

Review

The pathology of APP transgenic mice: a model of Alzheimer's disease or simply overexpression of APP?

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Summary. Alzheimer's disease (AD) is characterized by a number of pathological features, notably extracellular senile plaques composed of the beta-amyloid protein (A β) and neurofibrillary tangles (NFT's), which are intracellular inclusions of hyperphosphorylated tau protein. In their attempts to generate a model of AD, many laboratories have produced transgenic mice that overexpress the amyloid precursor protein (APP), in particular, mutant APP which is associated with familial forms of AD in man. Histopathological assessment shows that APP transgenic mice demonstrate an accumulation of A β in plaques from an early age; these plaques are invariably surrounded by activated inflammatory cells such as astrocytes and microglia, as is common in AD brain. Also, commonly associated with the plaques is hyperphosphorylated tau, although this does not take on the NFT phenotype observed in AD. Atrophy and neurodegenerative pathology are other common features of AD; some neuronal loss is evident in close proximity to plaques in APP transgenic mice although this is not extensive. Consequently, it is evident that APP transgenic mice exhibit, to some degree, many of the pathological features of AD.

Key words: Alzheimer's disease, Neurodegenerative pathology, Amyloid plaques

Introduction

One of the major pathological features of Alzheimer's disease (AD) are extracellular amyloid-containing senile plaques, as originally described by Alois Alzheimer over a century ago. Arguably, one of the seminal papers in recent AD research has been the chemical identification of the amyloid protein in AD, a

protein given the name "beta protein" (Glennner and Wong, 1984). Purification of the senile plaque core amyloid showed that it was similar to amyloid of cerebrovascular origin and to the cerebral amyloid deposits found in patients with Down syndrome (Masters et al., 1985), the latter possessing an extra copy of chromosome 21, the location of the amyloid precursor protein (APP) gene. Analysis of the beta protein cDNA suggested it was part of a larger precursor protein with distribution in a large number of tissues (Tanzi et al., 1987). A number of groups have proceeded to demonstrate the proteolytic cleavage of APP by enzymes referred to as α , β and γ secretases, the identification of which has only been made in recent years (for review see Vardy et al., 2005). (The "beta protein" has assumed various names (including beta-amyloid, beta-A4, amyloid beta protein). For the purposes of this review, the protein will be referred to as A β).

There is compelling evidence linking the deposition of A β protein in plaques in the brains of AD sufferers to neuronal loss and disease progression, evidence which has given rise to the "amyloid hypothesis" of AD (Hardy and Higgins, 1992). In particular, genetics factors which either cause (familial AD (FAD) mutations in APP, presenilin-1 (PS-1), presenilin-2) or increase the risk of developing AD (apolipoprotein E4 status) are all associated with increased A β , production and/or deposition (see Howlett et al., 2001).

The links between APP, PS-1 and familial forms of AD provided a potential means of generating rodent models of the disease and the last 12-15 years have seen the emergence of significant number of transgenic mouse models of AD. The topic of this review, is whether these mice mimic the disease or are simply models of APP overexpression and A β deposition.

The pathology of APP transgenic mice

The most successful APP transgenic mouse models,

at least in terms of A β deposition, have been those employing transgenes for human APP with FAD mutations. This has resulted in some confusion since the APP utilised is referred to by the isoform (695, 751 or 770) while the mutation is often given 770 numbering (eg. APP695_{K670N,M671L} where the 670,671 numbering actually refers to the 770 isoform). The most common isoforms and mutations are shown in Table 1. For clarity, in this review, mice are referred to according to the description in the quoted literature.

Mutant APP mice

Early attempts at developing APP transgenic mice employed expression of full-length human APP. These were not greatly successful although diffuse plaque-like deposits were reported by Cordell and colleagues (Quon et al., 1991). Dense core plaques were not seen in these mice but the fact that deposits could be induced in the rodent brain where accumulation of A β was not normally observed, provided the encouragement to persevere with the development of this type of model.

A major advance in model development was accomplished with the utilisation of mutant human transgenes for APP, these mutations being normally associated with familial forms of the disease. The PDAPP mouse, expressing the V717F Indiana mutation under the control of the PDGF promoter was the first transgenic mouse exhibiting AD-like plaques (Games et al., 1995). This mouse exhibited extracellular A β plaques of varying morphology, many plaques having dense compact cores, others being much more diffuse in appearance. The plaques appeared from about 6-9 months of age, the number increased with age and they were found in the cerebral cortex, the hippocampus and also in the corpus callosum.

This model was followed by the development of transgenic mice overexpressing human APP containing the Swedish mutation (Hsiao et al., 1996; Sturchler Pierrat et al., 1997) and the V717I London mutation (Moechars et al., 1999). Hsiao and colleagues reported the development of the transgenic mouse line now referred to as the Tg2576, characterised by both diffuse and dense core amyloid plaques which, as with the PDAPP mice, were found throughout the cortex and hippocampus. The plaques were shown to be labelled with the histological dyes Congo red and thioflavin S and by a variety of A β antibodies, demonstrating the presence of beta-sheet and A β forms beginning at Asp-1 and ending at both Val-40 and Ala-42. The predominance of A β commencing with the Asp-1 residue contrasts with that found in AD brain where much of the A β is N-terminally truncated, although such modifications have been reported in old Tg2576 and TASTPM mice (Kawarabayashi et al., 2001; Howlett et al., 2008). The Tg2576 mouse has the APP695swe transgene under the control of the hamster prion promoter (Hsiao et al., 1996). Alternative models are the APP23 animal where APP751swe cDNA has been coupled to the murine thy-1 gene (Sturchler Pierrat et al.,

1997) and the APP/Ld mouse with a thy-1-APP695London mutant transgene (Moechars et al., 1999). The APP23 mouse shows both diffuse and dense core plaques in the neocortex and hippocampus which begin to develop from around 6 months of age, spreading to other areas such as the thalamus, olfactory nucleus and occasionally to the caudate putamen in very old animals (Sturchler Pierrat et al., 1997). The morphology of the plaques in the APP/Ld mouse is similar to the APP23, starting with plaques in the cortex and hippocampus although deposition appears between 13 and 18 months of age (Moechars et al., 1999).

A further development of mutant APP mice involved the expression of transgenes containing both Swedish and Indiana or Swedish and London mutations (Chishti et al., 2001; Rockenstein et al., 2001). In the former, Chishti and colleagues described the TgCRND8 mouse with a hamster prion promoter controlled APP695-Swedish+Indiana transgene. In these animals, single plaques were found as early as 43 days of age; multiple plaques were detected in all animals by 65-90 days after which time plaque density continued to increase with age. During this time the authors reported a spreading pathology, not unreminiscent of AD, beginning in the subiculum and frontal cortex, spreading to the cortex and hippocampus by 101 days, to the thalamus (111 days) and striatum and cerebral vasculature (196 days). In very old animals plaques were also observed in the cerebellum and brain stem. The earliest plaques in TgCRND8 mice appeared as small cored deposits which were thioflavin S and Congo red positive, indicating the presence of A β in folded beta-sheet formation. Interestingly, diffuse A β plaques did not appear until much later. A similar situation has been described in many other models with diffuse amyloid deposits developing long after core or compact plaques (Reilly et al., 2003; Harigaya et al., 2006). These observations would counter the belief that diffuse plaques might go on to form dense core deposits, at least in transgenic mice. The mThy1-hAPP751 mouse (Rockenstein et al., 2001) is similar to the TgCRND8 although in this animal, rather than combining the APP_{swe} and APP_{Indiana}

Table 1. Transgenes of the most commonly used APP transgenic mice referred to in this review.

