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What Can Rodent Models Tell Us About Cognitive Decline in Alzheimer's Disease?

Sabrina Davis* and Serge Laroche

Laboratoire de Neurobiologie de l'Apprentissage, de la Mémoire et de la Communication, CNRS UMR 8620, Université Paris-Sud, 91405 Orsay, France

Abstract

The prolongation of life and the rapidly increasing incidence of Alzheimer's disease have brought to the foreground the need for greater understanding of the etiology of the disease and the means to prevent or at least slow down the process. Out of this need the transgenic mouse and the production of synthetic amyloid peptides have been developed in an attempt to create experimental models of Alzheimer's disease that will help our understanding of the cellular and molecular mechanisms by which the pathology leads to memory dysfunction and to test potential therapeutic strategies. Despite 10 or so years of reasonably intensive research with these models, both fall short of producing a viable and faithful model of the complete pathology of Alzheimer's disease and the behavioral consequences are far from modelling the progressive decline in cognitive function. Here we review the advantages and the caveats associated with the two models in terms of the pathology, the associated memory dysfunction, and the effect on synaptic plasticity. Given the more recent advances that have been made in the understanding of the neurobiological changes that occur with the disease and with the consideration of other environmental effects, which have been clearly shown to have an impact on the progression of the disease in humans, we emphasis the advantage of pharmacological or environmental in transgenic mice or rodents injected with synthetic peptides that may prove to be more fruitful in our understanding of the memory deficits associated with the disease.

Index Entries: Transgenic mice; synthetic amyloid peptides; synaptic plasticity; learning and memory; APP; PS1.

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* Author to whom all correspondence and reprint requests should be addressed. Email: sabrina.davis@ibaic.u-psud.fr

Introduction

Alzheimer's disease (AD) is the most common neurological disorder that leads to dementia of an unknown etiology. It is characterised at the clinical level as an age-related, irreversible brain disorder that results in the loss of memory, a decline in cognitive abilities, and behavioral and personality changes. It has an insidious onset, starting with mild, almost unnoticeable memory loss, and advances to the terminal stages between 8 and 10 yrs later, where there is complete memory loss for all life-time events and disruption in general cognitive ability, including the loss of verbal and motor control (*see* Reisberg et al., 1982). At a neuropathological level, postmortem examination shows neuronal and synaptic loss, brain atrophy, inflammation, and the widespread presence of the two classical signs of AD, the senile plaque (SP) and the neurofibrillary tangle (NFT). AD is also categorised as being either familial AD (FAD) and sporadic AD (SAD). FAD is a mendelian-inherited disease, identified in a number of different families and has an early onset, which can start in the early 40s. A number of studies have shown that the risk for developing AD during the lifetime of first degree relatives is close to 50% (Mohs et al., 1987; Farrar et al., 1995).

SAD, which constitutes the majority of cases, occurs with no obvious mendelian-inherited abnormalities, and yet patients with this form of the disease display essentially the same clinical and neuropathological profile to FAD. It constitutes the majority of the cases of AD; approx 90 to 95% of all reported cases with a late onset after about 60 to 65 yrs (Goedert et al., 1994). Certain environmental risk factors have been identified that may contribute to the development of this form of the disease, such as brain damage, stroke, and increased blood cholesterol levels. Other environmental factors may include low education, exposure to toxic substances, and head trauma (Stern et al., 1994; Snowden et al., 1996). To date, the cause(s) of SAD remains unknown, but as both FAD and SAD share almost identical clinical and neuropathological characteristics, it has been suggested that, at least some of the genes identified in FAD may be relevant to the nonfamilial form of SAD. One of the most important nonmendelian genetic risk factors is Apolipoprotein E4 (ApoE4), a lipoprotein that is synthesised in the brain by astrocytes and is thought to be involved in the mobilization and redistribution of cholesterol and phospholipids during membrane remodelling associated with synaptic plasticity. The ApoE4 allele shows a dose-dependent increase in the risk for AD, and has been estimated as being as much as a 50% risk for AD.

Although a multifaceted process that involves many different gene products and cellular pathways, the classic and definitive neuropathological features of AD are the SP and the NFT (*see* reviews by Dickson, 1997; Selkoe, 1999; Mandelkow and Mandelkow, 1998). The amyloid plaque is produced as a proteolytic product of the amyloid precursor protein (APP). APP is a large, ubiquitously expressed polypeptide that contains several functional domains. These include the kunitz protease inhibitory (KPI) domain (Kang et al., 1987), an OX.2 domain (Kitaguchi et al., 1988), and specific binding sites for heparin (Small et al., 1994), zinc (Bush et al., 1993), and copper (Hesse et al., 1994). Alternative splicing and posttranslational modifications give rise to several isoforms of the protein of differing lengths, but all which contain the β-amyloid peptide. Shorter forms of the polypeptide, that lack the KPI region are found exclusively in the central nervous system (CNS), and evidence has shown that it is involved in growth-promoting activities (Ohyagi and Tabira, 1993), neurite extension (Jin et al., 1994), and synaptic plasticity (Stéphan et al., 2002a). In patients with AD there is a strong correlation between the ratio of increase in the mRNA for APP751 to APP695 and the density of senile plaques in the hippocampus and entorhinal cortex (Johnson et al., 1989; 1990).

The Aβ peptide of 42–43 amino acids in length, spans the transmembranal portion of APP. Under normal or what is described as

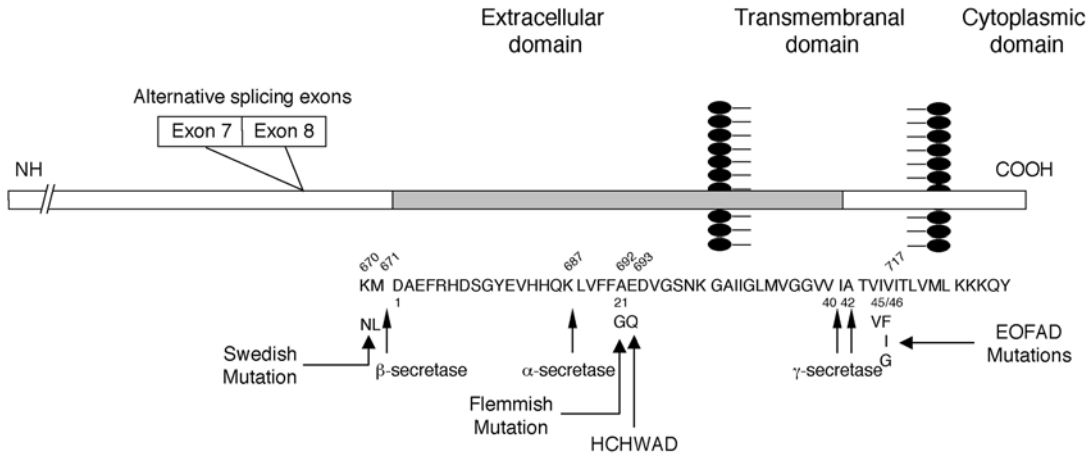

Fig. 1. Schematic representation of the Aβ peptide spanning the transmembranal domain. The peptide sequence is represented in gray and shows the amino acid sequence. Numbering above the sequence represents the amino-acid numeration based on the full length of the amyloid precursor protein (APP) and where point mutations have been identified in known cases of FAD. Numeration below the sequence represents that of the β-amyloid peptide. Small arrows indicate scission by the three secretases and the large arrows indicate the position and amino-acid substitutions of the different FAD families. (Adapted from Koscic [1999].)

