevant therapeutic strategy.

SAD – A Tauopathy Fuelled by APP Dysfunction

The parallelism and synergy between tau and Aβ aggregation led the Inserm team to search for an APP molecular event linking the two degenerating processes. APP is a ubiquitous protein found in all cell types of all species, suggesting a basic and important role that remains to be identified. A neurotrophic activity for APP and secreted APP (sAPP) is often mentioned.[7] Therefore, a loss of function of APP rather than a gain of toxic function of Aβ could also be a reasonable hypothesis to explain the stimulation of tauopathy and neurodegeneration.

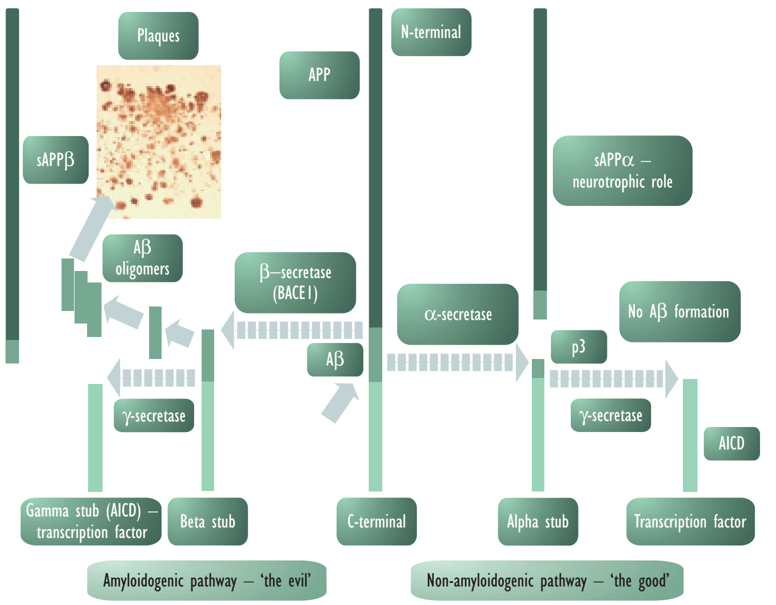
Complementary to this study of Aβ species, the Inserm team found no obvious modification of APP holoprotein in correlation with the pathology. However, carboxy-terminal fragments of APP (APP-CTFs) were found to be significantly diminished during the course of AD and well correlated with the progression of tauopathy.[8] Beta, alpha and gamma stubs were also significantly decreased in the brain tissue of individuals having an inherited form of AD linked to mutations of presenilin 1, showing a general defect common to FAD and SAD. An important role of the gamma stubs (also named APP intracellular domain (AICD)) as gene regulators could explain their involvement in the disease, as these fragments are dramatically reduced in AD.[9–11] These observations led to other therapeutic strategies focused on the concept of a loss of function of APP-stimulating tauopathy, in good agreement with other teams.[12–14] Thus, restoring the neuroprotection properties of APP could be a therapeutic strategy to slow down or cure AD.

The 'Four-hit' Hypothesis

In the literature, the key events of APP metabolism are generally summarised as follows:

- The neurotoxic Aβ is produced following an N-terminal cleavage by beta-site APP-cleaving enzyme (BACE)1, an aspartic protease that releases a beta stub (see *Figure 1*).[15] This beta stub is then cleaved by a γ-secretase activity to release Aβ and a cytosolic fragment named AICD.[16] This is the amyloidogenic, or 'the evil', pathway.
- In parallel, an APP cleavage takes place inside the Aβ region through an α-secretase activity (possibly

Figure 1: Key Events of APP Metabolism



Aβ = amyloid beta, AICD = APP intracellular domain, APP = amyloid precursor protein, BACE1 = beta-site APP-cleaving enzyme 1, sAPP = secreted APP.

a disintegrin and metalloproteinase domain 10 (ADAM 10) or ADAM 17) releasing an alpha stub. The latter is cleaved by the γ-secretase activity to release p3 and AICD.[17–19] This is the non-amyloidogenic, or 'the good', pathway, as there is no production of the neurotoxic Aβ but a release of metabolites with neurotrophic properties – sAPPα and AICD.