Name	APP isoform	Promoter	Mutation
TAS10	695	thy-1	APP Swedish
PDAPP	minigene	PDGF	APP Indiana
Tg2576	695	hamster prion	APP Swedish
APP23	751	thy-1	APP Swedish
APP _{Ld}	695	thy-1	APP London
TgCRND8	695	hamster prion	APP Swedish/Indiana
APP isoform	APP Swedish	APP Indiana (V46F)	APP London (V46I)
695	KM595/596NL	V642F	V642I
751	KM651/652NL	V698F	V698I
770	KM670/671NL	V717F	V717I

mutants (K670M/N671L + V717F) as in the TgCRND8, the APP^{swe} mutant is combined with the APP London mutant (V717I). The spread of pathology in the mThy1-hAPP751 is similar to that in the TgCRND8, beginning with dense deposits in the frontal cortex at 3-4 months of age, increasing in density and spreading to the subicullum and thalamus by 5-7 months and becoming more widespread by 9-11 months.

APP + PS-1 transgenic mice

The knowledge that a considerable number of mutations in the PS-1 gene are associated with AD prompted the development of mice overexpressing mutant PS-1 (Borchelt et al., 1996; Duff et al., 1996; Chui et al., 1998). These mice show elevated brain A β 42 levels and evidence of neurodegeneration associated with intracellular A β 42 but no plaque formation. However, when mutant PS-1 mice were crossed with APP transgenic mice, A β deposition appeared much earlier than had been detected in mice with single APP transgenes. Mice expressing APP^{swe} + PS-1 A246E showed evidence of plaque pathology from 9 months of age, compared to 18 months in APP^{swe} alone (Borchelt et al., 1997). Crossing the Tg2576 APP^{swe} mouse with a mutant PS-1 animal resulted in the PSAPP mouse where cortical A β deposition was apparent by 8-10 weeks of age (McGowan et al., 1999; Kurt et al., 2001) compared to 8-12 months in the single APP animal (McGowan et al., 1999). In the PSAPP mice, small compact plaques first appeared in the cingulate and motor cortex, later spreading extensively throughout the cortex and hippocampus and into the thalamus, striatum and other regions (including the occasional small cerebellar deposit) (McGowan et al., 1999). The plaques in these animals comprised A β 40 and A β 42 C-terminal species as well as N-terminally truncated forms. As with the TgCRND8 mice, diffuse plaques were only observed in relatively old animals (14 months of age). TASTPM mice (TAS10 thy1-APP^{swe} x TPM thy1-PS1.M146V) also show accelerated pathology (Howlett et al., 2004) compared to the thy1-APP^{swe} animal (TAS10) alone (Richardson et al., 2003) with plaques being apparent from 3 months of age in the double mutant. As with the PSAPP mouse, the TASTPM animal shows both A β 40 and A β 42 C-terminal forms, as well as species commencing at Asp-1 and pyro-3 glutamate (Howlett et al., 2008). Consistent with the notion that PS-1 acts as part of the gamma secretase complex, the presence of the familial AD-associated mutant protein influences processing at the C-terminus of A β and increases the proportion of the more amyloidogenic A β 42 form of the peptide (Borchelt et al., 1996; Holcomb et al., 1998; Howlett et al., 2004).

Other APP-related models

A number of alternative models have been generated in attempting to produce either more appropriate models of AD or to gain a better understanding of the function

of APP. Lamb and colleagues have reported, in a number of publications (see Kulnane and Lamb, 2001), on the introduction of the whole *APP* or *PS-1* genes (including FAD mutations), carried in yeast artificial chromosomes (YACs) into the mouse genome. This technology, unlike the more commonly used cDNA-based models cited above (eg. Tg2576, TgCRND8, PDAPP), overcomes doubts about the regional distribution of amyloid deposition arising as a function of the heterologous promoter sequence used. Indeed, although APP YAC mice exhibit age-related A β deposition accompanied by astrogliosis and microgliosis, the development of pathology, with diffuse plaques appearing before core plaques and the spread of this pathology through the brain of these animals being subtly different to that in cDNA-based mice (Kulnane and Lamb, 2001), points to an accurate representation of the disease state.

FAD APP and PS-1 mutations have also been inserted into their endogenous genes ("knock-in" mice) resulting in mice with pathological features not dissimilar to the more common transgenics (Wu et al., 2006; Zhang et al., 2007). The normal physiological function of APP (and A β) is not understood; the generation of APP-null mice ("knock-outs") has not greatly aided our knowledge. Some abnormalities have been observed in hippocampal pyramidal neurons in these mice (Seabrook and Rosahl, 1999) and some behavioural impairments have been reported (Dawson, Jr. et al., 1998; Dawson et al., 1999; Phinney et al., 1999).

Although it is not an APP transgenic model, the AD11 anti-NGF transgenic mouse is of interest since it exhibits a phenotype closely resembling AD, namely amyloid plaques, neurofibrillary pathology, cholinergic deficits and neuronal loss (Capsoni et al., 2002). The selectivity of the AD11 antibody for mature NGF as opposed to pro-NGF may result in a relative accumulation of the latter which can interact with the p75NTR/sortilin receptor complex (Capsoni and Cattaneo, 2006) leading to neuronal apoptosis and cell death (Harrington et al., 2004). Although it was initially believed that rodent A β with three amino acid substitutions near the N-terminus of A β (compared to human A β) was resistant to aggregation, the AD11 mice, expressing anti-NGF antibodies, demonstrate that endogenous rodent A β and tau can, under appropriate conditions, assume a more AD-like state.

Plaque formation

The precise mechanism by which senile plaques form has not been established. Plaques are very definitely extracellular structures found in diffuse, neuritic and core forms. It is not clear, however, whether there is a temporal or spatial relationship between these different forms or whether the aggregation process first begins intracellularly. As commented above, in APP transgenic mice, there does not appear to be a progression from diffuse to compact/core plaque. APP transgenic mice certainly show evidence of intracellular

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APP expression from a very young age, well before A β is observed, a feature which can be used to genotype the animals (Howlett, unpublished). The intracellular accumulation of A β , however, has been reported in a number of mice. A thyl-APP751 mouse with APP^{swe}+APP/Ld+PS1.M146L expression has been reported to show evidence of intraneuronal A β in the subiculum and cortical layers 4 and 5 from 3 months of age (Wirhth et al., 2002). The use of A β -specific antibodies precluded the possibility that the labelling was of intracellular APP. Intracellular labelling of neurons has also been reported in Tg2576 mice (Shie et al., 2003) and is observed in TASTPM animals (Fig. 1) although there have been reports to the contrary (Stalder et al., 2001; Radde et al., 2006). There is a risk that the non-specificity of some antibodies will result in falsely assessing APP labelling as A β . The use of A β C-terminal specific antibodies, as quoted above however, provides a

fairly robust assessment of the presence of intracellular A β in line with that observed in AD brain.