nonamyloidogenic processing, the amyloid peptide is cleaved by the α-secretase between amino acids 16 and 17 of the Aβ region, leaving an 83 amino acid sequence of the C-terminal fragment of APP in the membrane. This results in the release of a large soluble ectodomain fragment of APP. In the amyloidogenic processing pathway, the peptide is first cleaved by the β-secretase and then undergoes scission by the γ-secretase where the full-length peptide is released in its entirety into the extracellular space (*see* review by Selkoe, 1999). The β-secretase has been identified as the β-site APP cleaving enzyme or BASE (Vassar et al., 1999; Vassar and Citron, 2000), and it is believed that the presenilins, PS1 and PS2 could be components of γ-secretase (Yu et al., 2000; Sisodia et al., 2001) with PS1 taking precedence over PS2 (Wolfe et al., 1999) (*see* Figure 1). Once in the extracellular space, the Aβ peptide forms beta-pleated sheets which aggregate into dense-core senile plaques (*see* Figure 2). Over the past 10 yrs a considerable amount of research has been conducted to elucidate how soluble Aβ, secreted into the extracellular space progresses into the aggregated senile plaque. Studies have shown that in detergent-soluble conditions, Aβ generally forms an α-helix or monomeric conformation, whereas in its insoluble form it is in a β-pleated sheet or oligomeric conformation. It is thought that modifications in the side chains may act as a mechanism for switching the α-helical structure to the oligomeric β-sheet conformation. This oligomeric form is polymerized in a concentration-dependent manner to form protofibrils that are considered as small order fibrils or the precursors of fully formed fibrils. It has been suggested that protofibrils proceed into fully formed fibrils by a process of elongation and association with other protofibrils by an unknown mechanism (*see* Serpell, 2000; Dumery et al., 2001; Pallitto and Murphy, 2001 for reviews). The fully formed fibril forms the core of the senile plaque and become surrounded by dystrophic neurites, glia and astroyctes, which induce inflammation, and eventually the plaque burns out. Studies in cell cultures have shown that Aβ is neurotoxic (Cotman et al., 1992; Mattson, 1997; Pike et al., 1991; 1993) and can activate proteins and genes involved in apoptosis (Loo et al., 1993; Estus et al., 1997; Stadelmann et al.,

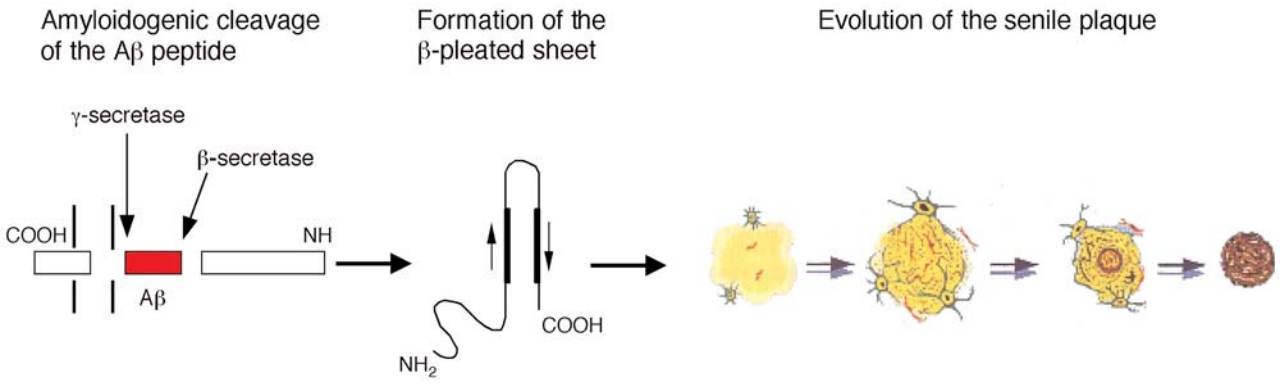

Fig. 2. Amyloidogenic processing of the Aβ peptide. Under amyloidogenic processing the Aβ peptide is cleaved by the β-secretase within the membrane and the γ-secretase in the ectodomain. The full-length peptide is released into the extracellular space where it begins to form a β-pleated sheet. It then starts to aggregate into an amyloid plaque and becomes surrounded by an increasing number of astrocytes and microglia, as it forms a dense core. Finally it burns out and astrocytosis and microgliosis diminish. (Adapted from Griffin et al. [1997].) Color image available for viewing at **www.humanapress.com**

1999; Mattson, 2000). The predominant forms of Aβ are the Aβ40 and Aβ42 (Wang et al., 1996). They appear to be generated in different intracellular compartments and the Aβ42 has a greater tendency to self-aggregate (Jarrett and Landsbury, 1993), whereas Aβ40 tends to remain soluble. In humans without senile plaques at the age of less than 50 yrs there are very low detectable levels of soluble, nonaggregated Aβ42, whereas in AD patients over the age of 80 yrs there is a significant increase in both soluble and insoluble levels of Aβ42. A shift towards the production of more Aβ42 has been observed in patients with early-onset AD (Scheuner et al., 1996; Lendon et al., 1997) and genetically engineered mice (Citron et al., 1997), suggesting that this is the toxic species involved in the pathogenesis of AD (Younkin, 1995).

The neurofibrillary tangle consists of paired helical filaments that are composed of polymerized tau proteins which have been abnormally hyperphosphorylated (Grundke-Iqbal et al., 1986a; 1986b; Lee et al., 1991). There is a presence of NFTs in the early stages of the disease and the presence of "ghost tangles" in the later stages that suggest NFTs may be associated with cell loss (Gomez-Isla et al., 1997). Unlike the genes encoding APP and PS, which in mutated form give rise to several different forms of FAD, there is no genetic linkage for the role of tau in AD. Mutations of the gene *tau* are associated with fronto–termporal dementia and Parkinsonism, forms of dementia that do not show plaque pathology (*see* Dewacher et al., 2000). Until more recently it was considered that the NFT and neuronal cell loss showed the best correlation with the clinical syndrome, with the presence of amyloid plaques showing only a poor correlation (Katzman et al., 1988; Terry et al., 1991; Arriagada et al., 1992; Berg et al., 1993). In light of more sophisticated techniques for measuring amyloid deposits however, evidence is mounting to suggest that amyloid may in fact be a good predictive marker (Cummings et al., 1996; Bartoo et al., 1997; Naslund et al., 2000); not as mature, burnt out plaques, but in the form of small Aβ oligomers or protofibrils (Hartley et al., 1999; Wang et al., 1999; Mucke et al., 2000).

In addition, recent evidence suggests that inflammation and oxidative stress in the brain may have a more important contributory role in the pathological progress of AD than was previously thought. Postmortem studies show massive inflammation, accompanied by the

presence of activated microglia and reactive astrocytes in the brain tissue of patients with AD. Microglia surrounds mature amyloid plaques and can promote phagocytosis and remove neurotoxic plaques. Although it can take up and degrade amyloid plaques, the rate of degradation cannot keep up with the amount of Aβ present in the cells (Paresce et al., 1997; Weldon et al., 1998) and the cells may become overwhelmed by Aβ. It has also been suggested that their presence may exacerbate the pathology, as many proinflammatory proteins such as the acute phase proteins, complement proteins, inflammatory cytokines, protease inhibitors, and prostoglandins have been identified in AD brains; many of which are activated by microglial cells (*see* reviews by McGeer and McGeer, 2001; Strohmeyer and Rogers, 2001). In addition, Aβ has also been shown to interact directly with microglia and induce a microglial reaction via a cell-surface receptor, RAGE (Yan et al., 1996). Importantly, activation of this receptor and an unrelated scavenger receptor (SR) by Aβ can also lead to oxidative stress of microglia (El Khoury et al., 1996; Yan et al., 1996). Growing evidence suggests that the inflammatory response may not merely constitute a secondary, or side effect of amyloid and tangle pathology, but may have a more direct and considerably more important role in the pathology. Longitudinal epidemiological studies, for example, have shown that there could be up to a 50% reduction in the risk of AD associated with the consumption of nonsteriodal anti-inflammatory drugs (Breitner et al., 1995; Stewart et al., 1997; McGeer and McGeer, 1998).