Stimulating the non-amyloidogenic pathway at the expense of the amyloidogenic one seems the most promising avenue to prevent or treat AD.[20]

BACE1 As a Therapeutic Target

BACE1 is, in principle, an excellent therapeutic target for strategies to reduce the production of Aβ in AD. However, it is known that BACE1 also has important physiological roles and that knocking down this enzyme is lethal.[21] The beta stubs are normal metabolites of the brain and their total suppression could be detrimental. They are also already decreased in AD.[22] These data challenge the general idea of BACE1 as a safe drug target.[21] Interestingly, however, a moderate decrease in BACE1 activity provokes a shift towards the non-amyloidogenic pathway. This has been observed for BACE inhibitors such as 4-(2-aminoethyl)benzene-sulphonylfluoride (AEBSF).[23] The possible inhibition of γ-secretase to block Aβ secretion has also been explored, but this secretase activity is involved in ubiquitous and important physiological pathways rendering this approach dangerous.[24–26]

α-Secretase As a Therapeutic Target

Another possibility is to stimulate the α-secretase pathway, which is generally activated through stimulation of muscarinic receptors or protein kinase C (PKC) activation.[27–30] Drugs such as epigallocatechin gallate (EGCG) have successfully elevated α-secretase activity and reduced the number of plaques on a transgenic model of amyloidosis in AD.[31,32]

Aβ As a Therapeutic Target

Aβ could be the neurotoxic that causes AD. However, if true, the neurotoxic mechanisms involved are not yet known; it is uncertain whether it is through plaques, protofibrils or oligomers, and it could be when this peptide is either inside or outside the cell. It is unclear whether the N-truncated forms are more toxic than full-length Aβ; they may be toxic at the first stage of the disease or in later stages.

Whatever the answers, there is consensus that anti-Alzheimer drugs should decrease, maybe moderately, the secretion of Aβ peptide, something which both BACE1 inhibition and α-secretase activation do.

Tau As a Therapeutic Target

Tau is a therapeutic target for more than 15 degenerative disorders.[33] However, the Inserm team has noted that the sequential pattern of tauopathy in AD, along cortico-cortical connections, is likely to be explained by a loss of neurotrophic factor. Theoretically, as nerve cell populations survive through a chemical cross-talk of neurotrophic factors, if one brain area is degenerating, a progressive collapse of the neuronal network is expected. Stimulating the production of sAPPα and AICD while inhibiting the possible neurotoxic factor should, hypothetically, slow down the progression of tauopathy in AD.

Conclusions

From its study on tau and Aβ in the human brain, the Inserm team proposes that a good anti-Alzheimer drug should increase the α-secretase activity and thus:

- decrease the production of beta stubs and Aβ, a potential neurotoxic;
- increase, in the same mechanism, the secretion of sAPPα, a potential neurotrophic factor;
- increase the production of the potential transcription factor AICD; and subsequently
- the beneficial effects should slow down the progression of tauopathy.

Theoretically, this drug should be able to reduce or stop the deleterious effect of AβPP loss of function, and, thus, be able to stop the burden that fuels tauopathy and provoke dementia in AD. As already mentioned, drugs that have this property have already been developed.[32,34] ■