The development of pathology in the APP tg mouse is a temporal event, be it plaques, astrocytes, microglia, phosphotau or other features. As noted above, plaques are detected as early as 8 weeks of age in the PSAPP mouse and continue to develop with age (Kurt et al., 2001). Similarly in TASTPM mice, the deposition of A β appears to progress throughout the life of the animal and is accompanied by astrocytosis and phosphotau accumulation (Howlett et al., 2008). This is likely to be partly a function of expression levels since we have found that deposition in homozygote TASTPM mice precedes that in heterozygote animals by approximately 2 months (Fig. 2). There is no doubt that in elderly APP transgenic mice the plaque load is far greater and more widespread than observed in AD brain but yet the functional manifestations of the pathology, in terms of

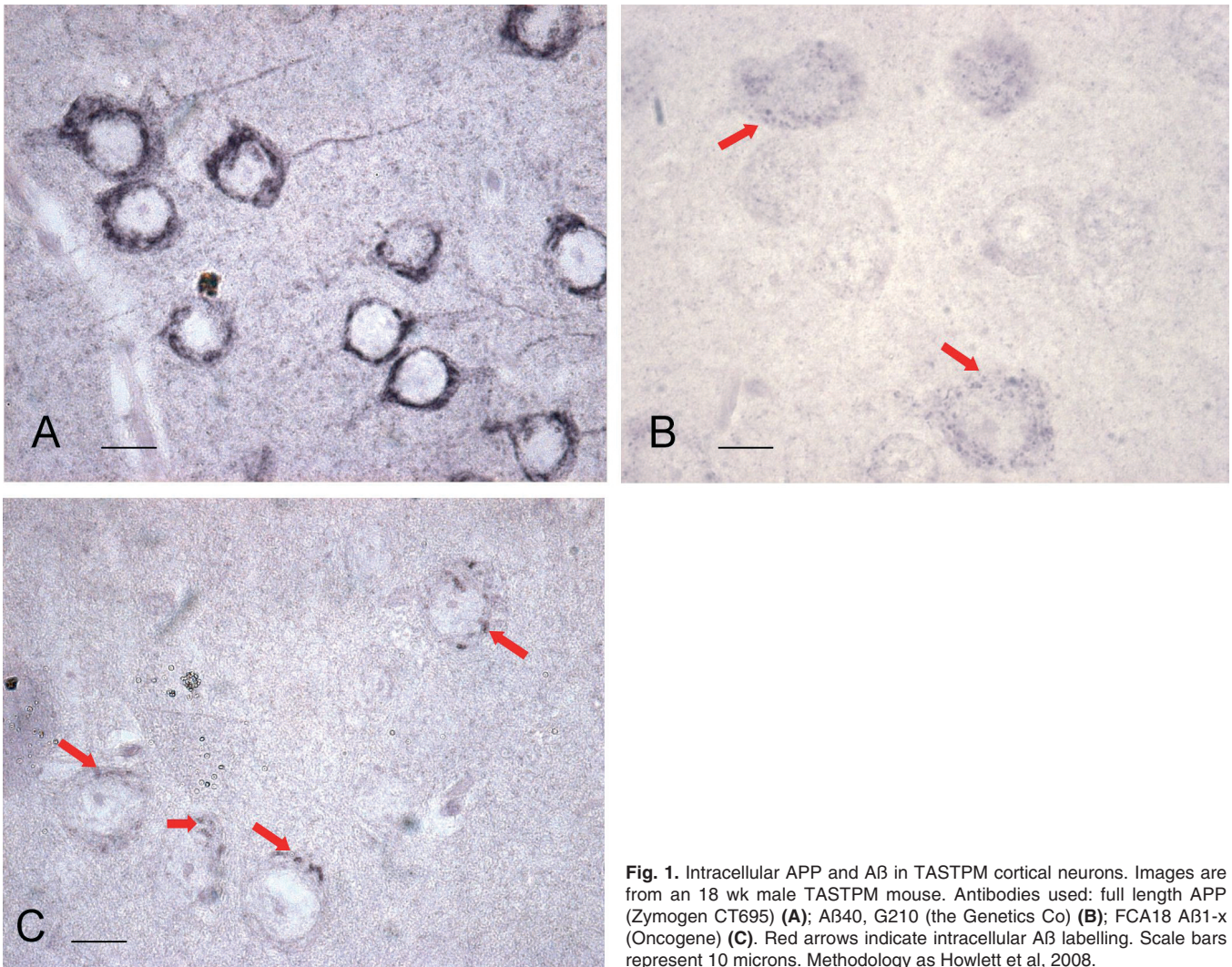


Fig. 1. Intracellular APP and A β in TASTPM cortical neurons. Images are from an 18 wk male TASTPM mouse. Antibodies used: full length APP (Zymogen CT695) (A); AB40, G210 (the Genetics Co) (B); FCA18 AB1-x (Oncogene) (C). Red arrows indicate intracellular A β labelling. Scale bars represent 10 microns. Methodology as Howlett et al, 2008.

Pathology of APP transgenic mice

cognitive impairment, are considerably more subtle (eg. Arendash et al., 2001; Kelly et al., 2003).

In general, A β deposition in APP transgenic mice is seen from around 12 months of age in the single mutants and some months earlier in the double mutants. In both types of mice, although governed by specific promoters that predominantly drive expression to the cortex and hippocampus, A β deposition begins in the cortex and hippocampus but then spreads throughout the brain, including regions with low transgenic APP expression. The deposition is initially as dense core plaques; diffuse A β only appears in the later stages of the animal's life and the forms of A β , with varying N- and C-termini are not dissimilar to that observed in AD. In terms of A β deposition, therefore, APP and APPxPS1 transgenic mice probably provide a useful model of AD.

A β oligomers

A growing belief that the dense aggregates of fibrillar A β found in senile plaques are relatively inert and are likely not a major source of neurodegeneration (eg. Ward et al., 2000; Walsh et al., 2002; Takahashi et

al., 2004) has diverted attention away from one of the major pathological features of the disease. The fact that the so-called "toxic species" of A β may be a small soluble oligomer of the peptide suggests that the search for relevant pathology should consider non-fibrillar forms of the peptide. The use of conformation specific antibodies has aided this quest. Amyloid derived diffusible ligands (ADDLs) are low molecular weight forms of A β 1-42 which are toxic to cells in culture (Lambert et al., 1998; Wang et al., 2002). The use of an ADDL-specific antibody has permitted the identification of this particular A β form in biochemical extracts of AD brain (Gong et al., 2003) although it has yet to be determined pathologically. Similarly, ADDLs and have been extracted from Tg2576 brain (Chang et al., 2003), as have other memory-impairing oligomers (Lesne et al., 2006), although neither have been reported immunohistochemically. This may reflect the level of sensitivity of light microscopy since an antibody raised to a small oligomeric form of A β 1-42, showed some apparent association with cell processes in Tg2576 mouse brain when studied by EM but not by light microscopy (Kokubo et al., 2005).

Strain differences

Pathological comparisons between different APP transgenics are not only complicated by the different promoters, APP isoforms and APP mutations employed but also by the strain of mouse utilised. For instance, inbred strains show lethality at APP concentrations tolerated by outbred lines (Carlson et al., 1997) and introducing the same APP YAC construct into 3 inbred mouse strains demonstrated a marked difference in A β pathology, depending upon the strain examined (Lehman et al., 2003). Initial studies by (Hsiao et al., 1995) reported that overexpression of various APP isoforms and mutants in FVB/N mice produced a senescence-type pathology while subsequent overexpression in C57B6 x C57B6/SJL F2 animals resulted in plaque pathology and memory deficits (Hsiao et al., 1996). Other groups, however, have reported little difference between expression on C57/B6 and FVB/N backgrounds (Moechars et al., 1999). Nevertheless, strain differences may, in part, explain the lack of neurodegeneration on APP transgenic mice in that the selection of viable lines may also select for an ability to tolerate high concentrations of APP (and A β). This viability presumably reflects their genetic background with the expression of genes such as SOD1 offering protection and FGF2 conferring susceptibility (Carlson et al., 1997). A dependency of overall genetic background, rather than a specific mutated gene, has profound implications for the aetiology of AD.