Oxidative stress or damage to the cells results from overproduction of free radicals; molecules primarily formed as by-products of oxygen metabolism (Halliwell, 1992; Friedlich et al., 1994; Benzi and Moretti, 1995). These and other toxic compounds such as hydrogen peroxidase are collectively referred to as reactive oxygen species (ROS). The overproduction of ROS results in an imbalance in the homeostatic defence mechanisms of the cell, triggering nucleic-acid breakdown, increases in intracellular calcium, protein damage, and lipid peroxidation (Mattson, 2000). In vitro studies have shown that Aβ proteins can generate free radicals (Behl et al., 1994; Hensley et al., 1994; Harris et al., 1995; El Khoury et al., 1996; Yan et al., 1996) and this toxicity can be reduced by antioxidants (Bruce et al., 1996; Tomiyama et al., 1996). Anti-oxidant compounds, tested in clinical trials, have shown that although modest, the treatment does have some benefit to patients (Mangoni et al., 1991; Sano et al., 1997).

Over the past 20 yrs much advancement has been made in our understanding of how the disease progresses in terms of the molecular and cellular mechanisms underlying neuropathology. For example, evidence is now emerging to suggest that there may be links between the various elements in the pathology that were not previously obvious. Three key discoveries have been: (1) amyloid and PS1 may be linked with hyperphosphorylated tau via the WNT/wingless pathway and the proapoptotic enzyme GSK3β (Takashima et al., 1993; 1998a; 1998b; Soriano et al., 2001; Mudher and Lovestone, 2002); (2) Aβ can interact with and promote inflammatory response elements and oxidative stress (*see* above); (3) oligomeric Aβ and protofibrils cause neurotoxicity (Roher et al., 1996; Lambert et al., 1998; Walsh et al., 1999; Mucke et al., 2000), perturb cell metabolism and cause cell loss (Hartley et al., 1999). Although these data provide important information that may lead to a more clear understanding of how the pathology may progress, the actual cause of the disease has, to date, remained somewhat illusive.

The most critical risk factor in the disease is age. Postmortem examination of aged brains from persons known not to be suffering from AD, also show similar pathological features as that in the AD brain, although to a much lesser extent (Morris et al., 1991). For example, there is a presence of amyloid plaques, although they are less numerous, and more diffuse (Morris et al., 1996; Troncoso et al., 1996). In addition, overproduction of ROS, altered calcium homeostasis, and an increase in the pres-

ence of activated glia and astrocytes are common features of the aged nondemented brain (*see* Mattson, 1997).

In an attempt to understand the etiology of the disease and exactly how the pathological elements of the disease induce the devastating effects on memory, two major approaches have been adopted over the past 15 yrs : the development of transgenic mice overexpressing mutated or nonmutated human genes commonly associated with AD, and the use of synthetic amyloid peptides to induce aggregated amyloid in rodents brains. Each approach has its merits and has certainly helped our understanding of the disease immensely, but they also have their caveats and these must be considered with caution.

APP Transgenic Mouse Models of AD

The production of transgenic mice overexpressing genes associated with AD arose out of the identification and sequencing of the mutated genes in families with FAD. To date, these families have shown mutations in genes encoding the amyloid precursor protein (APP) and presenilin 1 (PS1) and 2 (PS2). Six mutations of the *APP,* located on chromosome 21, have been linked to families with AD, but only one mutation, a substitution of valine for isoleucine at codon 717 has been shown in more than one family; in fact it has been observed in 16 families of European and Japanese origin. Widescale analyses of cases of FAD show that mutations in *APP* constitute between 5% and 20% of all known cases of FAD and is a rare cause of the disease (Schellenberg et al., 1991; Tanzi et al., 1992; Campion et al., 1995). More recently, certain families with FAD have been shown to have mutations in the *presenilin* genes. Over 50 families of different ethnic origins have been found to have mutated forms of the *PS1* gene located on chromosome 14, whereas mutations in *PS2* located on chromosome 1 have been identified in several Volga German families (Levy-Lahad et al., 1995a; 1995b) and one Italian family (Rogaev et al., 1995). As with mutations on *APP,* the mutations on *PS2* constitutes only a rare form of the disease, whereas 50 missense mutations on the *PS1* gene accounts for between 30 and 50% of all early onset cases of the disease (Cruts et al., 1996). An additional fourth gene, *apolipoprotein E (ApoE)* located on chromosome 19, has been identified which confers an increased risk for the development of AD, based not on an autosomal dominant pattern as with the other genes, but on frequency of the e4 allele (Strittmatter et al., 1993). Increased frequency of ApoE4 has been shown to be present in both early and late onset AD (Strittmatter et al., 1993; Roses, 1994), and constitutes a genetic risk factor.

Amyloid Pathology in APP Transgenic Mice

The first generation of transgenic mice were engineered to overexpress different lengths or portions of nonmutated human *APP* transgenes, including the β-amyloid peptide (Wirak et al., 1991), the C-terminal portion of *APP* (Kawabata et al., 1991; Sandhu et al., 1991; Fukuchi et al.,1992; Kammesheidt et al., 1992; Greenberg et al., 1995), or the full length *APP751* (Quon et al., 1991; Higgins et al., 1993; Mucke et al., 1994; Higgins et al., 1995; Moran et al., 1995, and *APP695* (Quon et al., 1991; Greenberg et al., 1993; Higgins et al., 1993; Mucke et al., 1994; Higgins et al., 1995) or isoforms of *APP,* either as wild type (Mucke et al., 1994) or as a FAD mutation (Mullan et al., 1992; Mucke et al., 1994). Despite the number of variations and the number of different groups engineering these transgenic mice, few of these studies showed an increase in the levels of *APP* RNA above the endogenous levels and none showed development of age-related amyloid pathology in a convincing manner.

This led to the second-generation mice that were constructed with mutations on human *APP* or *PS1* transgenes, or a combination of both. All appear to show an age-related increase in the development of fully matured amyloid pathology similar to that observed in humans (Games et al., 1995; Hsiao et al., 1996; Moechars et al., 1999). The PDAPP transgenic

mouse (Games et al., 1995) was generated using a PDGF promoter to drive a human *APP* minigene encoding the full-length APP containing a mutation at codon 717, as has been observed in a single family (Murrell et al., 1991). In contrast, the tg2576 line (Hsiao et al., 1996) has a double mutation on the *APP695* isoform that is present in a single Swedish family with early onset AD (Mullan et al., 1992). The rationale for choosing the shorter isoform of APP was based on the fact that it is this isoform, lacking the KPI domain, which is predominantly expressed in neurons. The tgAPP/Ld transgenic mouse (Moechars et al., 1999) was based on a substitution of isolecine for valine at codon 717, reported in a London family with early onset AD (Goate et al., 1991) that was subsequently observed in 16 families of both European and Japanese origin.

In these three lines the development of age-related amyloid deposits appears to correlate with an increase in levels of Aβ42, in brain regions normally showing amyloid plaques in humans with AD (Games et al., 1995; Hsiao et al., 1996; Masliah et al., 1996; Moechars et al., 1999). Aβ deposits are associated with dystrophic neurites and are surrounded by reactive microglia and astrocytes, indicating an inflammatory response. None of the mice, however, showed the presence of NFTs or loss of cells, but did show hyperphosphorylated tau (Games et al., 1995; Hsiao et al., 1996; Irizzary et al., 1997a; 1997b; Moechars et al., 1999). In all three lines there was an increase in the level of APP protein, between a 5 to 6-fold (Hsiao et al., 1996; Moechars et al., 1999) and 10-fold increase (Games et al., 1995), but the development of amyloid plaques differed between the three lines. PDAPP mice showed no overt expression of the pathology between the age of 4 to 6 mo, but by 6 to 9 mo the pathological markers began to appear in brain structures known to be targeted by AD pathology, developing into robust amyloid pathology after 9 mo (Games et al., 1995; Johnson-Wood et al., 1997). In the tg2576 line, mice displayed both diffuse and dense-core amyloid plaques at the age of 9 mo and by 11–13 mo there was a 5-fold increase in Aβ40 and a 14-fold increase in Aβ42 (Hsiao et al., 1996). In the tgAPP/Ld line there was no presence of amyloid plaques until the age of 12 mo (Moechars et al., 1999).