References

1. Delacourte A, Sergeant N, Champain D et al., "Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease", Neurology (2002);59: pp. 398–407.
2. Goate A, Chartier-Harlin M C, Mullan M et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease", Nature (1991);349: pp. 704–706.
3. Hardy J, Selkoe D J, "The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics", Science (2002);297: pp. 353–356.
4. Selkoe D J, "Deciphering the genesis and fate of amyloid beta-protein yields novel therapies for Alzheimer disease", J Clin Invest (2002);110: pp. 1,375–1,381.
5. Borchelt D R, Thinakaran G, Eckman C B et al., "Familial Alzheimer's disease-linked presenilin 1 variants elevate Abeta1-42/1-40 ratio in vitro and in vivo", Neuron (1996);17: pp. 1,005–1,013.
6. Delacourte A, David J P, Sergeant N et al., "The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease", Neurology (1999);52: pp. 1,158–1,165.
7. Turner P R, O'Connor K, Tate W P, Abraham W C, "Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory", Prog Neurobiol (2003);70: pp. 1–32.
8. Sergeant N, David J P, Champain D et al., "Progressive decrease of amyloid precursor protein carboxy terminal fragments (APP-CTFs), associated with tau pathology stages, in Alzheimer's disease", J Neurochem (2002);81: pp. 663–672.
9. Cao X, Sudhof T C, "A transcriptively active complex of APP with Fe65 and histone acetyltransferase tip60", Science (2001);293: pp. 115–120.
10. Cao X, Sudhof T C, "Dissection of amyloid-beta precursor protein-dependent transcriptional transactivation", J Biol Chem (2004);279: pp. 24,601–24,611.
11. Pardossi-Piquard R, Petit A, Kawarai T et al., "Presenilin-dependent transcriptional control of the Abeta-degrading enzyme neprilysin by intracellular domains of betaAPP and APLP", Neuron (2005);46: pp. 541–554.
12. Neve R L, Robakis N K, "Alzheimer's disease: a re-examination of the amyloid hypothesis", Trends Neurosci (1998);21: pp. 15–19.
13. Neve R L, "A beta may be a planet, but APP is central", Neurobiol Aging (2001);22: pp. 151–154.
14. Lee H G, Casadesus G, Zhu X et al., "Challenging the amyloid cascade hypothesis: senile plaques and amyloid-beta as protective adaptations to Alzheimer disease", Ann N Y Acad Sci (2004);1,019: pp. 1–4.
15. Vassar R, "Beta-Secretase, APP and Abeta in Alzheimer's disease", Subcell Biochem (2005);38: pp. 79–103.
16. Tsai J Y, Wolfe M S, Xia W, "The search for gamma-secretase and development of inhibitors", Curr Med Chem (2002);9: pp. 1,087–1,106.
17. Kojro E, Fahrenholz F, "The non-amyloidogenic pathway: structure and function of alpha-secretases", Subcell Biochem (2005);38: pp. 105–127.
18. Postina R, Schroeder A, Dewachter I et al., "A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model", J Clin Invest (2004);113: pp. 1,456–1,464.
19. Vincent B, "ADAM proteases: protective role in Alzheimer's and prion diseases?", Curr Alzheimer Res (2004);1: pp. 165–174.
20. Dewachter I, Van Leuven F, "Secretases as targets for the treatment of Alzheimer's disease: the prospects", Lancet Neurol (2002);1: pp. 409–416.
21. Dominguez D, Tournoy J, Hartmann D et al., "Phenotypic and biochemical analyses of BACE1- and BACE2-deficient mice", J Biol Chem (2005);280: pp. 30,797–30,806.
22. Sergeant N, David J P, Champain D et al., "Progressive decrease of amyloid precursor protein carboxy terminal fragments (APP-CTFs), associated with tau pathology stages, in Alzheimer's disease", J Neurochem (2002);81: pp. 663–672.
23. Citron M, Diehl T S, Capell A et al., "Inhibition of amyloid beta-protein production in neural cells by the serine protease inhibitor AEBSF", Neuron (1996);17: pp. 171–179.
24. Takasugi N, Tomita T, Hayashi I et al., "The role of presenilin cofactors in the gamma-secretase complex", Nature (2003);422: pp. 438–441.
25. De Strooper B, "Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex", Neuron (2003);38: pp. 9–12.
26. Marjaux E, Hartmann D, De Strooper B, "Presenilins in memory, Alzheimer's disease, and therapy", Neuron (2004);42: pp. 189–192.
27. Zimmermann M, Borroni B, Cattabeni F, Padovani A, Di Luca M, "Cholinesterase inhibitors influence APP metabolism in Alzheimer disease patients", Neurobiol Dis (2005);19: pp. 237–242.
28. Zhu G, Wang D, Lin Y H et al., "Protein kinase C epsilon suppresses Abeta production and promotes activation of alpha-secretase", Biochem Biophys Res Commun (2001);285: pp. 997–1,006.
29. Lanni C, Mazzucchelli M, Porrello E, Govoni S, Racchi M, "Differential involvement of protein kinase C alpha and epsilon in the regulated secretion of soluble amyloid precursor protein", Eur J Biochem (2004);271: pp. 3,068–3,075.
30. Canet-Aviles R M, Anderton M, Hooper N M, Turner A J, Vaughan P F, "Muscarine enhances soluble amyloid precursor

protein secretion in human neuroblastoma SH-SY5Y by a pathway dependent on protein kinase C(alpha), src-tyrosine kinase and extracellular signal-regulated kinase but not phospholipase C", Brain Res Mol Brain Res *(2002);102: pp. 62–72.*

31. *Levites Y, Amit T, Mandel S, Youdim M B, "Neuroprotection and neurorescue against Abeta toxicity and PKC-dependent release of nonamyloidogenic soluble precursor protein by green tea polyphenol (-)-epigallocatechin-3-gallate",* Faseb J *(2003);17: pp. 952–954.*
32. *Rezai-Zadeh K, Shytle D, Sun N et al., "Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice",* J Neurosci *(2005);25: pp. 8,807–8,814.*
33. *Delacourte A, "Tauopathies: recent insights into old diseases",* Folia Neuropathol *(2005);43: pp. 244–257.*
34. *Delacourte A, Melnyk P, "MSBD, a new class of anti-Alzheimer drugs", unpublished data.*