Neurofibrillary pathology

Aside from A β laden senile plaques, the other major

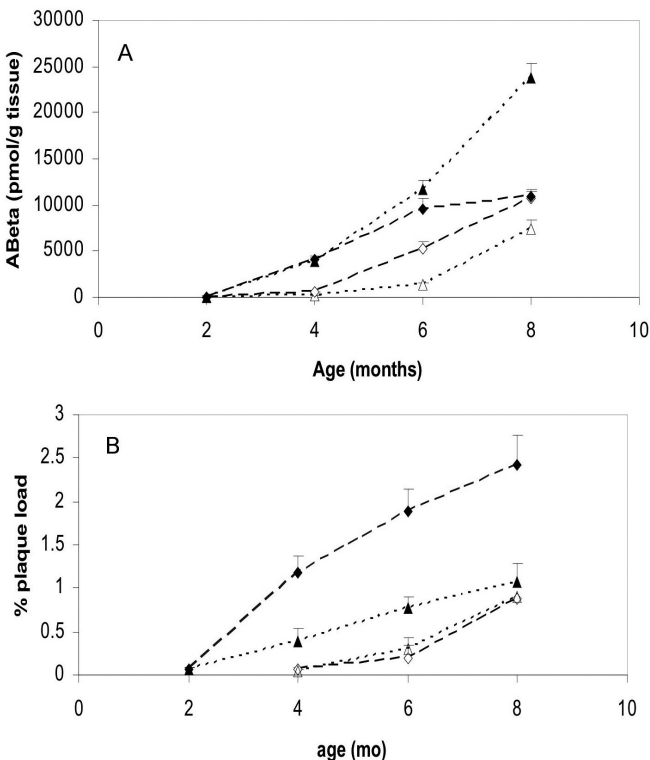


Fig. 2. Brain A β concentration and plaque load in homozygote (Ho) and heterozygote (Het) TASTPM mice Brain A β concentration (top) and plaque load (lower) were determined by immunoassay and immunohistochemistry as previously described (Howlett et al., 2004; Howlett et al., 2008). Filled diamonds: Ho AB42; filled triangles: Ho AB40; open diamonds: Het AB42; open triangles: Het AB40

pathological features of AD are neurofibrillary tangles (NFTs) and general atrophy. Alzheimer noted fibrillary structures in pyramidal neurons of his patient, Auguste D. Initially highlighted by Bielschowsky's silver stain, these features are today described immunohistochemically by a variety of antibodies to phosphorylated tau protein. Nevertheless, NFTs are not an unequivocal diagnostic feature of AD as they occur in a wide range of neurological conditions such as amyotrophic lateral sclerosis, progressive nuclear palsy and frontotemporal dementia and Parkinsonism associated with chromosome 17 (FTDP-17). The precise role of NFTs in the neurodegenerative process in AD is unknown and they may not be the sole determinant of disease progression. However, the general view is that it might not be unreasonable to expect an animal model of AD to have NFTs. Sadly this is not the case; none of the transgenic

mice possessing APP transgenes alone or APP + PS1 transgenes show signs of NFTs. Only when tau genes are incorporated are tangle-like structures observed (see Oddo et al., 2003)

However, it is important to note that neurofibrillary pathology, as originally described (Kidd, 1963) extends to dystrophic neurites scattered throughout the neuropil and there is no doubt that phosphorylated tau positive dystrophic neurites are seen in a variety of APP transgenic mice (Sturchler Pierrat et al., 1997; Moechars et al., 1999; Masliah et al., 2001; Rockenstein et al., 2001). Furthermore, the tau reported in dystrophic neurites is phosphorylated at some, but not all, of the sites described in AD brain. Thus the "AT8-site" (phosphorylation of residues S199/S202) is noted in many mice, but not the more AD-specific phospho-epitopes at residues S396, S404 and S422 (Fig. 3). More

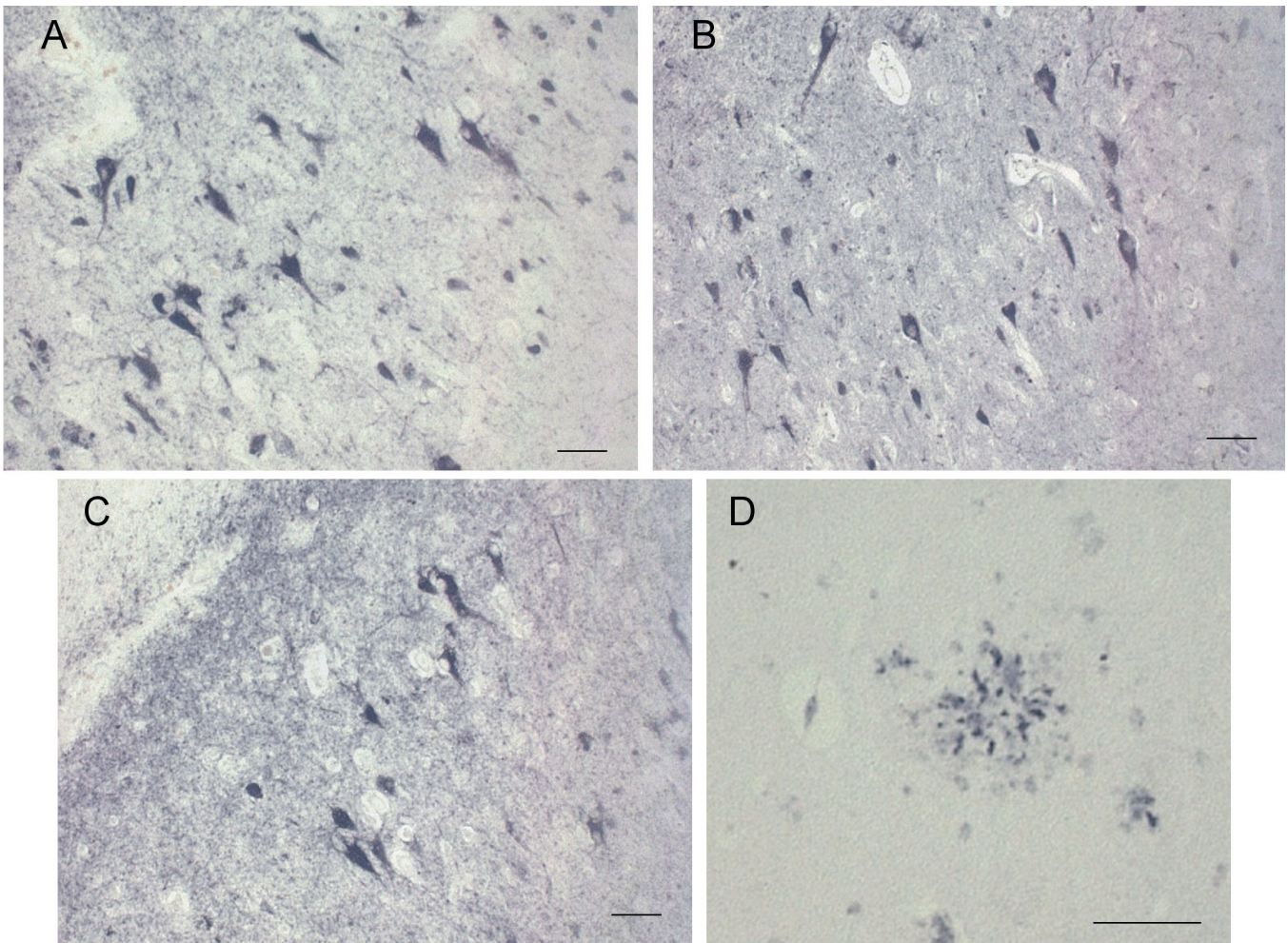


Fig. 3. Phospho-tau pathology in AD and TASTPM brain. **A-C.** Cortex from an AD patient labelled with antibodies to pSer396-tau (**A**), pSer404-tau (**B**) and pSer422-tau (**C**). **D.** Labelling of pSer202-tau dystrophic neurite-like features around a plaque in a 10 mo old TASTPM mouse. The antibodies to pSer396, 404 and 422 (all Biosource) produced no specific labelling in TASTPM brain. pSer202-tau was labelled with antibody AT8 (Innogenetics). Scale bars represent 25 microns.