Two experimental lines of transgenic mouse, not related to specific human kindred's have been developed, combining the K670N/M671 (Hsiao et al., 1996) and the V717I (Moechars et al., 1999) mutation sites (Sturchler-Pierrat et al., 1997) or the K670N/M671 and V717F (Games et al., 1995) mutation sites (Chishti et al., 2001). As transgenic mice with the individual mutations have been shown to develop amyloid pathology, the aim of double mutations was presumably to either accelerate the development of the pathology or to intensify it. The tgCNRD8 (combination of K670N/M671 and V717F mutations) transgenic mouse developed amyloid plaques that also showed a parallel increase in Aβ42 at the age of 3 mo. The plaques were dense-core from an early age and increased in size with age such that at the age of 5 mo mice exhibited dystrophic neurites similar to AD pathology. As with the other transgenic mice, these mice showed reactive microglia and astrocytes, hyperphosphorylated tau, but lacked the presence of neurofibrillary tangles (Chishti et al., 2001). The combined K670N/M671–V717I mutation (Sturchler-Pierrat et al., 1997; Calhoun et al., 1998) showed a 7-fold increase in APP expression, and the presence of congophilic amyloid in mice at the age of 6 mo. There was heavy presence of inflammation (Sturchler-Pierrat et al., 1997; Bornemann et al., 2001) which correlated with plaque burden and the presence of hyperphosphorylated tau. Unlike the other APP transgenic mice, there was a reported observance of about 25% loss of cells in CA1 in 14–18-mo old mice (Sturchler-Pierrat et al., 1997). All of these lines of transgenic APP mice, show similar pathology that most closely resembles the amyloid pathology in AD. Although they constitute the best rodent models of FAD neuropathology to date, none faithfully mimic the pathology in humans and they are based on rare cases of FAD.

Presenilin Transgenic Mouse Models of AD

As the majority of familial cases of AD have been shown to have missense mutations on the gene-encoding presenilin 1, several lines of transgenic mice were developed to determine its role in the pathogenesis of AD. *Presenilin* genes encode polytopic transmembrane proteins localized in the nuclear envelope, the endoplasmic reticulum, and golgi apparatus (Levy-Lahad et al., 1995a; 1995b; Rogaev et al., 1995; Sherrington et al., 1995). It has been shown that missense mutations on *PS1* result in an overproduction of Aβ42 (Lemere et al., 1996; Scheuner et al., 1996; Iwatsubo, 1998) and its suggested role is either to guide APP to compartments where it is cleaved by the γ-secretase (Naruse et al., 1998) or it may in fact be the γ-secretase itself (Wolfe et al., 1999). Transgenic mice carrying missense mutation of *PS1* show a significant elevation in the levels of Aβ42 (Duff et al., 1996; Borchelt et al., 1996, Citron et al., 1997; 1998; Chui et al., 1999) but to date there have been no reports suggesting there is an increase in the level of Aβ deposits or any of the other phenotypic pathology of AD. This is rather surprising given the fact that the majority of FAD cases are linked to missense mutations in *PS;* however it has been suggested that mutated *PS1* may act as a gain-of-function in amyloid pathology. Although the physiological function of the presenilins is not fully understood, it is believed that they may be involved in developmental and apoptotic signalling or the processing of particular proteins which would include APP (Wolozin et al., 1996; Wong et al., 1997; DeStrooper et al., 1998). In particular, PS1 has been implicated in apoptosis, a process that has recently been observed in AD pathology (Loo et al., 1993; Estus et al., 1997; Stadelmann et al., 1999; Mattson et al., 2000), adding further support to the notion that PS1 mutations may accelerate the pathology (*see* review by Czech et al., 2000).

Given the increase in Aβ42 levels in *PS1* transgenic mice, certain groups have crossed these mice with mice carrying mutations in the APP gene, using either the tg2576 or tgAPP/Lo mutation to produce a double-transgenic mouse (Borchelt et al., 1997; Citron et al., 1998; Holcomb et al., 1998; Dewachter et al., 2000; Gordon et al., 2001; Gordon et al., 2002). In general all mice showed an increase in levels of Aβ42 and an acceleration of the formation of amyloid deposits in the brain, earlier than that observed in the APP transgenic mice alone. Interestingly, Gordon and colleagues (2002) found that although there was an early presence of fibrilar amyloid in these mice, there was no further substantial increase in number beyond the age of 12 mo. They suggest that overexpression of mutated PS1 does not constitute an age-related progression of the pathology; a conclusion also reached by Dewachter and colleagues (2000).

ApoE and Tau Transgenic Mouse Models of AD

Little force has been put into the development of *ApoE* or *tau* transgenic mice as neither proteins constitute an hereditary factor in the development of AD. Although it has been established that ApoE4 constitutes a risk factor in the disease, it has been shown to be neither necessary nor sufficient for its development (*see* Lendon et al., 1997) and has little predictive value (Roses, 1995). Little is known as to how ApoE4 may be implicated in the disease. Data from transgenic *ApoE4* mice (Sabo et al., 2000; Tesseur et al., 2000; White et al., 2001) and clinical reports (Teasdale et al., 1997; Horsburgh et al., 2000) suggest that ApoE4 has a detrimental role in recovery from head injury, which is also known to be a risk factor in AD. Although it has been shown that ApoE4 binds to senile plaques (Strittmatter et al., 1993) and that it might act as a chaperone to promote the formation of the β-sheet structure (Wisniewski et al., 1994), transgenic mice overexpressing *ApoE4* do not display Aβ deposits, even at the age of 14 mo (Smith et al., 1998a). However, when crossed with *APP* transgenic mice containing a Swedish mutation, the formation of Aβ deposits was accelerated (Bales et al., 1999; Carter et al., 2001).

Although abnormal phosphorylation of tau in AD is not based on an autosomal dominant mutation, several transgenic mouse lines have been developed to overexpress different isoforms of human tau (Spittaels et al., 1999; Probst et al., 2000; Ishihara et al., 1999; 2001) or the entire gene (Duff et al., 2000). With the exception of the 3 exon repeat domain (ON3R) isoform developed by Ishihara and colleagues (1999; 2001), none of these mice developed convincing neurofibrillary pathology, and the ON3R line developed rare tangles only at the age of 24 mo. More recent studies have identified mutations in *tau* linked to chromosome 17 in frontal–temporal dementia with Parkinsonism (FTDP-17) (Spillantini et al., 1998), and two transgenic mice developed with mutations at the same site in exon 10 (Lewis et al., 2001; Gotz et al., 2001) show tau pathology that recapitulates that which is observed in human tau pathological diseases such as FTDP, Picks disease, supernuclear palsy, and corticobasal degeneration, but not that of AD.

Very few studies have been reported on potential cognitive deficits observed in the *ApoE4* and *tau* transgenic mice; Tesseur and colleagues (2000) report a deficit in spatial learning in ApoE4 mice, but in general both ApoE4 and *tau* transgenic mice display severe motor problems at an early age that is accompanied by muscle wasting and loss of body weight. These fundamental problems exclude the potential for testing these mice in learning tasks in order to understand if ApoE4 and tau play a causal role in the progressive cognitive decline in AD.