recent work by Kidd and colleagues (Kurt et al., 2003) has described the existence of paired-helical filament-like structures in the brain of an 8 month old PSAPP mouse and an age-dependent increase in phosphotau immunoreactivity associated with plaques (probably dystrophic neurites) has also been demonstrated in TASTPM brain (Howlett et al., 2008). Consequently, while hyperphosphorylated mouse tau does not show a great tendency to adopt a NFT-like structure in APP transgenics, there seems little doubt that hyperphosphorylation of tau does occur in the brains of these mice and consequently the animals satisfy, in part, the phosphotau requirements of a model of AD. It is apparent, however, that tangle-like structures occur in the brains of the AD11 mice discussed earlier (Capsoni et al., 2000) indicating that, as with rodent amyloid, rodent tau is able to form pathological structures. Incorporating a mutant human tau transgene (P301L) into an APP x PS1 mouse changes the pathology somewhat with not only A β deposits, but phosphotau immunoreactive pyramidal neurons in the hippocampus (Oddo et al., 2003). This intracellular tau is phosphorylated at epitopes observed to be hyperphosphorylated in tangles in AD brain; some of the tau also appears to be aggregated in that it stains with Gallay's and thioflavin S. Whether these intracellular inclusions reflect neurofibrillary tangles as seen in AD is not clear; tangles in AD are not the product of three mutated transgenes!

Inflammation

In apparent intimate contact with plaques in AD are inflammatory cells such as astrocytes and microglia, activation leading to the release of chemokines and cytokines such as IL-1 and IL-6 (Griffin et al., 1989; Bauer et al., 1991). Interest in the role of the inflammatory response was spurred on by the observation that long-term use of non-steroidal anti-inflammatory drugs by rheumatoid arthritis patients leads to a lower risk of developing AD (McGeer et al., 1990; Breitner et al., 1994). Post-mortem studies of AD brain suggest that this protection is associated with a decrease in microglia activation (Mackenzie and Munoz, 1998). In transgenic mice, the link between anti-inflammatory drugs and a protective effect in AD is supported by the observation that ibuprofen administration to Tg2576 mice results in a decrease in plaque and microglial pathology and in IL-1 β and GFAP protein levels (Lim et al., 2000). Such findings have been confirmed in some studies (Heneka et al., 2005) but not others (Lanz et al., 2005).

Generally, the presence of astrocytes and microglia appears to be a response to the development of the A β plaque rather than the amyloid deposition being a product of the inflammatory cell. It is also apparent that oligomeric A β produces a much greater glial response than fibrillar peptide (White et al., 2005). Although it has been claimed that both cultured astrocytes and microglia

possess APP and processing enzymes (Blasko et al., 2000; Carlson et al., 2000), demonstration of this is lacking in APP transgenic mice. As described above, PSAPP mice show plaque pathology from around 3 months of age and, closely associated with these deposits, are astrocytes and activated microglia (Matsuoka et al., 2001). We have also shown that astrocyte pathology in the cortex (and, to a lesser extent, the hippocampus) increases in parallel to A β deposition in TASTPM mice (Howlett et al., 2008). The link between plaque and microglial activation has been demonstrated by correlating microglial density with distance from the plaque core, density being much higher within plaques compared to neighbouring areas (Frautschy et al., 1998). It has been reported that the activated microglia in PSAPP mice show an increased expression of the complement cascade factor C1q and the cyclooxygenase COX-2 (Matsuoka et al., 2001) indicative of both immune and inflammatory responses, respectively. However, a report in Tg2576 and APP23 mice single APP transgenic mice suggested that the inflammatory responses to A β deposition in these models was, at best, modest and was considerably weaker than that observed in AD brain (Schwab et al., 2004). It is possible that the state of microglial activation varies between the different transgenic lines; the PSAPP study (Matsuoka et al., 2001) described marked CD11b associated with plaques in PSAPP mice whereas very little CD11b labelling was observed in the Tg2576/APP23 study (Schwab et al., 2004). Our own data has shown little evidence of CD11b upregulation in TASTPM mice (Howlett, unpublished) although the microglia in these mice show greatly enhanced expression of iba-1 (Howlett et al., 2008). A number of other proteins which might be described loosely as "stress proteins" have been shown to be upregulated in APP mouse brain. Labelling of both JNK-1 and SAPK3 is increased in brains from PSAPP mice (Howlett, 2000); JNK and p38 pathways have also been shown to be activated in close association with A β deposits in APPswe x PS1.P264L mice (Savage et al., 2002). Confocal microscopy of immunolabelled sections of Tg2576 brain showed that not only were phospho-JNK/SAPK/p38 kinases upregulated but that this labelling colocalised with that for phosphorylated tau protein in dystrophic neurites (Puig et al., 2004) supporting a role for these kinases in tau phosphorylation, at least in APP transgenic mice. Activation of the p38 pathway has been associated with inflammatory pathology in AD brain (Hensley et al., 1999) and MAPK-activated protein kinase-2 (MK2) is upregulated in microglia associated with A β deposits in TASTPM brain (Culbert et al., 2006). Also upregulated in this latter study were the pro-inflammatory mediators TNF-alpha and the chemokine CCL3 (MIP-1alpha). However, although the presence of TNF-alpha has also been demonstrated in Tg2576 brain, other cytokines are notably absent compared to AD brain as are AGE-modified proteins (Munch et al., 2003). It would appear,

therefore, that some, but not all the inflammatory pathology present in the AD brain are observed in the brains of APP transgenic mice. The lack of full blown inflammatory and complement cascades may explain why APP transgenic mice do not, on the whole, exhibit marked neurodegeneration. However, the low level of chronic inflammation observed in these models is more reminiscent of the disease state than seen in, for example, acute LPS models (Stalder et al., 1997)

Rodent A β is found in plaques in APP transgenic mice

The reason why rodents, particularly mice, which have become the species for the majority of transgenic models, do not develop plaques or show any sign of accumulation of their endogenous A β is not understood. Non-human primates, dogs, polar bears (Selkoe et al., 1987) have all been described as having A β deposits. It has been widely thought that the mouse/rat A β variant with Gly-5, Phe-10 and Arg-13 replacing the human residues Arg-5, Tyr-10 and His-13 was less likely to fibrillize and be deposited although data is somewhat equivocal on the fibrillogenic nature of rodent A β (Hilbich et al., 1991; Dyrks et al., 1993). Interestingly, in recent years, rodent A β has been shown to accumulate in mice, albeit in transgenic animals overexpressing the human mutant APP and PS-1 transgenes (van Groen et al., 2006). In these animals, rodent A β is observed associated with the human A β , although some differences in distribution were reported with the mouse A β being localised to dystrophic neurites surrounding plaque cores containing human A β . It is not clear why this happens; does the human A β act as a seed, facilitating the aggregation of rodent A β ? Maybe the human A β deposit behaves like a piece of fly-paper, attracting the rodent form? Or possibly the increased human A β saturates the clearance mechanisms for human (and rodent) A β leading to accumulation of both? Obviously this is a major difference from AD plaques but understanding the rodent deposition process may help us understand the development of AD pathology.

In other ways, mouse plaques are fairly similar to human plaques in terms of the temporal deposition of A β 40 and A β 42 (Terai et al., 2001) although western blotting, reverse-phase HPLC and mass spectrometric examination of Tg2576 and APP23 animals points to subtle differences in the forms and species of A β present compared to AD brain (Kuo et al., 2001; Kalback et al., 2002). In terms of morphology, however, in Tg2576 mice, the earliest plaques are A β 42 positive with accumulation of A β 40 occurring in the core of the plaque in a similar manner to that described in AD brain (Terai et al., 2001).

Cerebrovascular amyloid

While undoubtedly senile plaques, together with neurofibrillary tangles are the main pathological features

of AD, the presence of cerebrovascular A β is a further common phenomenon, although its occurrence is not confined to AD. Interestingly, although the expression of APP in transgenic mice is directed, by virtue of the promoters used, to neurons, A β is found in the vessel walls of a number of these mouse lines posing the question as to how it got there. Vascular amyloid has been described associated with a range of vessels in APP23 mouse brain, particularly pial and larger vessels (Calhoun et al., 1999). These authors also reported the presence of microhemorrhages and iron-positive microglia suggesting that the angiopathy can lead to neurodegeneration. The A β is thought to be neuronal in origin, possibly reaching the vessel walls from the CSF via interstitial fluid drainage channels (Calhoun et al., 1999). Similar findings have been reported in other APP transgenic mice, such as APP.V717I animals where again the relatively high concentration of A β in the CSF compared to the plasma points to specific drainage pathways being involved in the movement of the A β to the vessel walls (Van Dorpe et al., 2000).

Structural changes in APP transgenic mice

A fundamental requisite of an AD disease model is that it demonstrates some aspects of a degenerative phenotype. Firstly, however, we need to consider how the disease develops and progresses. In AD, the disease process first affects the transentorhinal cortex, particularly the projection neurons of the superficial entorhinal layer (Braak Stage I). From here, the disease spreads into the superficial cellular layer itself and the first sectors of the hippocampus (Braak Stage II). As the disease develops, the lesions worsen and the deep entorhinal layers and adjoining neocortex become involved (Braak Stage III). Lesions continue to increase in density and begin to affect high order association areas of the neocortex (Braak Stage IV). Finally, in Braak Stages V and VI, the destructive pathology spreads throughout much of the neocortex (Braak and Braak, 1991). What is very obvious in the human disease process is that it is characterised by a spreading pathology.

An extensive study of plaque development and spread in PSAPP mice was described by Wengenack and colleagues (Wengenack et al., 2000). They reported that thioflavin S positive deposits were largely found in the cortex and hippocampus, the density being greatest in dorsomedial regions. The plaque number and area occupied by plaques increased linearly over the 12 month study period. In younger animals, plaque load was lowest in the entorhinal cortex, subiculum, CA1 and dentate gyrus although by 12 months all cortical and hippocampal regions had comparable densities. Another line of APP x PS1 mouse, the APPPS1-21 (Radde et al., 2006) expresses the APP-Swedish transgene plus the PS1.L166P mutation, both transgenes being under the control of the thy-1 promoter. These animals show A β deposits as early as two months of age in the neocortex.

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Deposition appeared in the dentate gyrus slightly later and in the striatum, thalamus and brain stem by 3-5 months. Most regions of the brain, including the cerebellum were affected by 19 months of age and the development of amyloid deposit was paralleled by the spread of astrocyte and microglial pathology (Radde et al., 2006). Differences in the transgenes employed appear to be responsible for subtle differences in A β deposition. The mThy1-hAPP751 mouse, expressing hAPP751 with both Swedish (K670M/N671L) and London (V717I) mutations initially shows compact deposits in the frontal cortex at 3-4 months, spreading to the subiculum, thalamus and olfactory cortex by 5-7 months and accompanied by astrocytosis and microgliosis (Rockenstein et al., 2001). Again, in older mice (9-11 months), plaques were observed in the cerebellum. In old APPS1-21 mice, A β deposits were also present in the cerebellum, a region with low transgene expression, consistent with ideas of a spreading pathology (Radde et al., 2006). This spread may be a function of the diffusion of soluble forms of A β through interstitial fluid and the extracellular space since grafts of wild-type neural cells into the cortex and hippocampus of APP23 mice resulted in the development of A β deposits and associated inflammatory pathology in the grafted tissue (Meyer-Luehmann et al., 2003).

Although familial forms of AD can be associated with mutated forms of the APP and presenilin proteins, there is no evidence that even these proteins are overexpressed. In APP transgenic mice, however, the human mutant transgenes are overexpressed and the expression has been driven by a variety of promoters which target neuronal populations in fairly gross areas. For instance, the PDGF promoter, employed in the development of the PDAPP mouse, targets expression to neurons of the cortex, hippocampus, hypothalamus and cerebellum (Games et al., 1995). It is probably hardly surprising, therefore, that the observed pathology does not totally follow the course of that of the human condition. The fact that it does spread in APP transgenic mice, as discussed earlier, does point to pathogenic similarities to AD.

Axonal disruption and neuronal loss

Although APP mice in general have suffered the criticism that they show little neuronal loss (Irizarry et al., 1997; Takeuchi et al., 2000), there are in fact a number of reports detailing loss and vulnerability of neurons. The first publication describing the PDAPP mouse refers to reduced synaptic and dendritic densities in the molecular layer of the dentate gyrus, identified by labelling with antibodies to synaptophysin and MAP-2, respectively (Games et al., 1995), a pathology resembling that observed in AD patients (Masliah et al., 1991, 2001). Further work in PDAPP mice has shown pronounced pathology in very specific neuronal populations of the dentate gyrus occurring some months

before the deposition of A β (Wu et al., 2004). Nevertheless, increases in active (cleaved) caspase-3 activity, indicative of apoptosis, have not been observed in APP transgenic mouse brain (Selznick et al., 1999; Puig et al., 2004; Howlett, unpublished observations) despite the apparent upregulation of a number of kinases, as noted earlier. In many cases, the question of neuronal loss or neuronal displacement by the physical presence of the amyloid deposit is difficult to assess. It is possible that the absence of neurons in the immediate vicinity of A β deposits in the cortex is due to displacement rather than cell loss. In regions such as the dentate gyrus with densely packed neuronal layers, however, displacement as an interpretation of the absence of neurons appears more unlikely (Radde et al., 2006; Howlett et al., 2008).

Synapse loss is a major feature of the pathology of the neocortex and hippocampus in AD and synaptic density has been shown to be correlated to cognitive decline (Davies et al., 1987; Scheff and Price, 2003). However, there is reported to be little or no correlation between neuronal loss and extracellular A β load in AD patients (Gomez-Isla et al., 1997). There is a loss of synaptophysin in many APP transgenic mouse lines (Games et al., 1995; Hsia et al., 1999; Richardson et al., 2003; Rutten et al., 2005) and synaptotoxicity has been reported prior to plaque deposition in PDAPP mice (Mucke et al., 2000).