Cognitive Deficits in APP Transgenic Mice

Despite the rather extensive characterization of the pathology in these mice, there is relatively little analysis of the potential cognitive deficits in these mice. What has been shown in terms of learning and memory deficits is difficult to assess because, apart from one study (King et al., 1999), there has been no systematic testing of the mice on a battery of learning tasks. In addition, although all transgenic lines have been tested for spatial learning using either the open-field water maze or the circular platform, there have been several variations in the task, making it difficult to make comparisons and assess exactly what type of cognitive deficits these mice present (Hsiao et al., 1996; King et al., 1999; Moechars et al., 1999; Pompl et al., 1999; Janus et al., 2000a; Chen et al., 2000; Morgan et al., 2000; Chishti et al., 2001).

tgCRND8 (Janus et al., 2000a; Chishti et al., 2001) and tgAPP/Lo (Moechars et al., 1999) transgenic mice were tested on the standard-reference memory task in the water maze using a hidden platform and displayed deficits in both the acquisition and retention phase. No impairment was observed in the cued version of the task or in exploratory behavior in the open field (Chishti et al., 2001), whereas tgAPP/Lo mice show hyperactivity, increased anxiety, and aggressive behavior (Moechars et al., 1999). Importantly, in both transgenic lines the cognitive impairment was observed prior to the overt presence of dense-core plaques and dystrophic neurites, suggesting that soluble, nonaggregated Aβ, known to exert a toxic effect on neurons (Cotman et al., 1992; Pike et al., 1991; 1993; Mattson, 1997), may be responsible for the learning impairment.

PDAPP transgenic mice show rather curious behavioral deficits. They are impaired in spatial discrimination tested on a radial arm maze at ages between 3 and 10 mo (Dodart et al., 1999), covering a period both before and after the development of amyloid deposits, and well before the appearance of robust amyloid pathology. In contrast, in a spatial-working memory-type task in the watermaze there is an age-dependent deficit that is not detected between 6–9 mo but is present at 13–15 mo, correlating with the presence of robust plaque pathology (Chen et al., 2000). One potential problem is that there is no age-dependent deficit that is observed in nontransgenic mice at the age of 22 mo, which one would likely expect. In addition, in an object-recognition task designed purely to test memory without confounding effects of learning, there are conflicting results in the hands of two different laboratories. Whereas Dodart and colleagues

(1999) report an age-related impairment when there is the appearance of amyloid pathology, Chen and colleagues (2000) show no discernible impairment in transgenic mice across all ages. Dodart and colleagues (1999) observe an early induction of brain atrophying and alterations in the synaptic densities at 3 mo that are not reported by Chen et al (2000), which may or may not offer some explanation as to the difference.

The tg2576 line is that which has undergone the most behavioral testing in different laboratories. Originally, Hsiao and colleagues showed the mice to have an age-related deficit in the standard reference memory task in the water maze, but also with the visible platform (Hsiao et al., 1996) and in a working memory task in the Y-maze (Hsiao et al., 1996; Chapman et al., 1999), showing significant impairments at 10 mo but not at 3 mo. In a slightly different version of the task, where they sank a radial arm maze into the pool of water, Morgan and colleagues (2000) showed a deficit at about the same age, corresponding with the onset of pathology. However, extensive behavioral studies carried out by Arendash and colleagues (King et al., 1999; Pompl et al., 1999), show a more complex picture of the deficits. They tested mice at the ages of 3 and 9 mo and found that they displayed no deficits at either age in Y-maze alternation, the acquisition phase in spatial navigation, or active and passive avoidance. There was a progressive deficit in learning the circular platform task which also has been shown by Pompl et al. (1999) at the age of 7 mo, as well as in the visible platform task (King et al., 1999). However, there was a gender and age-related complication as impairments were observed in the retention of information about the escape location in the water maze and the circular maze in 3-mo-old transgenic females (King et al., 1999).

Cognitive Deficits in Presenilin Transgenic Mice

Owing to the lack of amyloid pathology in the single PS1-mutated transgenic mice, very few behavioral studies have been conducted. In a single study conducted by Janus and colleagues (2000b), they showed no impairment in spatial learning in PS1 transgenic mice expressing mutations at either 6 or 9 mo of age, in keeping with the lack of amyloid pathology observed in single PS1 mutations in transgenic mice. In tgPS1 mice crossed with tg2576 mice, there are starkly contrasting results. Holcomb and colleagues (1998, 1999) showed that double-transgenic mice were impaired in a Y-maze alternation task at the early age of 3 mo, prior to the presence of amyloid fibrils in the brain which occurred around 6 mo. The impairment persisted to the ages of 6 and 9 mo; this impairment was not observed in the PS1 mutants alone. However, the older mice displayed no deficit in spatial learning, despite the increased Aβ burden (Holcomb et al., 1999). In contrast, Arendash and colleagues (Arendash et al., 2001; Gordon et al., 2001) and Puolivali and colleagues (2002) found that double-APP and -PS1 mutant mice at the age where there is a robust plaque pathology, did show deficits in spatial learning, both in a reference and working memory version of the task. Additionally, Arendash and colleagues (2001) found no impairment in Y-maze alternation at ages before the presence of amyloid plaques or even when they are floridly present.

What Do Transgenic Mice Model?

Clearly the behavioral phenotypes in all transgenic mice modelling AD present certain problems; it is not at all clear whether (1) there is any reproducible form of deficit in these mice; either with the different forms of mutation or even using the same mutation, or (2) whether the cognitive deficits map on to that observed in AD, both in terms of the type of learning deficits observed or in terms of the onset and progression of cognitive decline. In light of the variable results in behavioral deficits and the fact these mice do not display the full-blown pathology of AD, it begs the question as to their validity as a model of AD.

From the clinical assessment of cognitive decline in AD patients, there are several critical points to consider. The first problem, relating to whether there is reproducibility, is also related to the question of whether the deficits actually reflect what is observed in AD. It is becoming apparent that there is a great need to refine learning tasks for rodents and to also more accurately assess memory deficits at the clinical level, or use what would be described as "rodent-type" learning tasks such as maze learning in humans in an attempt to draw better parallels between the deficits in humans and rodents (*see* McDonald and Overmier, 1998; Guénette and Tanzi, 1999).

To date there is no obvious indication that the onset and progression of cognitive and memory dysfunction in mice follows that observed in humans. The early stages of memory dysfunction in AD patients is insidious, almost indistinguishable from the normal forgetfulness observed during the course of aging. Based on the Clinical Dementia Rating (CDR; Hughes et al., 1982; Morris, 1993) and anecdotal staging of the disease (Reisburg et al., 1982), it appears that the first overt signs of memory loss is that of working memory and wordfinding problems followed by disorientation and difficulties in finding their way around a novel environment in the early stages, and finally complete loss of old memories and an inability to form new ones. Certain studies have shown that mice have impairments in both short-term memory tasks in the water maze or Y-maze alternation, and also in spatial navigation tasks which may or may not correspond to the problems in orientation observed in AD, but they do not seem to map onto the progression of the disease. In addition, there have been no reports of complete memory loss in very old mice. What would seem necessary in these mice would be to observe a progressive decline in memory and cognitive function, with increasing deficits in a broader range of tasks.

As described previously, the introduction of improved methods of detecting the progression of amyloid pathology in AD patients, has shown that the onset of cognitive decline appears to correlate better with elevations in the load of Aβ40 and Aβ42 but not necessarily with the presence of maximal load or fully matured amyloid *fibrils* in the brain (Bartoo et al., 1997; Lue et al., 1999; Wang et al., 1999; Naslund et al., 2000). Naslund and colleagues (2000) go as far as reporting that the increased Aβ40 and Aβ42 levels correlate with a CRD score of 0.5, described as being a questionable level of dementia (Hughes et al., 1982; Morris, 1993). This gains support from experimental evidence suggesting that oligomeric or protofibrilar Aβ have toxic effects (Roher et al., 1996; Walsh et al., 1999; Mucke et al., 2000) causing neuronal loss (Hartley et al., 1999) and perturbations in elements of synaptic transmission (Hartley et al., 1999; Hsia et al., 1999) and plasticity (Walsh et al., 2002).

This implies that what we know to be the dense-core amyloid plaque may in fact not be the primary cause for the cognitive deficits or the progression of the pathology during the course of AD. Although this is contrary to the classic hypothesis, it gains support from a great deal of experimental evidence. First, oligomeric and protofibrilar Aβ cause toxic effects and presumably develop into cored fibrillary plaques. Second, fully matured plaques become burnt out and although they remain as proteinaceous masses of debris, they induce inflammation in the brain. As described above, the role of inflammation, oxidative stress, and even apoptosis are now being considered as playing a more prominent role in the pathogenic process. The fact that the postmortem examination of the brains of AD patients shows massive levels of senile plaques and neurofibrillary tangle may be due to an inability for microglia and astrocytes to adequately clear them. Since microglia and astrocytes, when overactivated, can activate pro-inflammatory cascades, the actual detrimental effects in the brain that lead to cognitive decline may be associated with these processes rather than directly with the presence of the mature plaque.

Considering this information, can we make sense out of some of the behavioral results that

have been reported in transgenic mice? To a certain extent Westerman and colleagues (2002) have attempted to address this question. Using four progressive age-groups (4–25 mo) of tg2576 mouse, they found that memory deficits in spatial navigation started earlier than had previously been reported (Hsaio et al., 1996), and coincided only with the appearance of detergent-insoluble Aβ, a conformation that equates to the oligomeric or protofibrilar form of Aβ. Detergent-soluble Aβ, which is presumably in the monomeric form, is present throughout the life of the mice—even in mice younger than 6 mo—and has no deleterious effect on behavior. In tg2576 mutant mice crossed with PS1 mutant mice, the formation of insoluble Aβ is accelerated, and the memory deficits shift to the earlier time of 4 mo when the insoluble Aβ is observed in these mice.

Interestingly, when Westerman and colleagues attempted to correlate insoluble Aβ levels with the learning score in mice across all ages they found no age-related correlation. When, however, they separated the mice into age groups, they found a negative correlation between insoluble Aβ levels and behavior score, and surmised that the deficits may be associated with the stage when Aβ is converted from the soluble to the insoluble state, rather than correlating with dense-cored amyloid plaques. Although the levels of oligomeric or protofibrilar Aβ were not measured, several other studies lend support to observance of cognitive deficits before the formation of robust amyloid pathology (Holcomb et al., 1998; 1999; Dodart et al., 1999; 2000; King et al., 1999; Moechars et al., 1999; Chishti et al., 2001; Janus et al., 2002a). This constitutes a huge reversal of the classical notion that dense-cored amyloid plaques are responsible for the behavioral deficits. Presumably, at the early stages, there is an increase in the levels of soluble, monomeric, and protofibrillar levels of Aβ in areas that produce destabilisation of neural circuitry in regions of the brain known to be important for the processing of memory, such as the hippocampus. In the later stages, however, these become more widespread and develop hard-core plaques, which cannot be cleared efficiently from the brain. Thus in the later stages of the disease, where there is the presence of the classic amyloid plaque, there is also a continuous ongoing process of the conversion of soluble to insoluble Aβ. It is this metastable process that Westerman and colleagues (2002) consider to be the critical element inducing memory impairment.

Considering the role of the small Aβ assemblies as potentially having a causal role in the onset of cognitive decline seems to reduce the level of disparity between the behavioral results reported in the transgenic mice. It further suggests that the disparity between the result may in fact lie in the time points chosen to test the mice and the need to refine the tests in order to detect more subtle changes in learning that may occur at earlier stages. This problem constitutes one of the major drawbacks of the transgenic mouse models of AD in knowing exactly when the cognitive decline occurs in relationship to the onset of the pathological changes. A complementary approach that would have wider scope to focus on this critical time point and follow the progression is the injection of synthetic amyloid peptides into the brain.

Injections of Synthetic Peptides

Numerous studies using injections of synthetic amyloid peptides either icv or into a particular structure of the brains of rodents have been carried out as an alternative strategy to the transgenic mice, to mimic the amyloid pathology and examine its contribution to cognitive performance. Biochemical evidence has shown that the Aβ40 length of the amyloid peptide constitutes the major species of soluble, or non-self, aggregating amyloid in the brain, whereas the longer peptide Aβ42/43 self-aggregates more rapidly and may constitute the nidus of plaque formation. Jarrett and Landsbury (1993) postulated, based on in vitro studies that small quantities of Aβ43 could "seed" or nucleate the formation of amyloid plaques if in the presence of metastable levels

of Aβ40, thereby accelerating the pathologic process. The other peptide sequence of Aβ that has been used is Aβ25/35, as this sequence in the peptide lies in the fold of the beta-pleated sheet, strengthening the ionic bonds during folding that occurs prior to the formation of the amyloid fibril (Barrow and Zagorski, 1991).

As with the behavioral and pathological studies carried out in transgenic mice the reports from injections of peptides have shown variable results. Part of the reason for these inherent differences are wide ranging variables, such as the length of the peptide used, the mode of injection, whether icv or local, the time delay after injection for behavioral testing and the behavioral tests that have been used. In general, however, these studies can be categorized as those investigating the short-term effects of toxicity of amyloid using either single injections or infusion of peptides and testing within a two-week period after injection or infusion, and those investigating whether there are progressive deficits occurring at later stages following the introduction of peptides into the brain.

Studies investigating the toxic effects of the peptides on behavior have used either icv chronic infusion of Aβ40 (Nabeshima and Nitta; 1994; Nitta et al., 1994; 1997; Yamada et al., 1999) or single injections of Aβ40 (McDonald et al., 1994; 1996; Terranova, et al., 1996; Sweeney et al., 1997; Malin et al., 2001) or Aβ25–35 (Dornan et al., 1993; Sigurdsson et al., 1995; Chen et al., 1996; Maurice et al., 1996; 1998; Delobette et al., 1997; Yamaguchi et al., 2001; Sun and Alkon, 2002) or Aβ42 (Terranova et al., 1996). They have all resulted in learning deficits in a range of tasks such as spatial navigation (Nitta et al., 1994; 1997; Sigurdsson et al., 1995; Maurice et al., 1996; Delobette et al., 1997; Yan et al., 2001; Sun and Alkon, 2002); short-term memory (Terranova et al., 1996; Sweeney et al., 1997; Yan et al., 2001); radial-arm maze learning (Yamaguchi et al., 2001); passive avoidance (Maurice et al., 1996; 1998; Yamaguchi et al., 2001); spontaneous alternation (Maurice et al., 1996; 1998; Yamada et al., 1999); or retrieval memory that can be overcome with cueing (McDonald et al., 1994; 1996).

The majority of these studies report that there is no presence of positively stained aggregated amyloid and suggest the deficits are induced prior to the formation of amyloid and is likely due to the toxic effects elicited by soluble peptides. This is in keeping both with the onset of deficits reported in some transgenic mice and more importantly with reports from clinical studies that show memory deficits occuring as early as the first two years of AD (Folstein and Whitehouse, 1983), well before the onset of the substantial plaque pathology (Braak and Braak, 1991). Importantly, in those studies using chronic icv infusion over several days (Nabeshima and Nitta; 1994; Nitta et al., 1994; 1997; Yamada et al., 1999), multiple-site injections (Malin et al., 2001), a combination of Aβ25–35 and ibotenic acid injections (Dornan et al., 1993) or injections of Aβ aggregates in the hippocampus, the learning deficits are accompanied by the presence of amyloid pathology. The injection studies show, regardless of whether aggregated amyloid is formed or not there are behavioral deficits, suggesting that even nonplaque pathology is playing an important role in inducing a toxic milieu that contributes to the memory deficits.

Fewer studies have investigated the later effects of injections of Aβ25–35 (Giovannelli et al., 1995), Aβ40 (Cleary et al., 1995; Giovannelli et al., 1995), Aβ42 (Winkler et al., 1994; O'Hare et al., 1999; Nakamura et al., 2001), or a combination of Aβ40 and Aβ42 (Stéphan et al., 2001). O'Hare and colleagues (1999) showed that injection of Aβ42 aggregates in the hippocampus induce a progressive decline in operant-task learning, where there are no deficit 5 d after the injections; learning got progressively worse after 30 d and continued until 90 d. Postmortem examination of the brains showed that there was the presence of immunopositive amyloid material and astrocytosis around the aggregated amyloid.