EM studies have shown that there is evidence of synapse loss within close proximity of A β deposits in Tg2576 mice (Dong et al., 2007) and significant decreases specifically in cholinergic synapse size and density in PSAPP animals (assessed by light microscopy) has been reported (Wong et al., 1999). These mice also show a variety of synaptic abnormalities in the vicinity of A β deposits which appear to lead to neurite breakage and disruption of neuronal connections (Tsai et al., 2004). This is also supported by tracer experiments in an alternative line of APPxPS1 mice (APP^{swe}+London x PS1.M146) where plaque-associated axonal dystrophy has been reported (Delatour et al., 2004), pointing to a disruption of cortico-cortical circuitry. These mice have also been reported to have an age-dependent loss of synaptophysin-immunoreactive presynaptic boutons in the dentate gyrus and CA1-3 of the hippocampus (Rutten et al., 2005). A loss of boutons and pyramidal neurons in areas free of plaques suggests the possibility of synaptic degeneration independent of extracellular fibrillar deposited A β (Schmitz et al., 2004; Rutten et al., 2005). The deposition of A β in APP23 mice is characterised by an induction of dystrophic boutons, ectopic presynaptic terminals and aberrant axonal growth (Phinney et al., 1999). Obviously the existence of such abnormalities in AD brain is likely to contribute significantly to the course of the disease process.

The existence of a "toxic gradient" of A β has been suggested (Urbanc et al., 2002; Schmitz et al., 2004) and a halo of neuronal loss surrounding extracellular

deposits in the dentate gyrus has been described in TASTPM animals (Howlett et al., 2008). Other APP transgenic mice do show significant neuronal loss. For instance, a novel transgenic model expressing APP^{swe}+London x PS1.M233T/L235P is reported to show greater than 50% neuronal loss in the CA1/2 of the hippocampus at 10 months of age (Casas et al., 2004). These mice exhibit extracellular plaques plus intraneuronal fibrillar A β and neuronal loss was shown to correlate with intraneuronal A β rather than extracellular A β deposits. A correlation between neuron loss and age has been noted in APP23 mice, although in younger animals (ie. pre-plaque) there was actually an increase in neuronal number (Bondolfi et al., 2002). This may be a function of the neuroprotective effects of soluble fragments of APP (Mattson et al., 1993) rather than an effect on neurogenesis of which there is little evidence in APP23 animals (Bondolfi et al., 2002).

Although, as commented above, active caspase-3 immunoreactivity is not apparent in APP (+/- PS1) mice, when Tg2576 mice were crossed with a nitric oxide synthase knock-out animal, the resulting APP^{swe}/NOS2^{-/-} mice exhibited activated caspase-3 in cell bodies and apical dendrites of the cortex and hippocampus (Colton et al., 2006). These animals were characterised by widespread cortical neurodegeneration with cleaved caspase-3 immunoreactivity being present in hippocampal neurons. It has also been shown that active caspase-3 colocalises with A β and tau intraneuronally in AD tissue (whereas extracellular plaques and tangles lacked caspase-3) (Rissman et al., 2004) suggesting that the neuronal loss in APP/NOS2^{-/-} mice may be mediated by the removal of NOS as an inhibitor of caspase-3 activation. In contrast, however, APP^{swe} x PS1.A246E/ NOS2^{-/-} mice demonstrate a decrease in amyloid plaque load and microglial activation, together with an increased life span (Nathan et al., 2005) pointing to some interaction between mutant PS-1 and nitric-oxide mediated neurotoxicity.

Early pathology

In general, the observed pathology develops alongside plaque deposition in mouse models - which is maybe not surprising seeing as the appearance of A β plaques are such a major feature of the ageing APP transgenic mouse brain. However, A β levels in the brain are elevated prior to plaque deposition (Hsiao et al., 1996; Kawarabayashi et al., 2001; Richardson et al., 2003) and, what is often neglected, expression of APP is greatly elevated from a few days post-natally, a feature dependent upon the particular promoter employed. Evidence for features preceding A β plaque appearance is not widespread. In PDAPPs, it has been reported that s100beta expression and lipid peroxidation were elevated prior to plaque deposition (Sheng et al., 2000) while dentate gyrus volume was decreased in 100 day old mice (Redwine et al., 2003). There is also evidence of dendritic abnormalities in the dentate gyrus of PDAPP

mice in 90 day old mice, preceding A β deposition by a number of months (Wu et al., 2004). Interestingly, cognitive impairments have been reported months before plaques appear (Hsiao et al., 1996; Richardson et al., 2003; Van Dam et al., 2003) suggesting that either soluble A β forms play a role or that APP and/or fragments have physiological activities.

Regulation of plaque deposition

The aetiology in the vast majority of cases of AD is unknown although it is presumed that environmental factors encountered during the patient's life may have contributed to the onset and development of the disease. In non-transgenic rodents, however, other than a few isolated reports where fairly aggressive surgical interventions have been used, there is little in the way of evidence for the deposition of endogenous rodent amyloid. It needs to be remembered that in man, A β plaque deposition is not an absolute determinant of AD and that many, if not all, cognitively normal elderly individuals have some degree of A β deposition, particularly those living into their ninth and tenth decades and beyond (Haroutunian et al., 1998; Leuba et al., 2001). Therefore, it may be reasonable to assume that the human brain is predisposed to AD in that the "ammunition" is already present and simply needs the appropriate trigger to be pulled, with the possibility of that trigger being some sort of environmental insult. The lack of correlation between plaque deposition and disease progression also points to other factors, possibly soluble oligomeric forms of A β , as being of aetiological significance.

A number of studies have investigated factors which may affect plaque deposition in APP transgenic mice. Although these studies have generally been aimed at factors reported to influence the development of AD in man, there is certainly a good correlation between the human data and that in transgenic models. One major area of study has been dietary intervention. Caloric restriction has been reported to protect against the development of AD (Pasinetti et al., 2007) and, similarly, a comparable restriction in diet in APP x PS1 mice decreased both plaque and astrocyte pathology (Patel et al., 2005; Wang et al., 2005). The possible benefits of therapies involving statins (Sparks et al., 2005; Kivipelto et al., 2005) have pointed to hypercholesterolaemia as a risk factor, although most studies do not, in fact, support this (Wood et al., 2005). Nevertheless, dietary composition appears to play some role in that hypercholesterolaemia accelerates plaque pathology in APP x PS1 mice (Refolo et al., 2000) while Tg2576 mice fed a diet enriched in the omega-3 fatty acid, docosahexaenoic acid (Lim et al., 2005) displayed attenuation of deposition. Also in support is the observation that interfering with cholesterol homeostasis by LDL-receptor knock-out enhanced plaque deposition in Tg2576 mice. The benefits of regular exercise for Alzheimer patients have been well documented (eg.

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Rolland et al., 2007) and exercise has been shown to decrease plaque load in APP23 mice (Adlard et al., 2005). It has also been claimed that maintaining an active mind offers protection against AD and, in a loosely comparable manner, environmental enrichment protected against plaque deposition in APP x PS1 mice (Lazarov et al., 2005), possibly by the stimulation of neurogenesis (Komitova et al., 2005). Conversely, stress may be a protagonist in plaque formation. Glucocorticoids increased deposition in 3Tg mice (Green et al., 2006) and Tg2576 animals showed signs of oxidative damage associated with the A β deposits (Smith et al., 1998). Furthermore, both C1q and alpha-1 antichymotrypsin facilitated deposition in APP x PS1 animals (Nilsson et al., 2001; Boyett et al., 2003; Fonseca et al., 2004). Thus, in a varied selection of situations, data relating to the regulation of plaque pathology in APP transgenic mice is supportive of data describing factors causing cognitive improvements or disease modifications in AD patients.