Similar progressive decline in learning has been observed with either injections of Aβ40 or

Aβ42. Cleary and colleagues (1995) have shown that decline in short-term working memory was observed 30 d following a 15 d injecting regimen of Aβ40 in the hippocampus, that was not observed with a single injection. Nakamura and colleagues (2001) showed greater deficit in Y-maze alternation, spatial navigation, and passive avoidance at 80 d in comparison with the performance at 20 d following icv infusion of Aβ40. Thioflavin S positive amyloid material (Cleary et al., 1995) and neuronal damage and brain atrophy (Nakamura et al., 2001) were observed in the brains following postmortem examination. Following single injections of either Aβ40 or Aβ25–35, Giovannelli and colleagues (1995) showed a differential effect on performance in an object-recognition task. An impairment was observed 1 wk after injections of Aβ25–35, which was not observed until 2 mo following the injection Aβ40. Postmortem examination showed that there was the presence of Congo red positive amyloid material around the site of injection in the nucleus basalis, 1 wk after injections of either Aβ40 or Aβ25–35 peptides. Although there was continued presence of this material 2 mo later with Aβ40, it had cleared by approx 3 wk after injections of Aβ25–35. This suggests that the aggregated material induced by the shorter peptides may be adequately cleared from the brain, but the active presence of the peptide seems to correlate with the behavioral deficit. Importantly, Winkler and colleagues (1994) tested the histological and behavioral effects of Aβ42 15 mo after bilateral injections into the hippocampus. Although there were Aβ positive deposits around the site of injection and a slight decrease in ChAT activity, there was no impairment in spatial learning. It is possible that amyloid material was restricted to the injection site, and that with the passage of that length of time, the deficits shown in other studies that have been attributed to the presence of amyloid deposits were overcome.

In our own experiments (Stéphan et al., 2001) we were prompted by the theory postulated by Jarrett and Landsbury (1993) that the formation of amyloid deposits could be accelerated if small quantities of Aβ42 were in the presence of metastable levels of Aβ40. We found that injections of a combination of soluble Aβ40 and Aβ42 together in the hippocampus induced modest but specific impairment in several working memory tasks, sparing reference-memory learning. Postmortem examination of the brains 16 wk after injections showed the presence of aggregated material restricted to the site of injection, cell loss, and the presence of a massive inflammatory response. This type of pathology or impairment in learning was not observed in rats injected with double the quantity of Aβ40 that was used in the combined injections, but there was an equivalent impairment to that observed with the combined injections of rats injected with double the quantity of Aβ42. These data suggest that there is a need for the longer Aβ42 peptide to prompt aggregated material which, at a higher concentration, can aggregate alone.

Despite the number of variables between the different experiments, there are a number of consistencies in these results that are important for our understanding of the role of amyloid pathology in the learning deficits in AD. First, clearly there are deficits that are elicited by several different lengths of the peptide in the absence of overt plaque pathology and these deficits are prominent shortly after injections. This is in keeping with the results from certain transgenic mice and also the more recent analysis of AD brains showing the onset of cognitive deficits before the presence of fully mature amyloid deposits. Second, in the studies examining the effects of the peptides over longer periods of time, there is the presence of amyloid deposits, accompanied by cognitive deficits and this seems largely due to the longer Aβ42 peptide, or the combination of both Aβ40 and Aβ42. This is in keeping with results suggesting that Aβ42 has a greater propensity to self-aggregate into amyloid fibrils or nucleate the aggregation of amyloid fibrils (Jarrett and Landsbury, 1993).

On the negative side, all authors report that there is no spread of the pathology very far

beyond the site of injection, which restricts the potential use of this model for understanding the plaque-induced cognitive decline in the early stages of the disease, unless subsequent injections are made in other regions of the brain that mimic the spread of the pathology at later stages. In this sense, the use of injections may provide a more refined tool than the transgenic mice do, as it is possible to have greater precision for determining what state of amyloid formation may give rise to behavioral deficits in a structure-dependent manner, and which pathological processes may induce memory decline.

*A*β *Induced Malfunctioning in Synaptic Plasticity*

One area of research in AD that has to a certain extent been neglected is the impact of plaque pathology on synaptic transmission and long-term synaptic plasticity, a model of input-specific, activity-dependent synaptic modification. Numerous forms of plasticity, including long-term potentiation, axonal sprouting, neurite extension, synapto- and neurogenesis, have been considered to be a life-long process that occurs in response to environmental demands. In particular, synaptic plasticity believed to underlie the processing and storage of memories, modelled by LTP is a critical mechanism thought to be susceptible to aberrant modulation during AD. There is growing evidence to suggest that cellular and molecular changes necessary for mediating learning-induced synaptic plasticity are effected in AD, leading to a hypothesis suggesting that the memory deficits in AD are due to an increased burden on mechanisms of plasticity, that is exacerbated by age (Mesulam, 1999; Arendt, 2001a; 2001b). As suggested by Small and colleagues (2001), it is critically important to understand how the neural circuitry that processes and stores memory may be disrupted. Although cell loss is one of the key degenerating factors that may ultimately be responsible for the loss of existing memories and the inability to form new memories in the later stages of the disease, the loss of synapses is substantially greater than can be explained by cell loss (Davies et al., 1987). Biopsies on AD brain tissue show downregulation of plasticity-mediated synaptic function to a stage of irreversible synaptic loss (Rapoport, 1999). Numerous studies suggest that amyloid plaque and related pathology may act to disrupt both synaptic transmission and plasticity in the brain. Several key examples have shown that Aβ disrupts calcium homeostasis, driving levels to being toxic (*see* Mattson, 1997) and activates the MAP kinase pathway (Combs et al., 1999; Dineley et al., 2001), leading to the loss of normal control over the cell cycle (Arendt, 2001a; 2001b). Krox24, an immediate early gene which is necessary for LTP and several forms of long-term memory (Jones et al., 2001) is colocalized with Aβ plaques and is overexpressed in AD brains (McGibbon et al., 1997), and Aβ can overstimulate the NMDA receptor via reactive microglia (Gahtan and Overmier, 1999).

To date, there are relatively few studies in which synaptic transmission and plasticity have been directly measured in transgenic mice or rodents that have been injected with amyloid peptides. Chapman and colleagues (1999) have reported that the maintenance of LTP in the dentate gyrus, both in vitro and in vivo, and to a lesser extent in CA1 in vitro, was deficient in 15–17 mo old tg2576 mice; an effect not observed in young transgenic mice. Basal synaptic transmission was not effected in these mice. A similar deficit in the maintenance of LTP in the CA1 slice has been reported in 18–22 mo old mice overexpressing the carboxy terminus of APP (Nalbantoglu et al., 1997) or the London mutated mice (Moechars et al., 1999) but there was no report of whether synaptic transmission was altered in either study. Both groups reported a correlated deficit in learning. In stark contrast, Fitzjohn and colleagues (2001), using the same Swedish mutated transgenic mouse, showed that synaptic transmission was substantially reduced, but long-term potentiation in CA1 and in the dentate gyrus measured in vitro, was normal in mice of 12–18

mo that showed a presence of amyloid plaques. Deficit in basal transmission and normal synaptic plasticity have been observed in other aged AD transgenic mice expressing amyloid plaques (Hsia et al., 1999; Larson et al.,1999). Importantly, Larson and colleagues (1999) showed enhancement of paired pulse facilitation and decremental LTP in CA1 in young PDAPP transgenic mice aged 4–5 mo, prior to the formation of amyloid plaques, an effect that clearly disappeared with age (*see* above). These results imply that Aβ levels, presumably in a nonfibrilar form, have a disruptive or neurotoxic effect on the neuronal circuitry. More recently it has been shown that oligomeric Aβ (Walsh et al., 2002) or soluble oligomeric Aβ42 (Lambert et al., 1998; Wang et al., 2002) can induce decremental LTP in the hippocampus. No reports were made of whether basal transmission was effected or not; however, these data at least suggest that even in prefibrilar form Aβ can induce dysfunctional synaptic plasticity.