Somewhat conversely, in contrast to their proposed deleterious role when activated to release cytokines, microglia are also capable of the uptake and degradation of multimeric forms of A β (Frautschy et al., 1992; Chung et al., 1999). Although CNS-resident microglia may be activated by A β peptides, it is possible that newly recruited bone marrow-derived microglia play a major role in clearance since cells of this type are specifically attracted to A β peptides (Simard et al., 2006). The clearance of A β may be mediated by Toll-like receptors since activation of microglia with Toll-like ligands increases the ingestion of A β *in vitro* (Tahara et al., 2006). The possible involvement of Toll-like receptors in A β clearance is also supported by data showing that the intranasal administration of the proteasome-based adjuvant Protollin to APP-J20 transgenic mice decreases A β deposition with activated microglia colocalising with the amyloid (Frenkel et al., 2005). Protollin is composed of LPS plus membrane proteins from *Neisseria meningitides*, both factors being able to stimulate microglial activation through Toll-like receptors (Weiner and Frenkel, 2006). Microglial phagocytosis of A β plaques has also been claimed to be responsible for the decrease in amyloid deposits following immunization with the A β peptide (Schenk et al., 1999). This latter belief is also supported by reports that the induction of microglia by intrahippocampal injection of lipopolysaccharide (LPS) results in the attenuation of A β deposition in APP transgenic mice (DiCarlo et al., 2001).

In contrast to these findings, the intraventricular injection (Qiao et al., 2001) or systemic administration of LPS (Sheng et al., 2003) results in astrocytosis and microgliosis, accompanied by an upregulation of APP and A β deposition. A further study demonstrated that systemic LPS administration to transgenic mice harboring mutant APP^{swe} + PS1.M146V + tau.P301L (3xTg-AD) stimulated microglial activation, had no effect on APP or A β expression/deposition but

exacerbated tau pathology with increases in Ser202/205 phosphorylated tau which accumulated in the CA1 region of the hippocampus (Kitazawa et al., 2005). It is not clear whether these opposing data reflect differences between the mouse models, the age of the animals at injection or the route of administration but the data may also hint that microglia can play very differing roles in the human brain.

In an attempt to gain some insight into the processes driving the development of plaque pathology in AD, additional surgical insults have been directed at various APP transgenic mice. Lesions of the locus coeruleus with the noradrenaline-depleting neurotoxin DSP4 were reported to promote astrocytic and microglial changes in LC projection areas, notably the hippocampus and frontal cortex in APP23 mice (Heneka et al., 2006). These pathological changes were accompanied by increased A β plaque deposition, neuronal degeneration and cell loss plus evidence of enhanced cognitive deficits. The entorhinal cortex is also important for the development of plaque pathology in the hippocampus since ablation of this area in APP x PS1 mice decreased the development of hippocampal A β plaques, A β load and APP-positive dystrophic neurites (Sheng et al., 2002). This suggests that connections arising from the entorhinal cortex play an important role in the spread of pathology to the hippocampus in AD.

Drug effects

One of the major driving forces behind the quest for mice which deposit A β in the brain is undoubtedly the need for an animal model for testing potential amyloid lowering therapeutics. Obviously, an acceptance of the amyloid hypothesis (Hardy and Higgins, 1992) and the seminal role of amyloid deposition in the pathogenesis of AD is crucial in the decision to adopt this type of model. In the search for amyloid lowering compounds, one of the first type of agents tested in APP transgenic mice were inhibitors of the fibrillization process itself. Many inhibitors of this process have been demonstrated to be effective *in vitro* (Howlett, 2001) although few have made the transition into animal models. One of the first was the so-called beta-sheet breaker pentapeptide iA β 5p, a non-aggregatory compound with homology to the central hydrophobic core of A β . When administered by ICV and intraperitoneal routes to APP x PS1 or single APP.V717I mice, significant decreases in plaque load, astrocytosis and microglial activation were observed together with increases in neuronal survival (Permanne et al., 2002). The Cu-Zn chelator clioquinol, although not a direct inhibitor of A β fibrillization, had a similar effect to the iA β 5p peptide in aged Tg2576 mice (Cherny et al., 2001). Oral administration of clioquinol over 9 weeks significantly lowered A β deposition although there was little evidence of changes in astrocytosis. These studies demonstrate that APP transgenic mice provide a means of assessing inhibitors of the amyloid fibrillization process.

The scarcity of brain penetrant compounds interfering with APP processing through either beta or gamma secretase inhibition has limited the use of APP transgenic mice for studying drugs of this type. Inhibition of both beta- (Hussain et al., 2007) and gamma-secretases (Lanz et al., 2003; Barten et al., 2005) has been demonstrated in acute studies in young transgenic mice. In older mice this inhibition has not translated into effects on plaque load (Lanz et al., 2003; Barten et al., 2005).

Other compounds which may regulate processing through as yet unknown or fully understood mechanisms have been reported as having effects on plaque pathology. Such drugs include ibuprofen (Lim et al., 2000; Heneka et al., 2005), curcumin (Lim et al., 2001) and pioglitazone (Heneka et al., 2005). Although it does not appear to have effects on A β , lithium administration has been shown to decrease tau phosphorylation in 3xTg-AD mice (Caccamo et al., 2007). Despite the effects on tau phosphorylation, the memory deficits in these animals was maintained, however, supporting a role of A β in cognitive abilities.

Arguably the most successful means of lowering A β plaque load in APP transgenic mice has been with amyloid antibodies, following either active or passive vaccination. The first report showed that immunization of young PDAPP mice with fibrillar A β 1-42 (active vaccination) prevented plaque formation and the associated pathology; immunization of older animals also attenuated the development of these pathologies (Schenk et al., 1999). Similar findings have been reported by other groups (Janus et al., 2000; Lemere et al., 2003b). Other reports have described the effects of peripheral administration of A β antibodies (passive vaccination); many of these decrease plaque pathology either by crossing the blood brain barrier (Bard et al., 2000) or by altering CNS and plasma clearance of A β (DeMattos et al., 2001). The many studies describing the effects of potential A β antibody therapeutics are beyond the scope of this review although in general, in parallel to the decreases in plaque load there are concomitant changes in other pathologies (eg. Sigurdsson et al., 2001; Lemere et al., 2003a; Buttini et al., 2005).

A human clinical trial of active vaccination with human A β was halted due to an unacceptable incidence of meningoencephalitis (Hock et al., 2003; Nicoll et al., 2003; Orgogozo et al., 2003). A similar response to both active and passive vaccination has been reported in Tg2576 mice (Lee et al., 2005). The occurrence of this effect, typified by the presence of mononuclear infiltrates, was confined to regions of the mouse brain showing A β pathology suggesting that the changes are related to antibody binding to plaque and possibly eliciting an inflammatory response. It is possible that the deposition of immunoglobulin in the walls of the cerebrovasculature may lead to leakiness in the blood brain barrier and a triggering of an immune response. Certainly changes in vessel structure have been observed in APP23 mice following immunization (Pfeifer et al., 2002; Burbach et al., 2007).

Conclusions

To return to the title of this review, evidence does suggest that APP transgenic mice possess a number of the pathological features of AD. Principally they display A β plaques and the characteristics of these plaques are similar to those in the disease state, namely they contain various A β peptide species and they are surrounded by activated astrocytes and microglia. They also show phosphorylated tau associated with the A β deposits. Current thinking leads to the belief that neurodegenerative changes occurring in AD brain may be a product of small oligomers of A β . What these models have also shown is that increases in A β production per se, whether it be in oligomeric or fibrillar form, is not sufficient to elicit neurofibrillary tangle formation, at least within the time frames studied. Similarly, although there is some local neuronal loss in close proximity to the plaques, evidence of neurodegeneration or synaptic loss resembling that seen in the disease state is minimal. The extent to which these animals prove to be useful models of AD, where drug interference with the A β deposition process can be translated into clinical efficacy, is yet to be proven.

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