There is very little rational explanation as to the contradictory results, particularly in terms of the effect of Aβ on synaptic transmission. One potential explanation, at least for the decremental LTP that occurs at both the fibril and nonfibril stage of Aβ, is that there may be different mechanisms of the amyloid pathology that contribute to the decremental LTP. It is known that high levels of soluble Aβ, or Aβ in a prefibrillar form, is neurotoxic (Lambert et al., 1998; Hartley et al., 1999; Mucke et al., 2000; Klein et al., 2001) and this may well account for the decremental LTP at the prefibrillar stage. Fibrillar Aβ is known to activate microglia (*see* Giulian, 1999; McGeer and McGeer, 2001; Strohmeyer and Rogers, 2001) and evidence suggests that the neurotoxicity induced at this stage is largely mediated via activated microglia and astrocytes, rather than Aβ fibril interaction with neurons *per se* (Weldon et al., 1998). In support of this notion, Stéphan and colleagues (2001) showed that a combination of Aβ40 and Aβ42 injected into the hippocampus resulted in decreased basal transmission and decremental LTP 16 wk after injections, when there was a presence of aggregated amyloid deposits and correlated memory deficits. However, when rats injected with the combined peptides were also treated with the nonsteroidal anti-inflammatory drug, indomenthacin, the Aβ-induced decremental LTP and behavioral deficits were alleviated. Although there was a substantial reduction in reactive microglia, there was no qualitative difference in the amount or presence of aggregated amyloid (Stéphan et al., 2002). Although some evidence is beginning to emerge, exactly how the amyloid and its related pathology lead to decremental synaptic plasticity requires a great deal of further investigation.

Where Do We Go with These Models Now?

Given that the aim of the development of rodent models of AD is ultimately to design therapeutic strategies to combat or slow down the progression of the disease, particularly in terms of the decline in cognitive ability—which to a certain extent determines the quality of life—what can we say about these two models contributing to this overall aim. The short answer is, not as much as was anticipated and this is confirmed by the disastrous results from the first inoculation studies in humans, where trials had to be stopped due to the induction of inflammation in the brain (*see* Check, 2002). As always, rodent models designed to mimic diseased states or memory deficits are never completely faithful to the human condition. As discussed above, there are certain factors that contribute to the shortfall in both models. These include the lack of the full-blown pathology in both models, the lack of spreading pathology in the model using injections of Aβ peptide, and although memory deficits have been reported, there is similarly lack of convincing age-related progression in cognitive decline. Importantly, it has been shown that the Aβ deposits in certain transgenic mice are chemically and morphologically different from those observed in humans (Kuo et al., 2001; Kalback et al., 2002),

adding yet a further restriction to the use of the present rodent models.

However, on the positive side, both models have contributed to our understanding of the disease process. There appears to have been a slow shift in emphasis with regards to the role of factors other than the senile plaque and the neurofibrillary tangle in the pathology and cognitive decline. The previous ideology driving the development of rodent models of the disease was based on the need to observe a correlated increase of cored amyloid burden with memory deficits, if not the presence of neurofibrillary tangles and the loss of cells. The rodent models have shown, in parallel with more recent studies in humans, that at least the dense-cored plaques may not be the critical determinant inducing dysfunction in neural circuitry that leads to the progressive decline in memory and cognition. Important factors that must now be considered as playing a more prominent role in the disease process are inflammation and oxidative stress, apoptosis, monomeric or protofibrils and what their contribution entails to the memory decline in AD. To date, understanding whether different species of Aβ, as it evolves to form the dense-cored plaque, induce different forms of memory dysfunction correlating with the appearance of specific features of the pathology is still in its infancy, but appears to be a critical factor to target in developing further therapeutic strategies.

There are already certain studies that have been investigating the role of inflammation in the disease process in AD using these rodent models. For example, lipopolysaccharide-induced neuroinflammation can exacerbate the amyloid pathology in APP transgenic mice (Qiao et al., 2001), and chronic treatment with nonsteriodal anti-inflammatory compounds in transgenic mice (Lim et al., 2000; 2001) reduces Aβ deposits, the number of dystrophic neurites and the inflammatory response. In addition, the localized amyloid pathology, associated-inflammation, and learning impairments observed in rats injected with synthetic amyloid peptides can be reversed by injections of NSAIDs (Frautschy et al., 2001; Stéphan et al., 2002b) or anti oxidants (Yamada et al., 1999). Interestingly, in the study conducted by Stéphan et al. (2002b). They found a reduction in the inflammatory response and complete rescue of the behavioral deficits and decline in synaptic plasticity after prolonged treatment with indomethacin, however there was no reduction in the presence of aggregated amyloid material. This suggests that the amyloid deposits *per se* were not directly responsible for the deficits in learning or dysfunctional plasticity. As there has been a certain measure of success in attenuating certain cognitive deficits in those AD patients that have a history of NDAID consumption (Breitner et al., 1995; Stewart et al., 1997; McGeer and McGeer, 1998), this may prove an important therapeutic route to pursue.

A more in-depth biochemical analysis can surely lead to greater understanding of how other cellular processes may be implicated in the progression of the pathology. For example, large scale micro-array analysis of differentially regulated genes (Walker et al., 2001; Loring et al., 2001; Pasinetti, 2001; Stein and Johnson, 2002) and proteomic analysis (Schonberger et al., 2001; Tsuji and Shimohama, 2001; Castegna et al., 2002) in tissue from humans and transgenic mice is beginning to provide important data on genes and proteins that are abnormally up- or downregulated in AD. This will help shed light on the complexity of the pathology and lead to potential markers of the different stages of the disease, while at the same time providing important information as to which processes may underlie the dysfunctional synaptic plasticity and the deficits in learning and memory.

A second important approach that needs to be considered is the environmental impact on these models. As the majority of AD cases are of the sporadic type and not all members of the known families with FAD suffer from the disease, the disease process may be under the strong constraint of environmental factors. It has been suggested that life-style or environment influences such as stroke and head trauma, may have an impact on the development of the disease (*see* for example Mattson et

al., 2001; Prolla and Mattson, 2001). Several studies have shown that dietary restriction, exercise, and experience in enriched environments have positive effects on memory performance in aged rodents. As aging is the greatest risk factor in AD, it would seem that manipulating these variables over time in transgenic mice or rats injected with amyloid peptides, either by improving or restricting these environmental elements, may provide important information both at the behavioral and neuropathological levels. Certain studies have shown that experimentally-induced head injury in PDAPP transgenic mice enhances the memory deficits in spatial navigation, and although no signs of an increase in Aβ plaque formation was observed, there was a substantial increase in the levels of Aβ40 and Aβ42 as well as neuronal loss in the hippocampus (Smith et al., 1998b; Uryu et al., 2002).

Conclusion

In summary, rodent models of AD have to date concentrated primarily on developing age-related amyloid pathology, as with the transgenic mouse models, or on studying the role of amyloid pathology in learning deficits and synaptic plasticity using injections of amyloid peptides. Each model provides complementary information about AD but do not, as yet, alone present adequate models of the disease. More recently, data on the non Aβ pathological processes that could be triggered by Aβ or that could lead to progressive increase in plaque burden, and on the role of preplaque amyloid, have prompted modifications in the hypotheses of the etiology of AD, at least in terms of the cognitive and learning deficits. The importance of expanding the repertoire of behavioral paradigms to mimic the cognitive deficits in humans more closely, and a more in-depth investigation of the cellular mechanisms underlying cognitive processing that goes awry in these rodent models, is a critical next step. Future use of the existing rodent models of AD may provide a closer understanding of the disease for the development of therapeutic strategies by manipulating environmental factors and other signalling pathways in the brain that have to date been considered secondary factors.

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