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Current theories for the molecular and cellular pathogenesis of Alzheimer's disease

Gunnar K. Gouras

Over the past decade, the prevailing view for the molecular and cellular pathogenesis of Alzheimer's disease (AD) has centred on the β-amyloid (Aβ) peptide that accumulates in vulnerable brain areas in the disease. The amyloid cascade hypothesis postulates that the build up of Aβ in the brain causes damage to neurons, leading to dysfunction and loss of neurons, and the clinical phenotype of the amnestic dementia characteristic of AD. All known mutations that result in autosomal dominant forms of early-onset familial AD cause increased production of Aβ42, a form of Aβ that is particularly relevant in AD. Other proteins that are crucial to the pathogenesis of AD are the presenilins 1 and 2, which are intimately involved with Aβ production and when mutated in familial forms of AD cause increases in Aβ42. Currently, challenges in AD research include determining the earliest pathological effects of Aβ42, how the important AD risk factor apolipoprotein E affects the disease process, whether presenilin is the elusive γ-secretase, and how levels of Aβ can be effectively reduced therapeutically.

Alzheimer's disease (AD) is the leading cause of dementia and the most prevalent neurodegenerative disease of aging. In the USA alone an estimated 4 million individuals are affected by AD. With the continuing increases in life expectancy, the number of patients and the staggering costs associated with the care of patients debilitated by AD continue to rise. Over the past two decades, enormous strides have been made in our understanding of the underlying pathophysiology of the disease. But despite the many advances in basic research on AD, as yet there is no cure or even consensus among researchers for the crucial molecular events that underlie the disease process. Owing in part to the sheer number of investigators involved in AD research, there is no dearth of hypotheses to explain AD pathogenesis. I review some of the leading current hypotheses in this article.

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Defining features of AD

It was almost a century ago when Alois Alzheimer first described the clinico-pathological findings from a patient he followed a few years after the onset of dementia in her late 40s until her death at age 53 (see 'Further reading, resources and contacts' for additional history on AD). Using newly developed silver stains, Alzheimer observed the two defining neuropathological lesions later associated with all forms of AD: senile plaques (SPs) (Fig. 1) and neurofibrillary tangles (NFTs). The modern era of molecular discovery in AD began in the mid-1980s with the isolation and characterisation of β-amyloid (Aβ), the principal constituent of SPs (Refs 1, 2). Although the two pathological hallmarks, when found in sufficient quantity in association with a history of dementia, define the disease, SPs are more specific for AD; indeed NFTs, composed of hyperphosphorylated and aggregated microtubule-associated tau proteins, occur in a variety of clinically and anatomically specific neurodegenerative diseases. The identification of Aβ led to the cloning of the gene encoding its precursor protein, the Aβ precursor protein (βAPP) (Ref. 3), followed by cell biological studies on the intracellular processing of βAPP in tissue

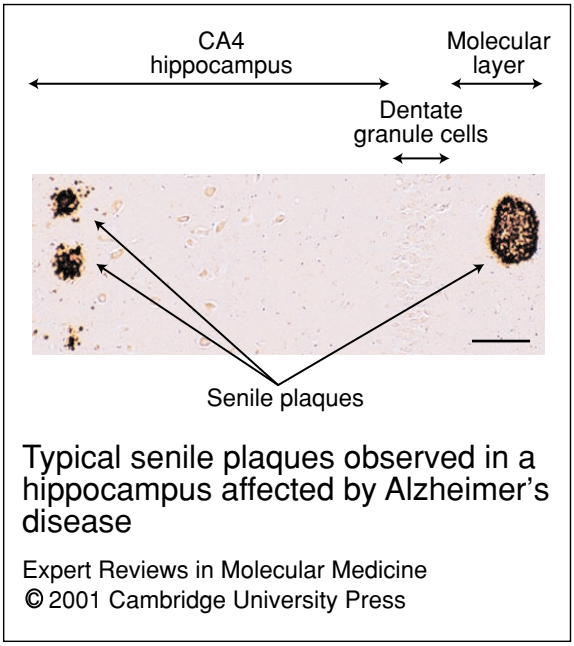

Figure 1. Typical senile plaques observed in a hippocampus affected by Alzheimer's disease. The plaques were demonstrated by β-amyloid 42 (Aβ42) immunohistochemistry. Note Aβ plaques as well as intraneuronal Aβ42 within CA4 pyramidal neurons. Bar = 100 μm **(fig001ggn)**.

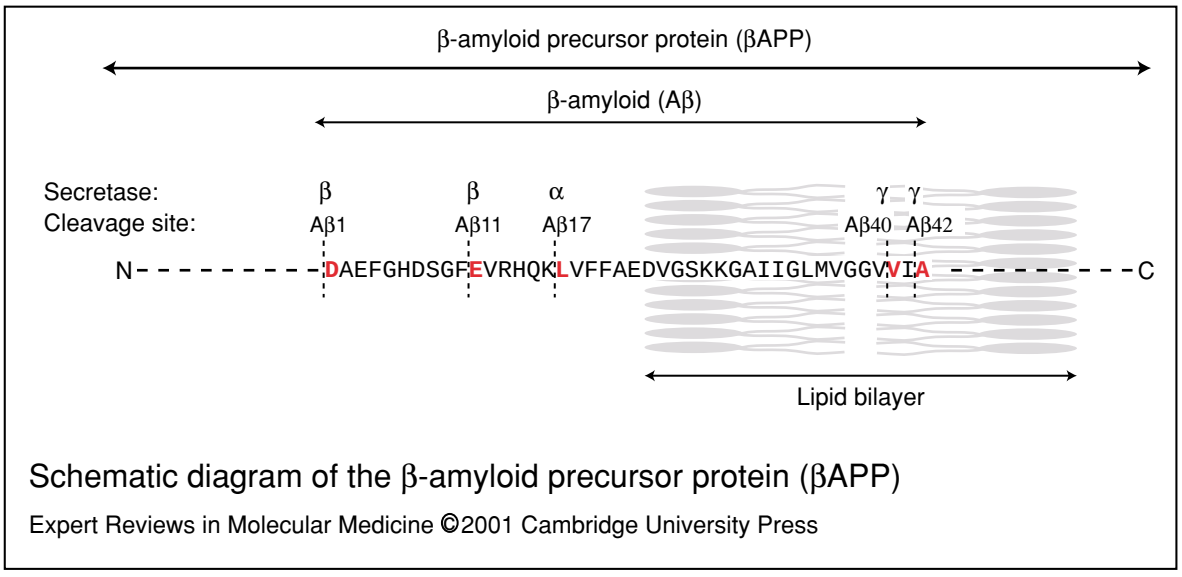

Figure 2. Schematic diagram of the β-amyloid precursor protein (βAPP). The amino acids of the β-amyloid (Aβ) portion of the βAPP holoprotein are given in single-letter code; N and C refer to the termini of the precursor protein. The α-, β- and γ-secretase cleavage sites are indicated. The β-secretase cleaves at Aβ1 and Aβ11, and γ-secretase cleaves at Aβ40 and Aβ42 within the lipid bilayer; the successive actions of β- and γ-secretases generate Aβ. Aβ is generally described as a 40 or 42 mino acid peptide, but can also be truncated at the N-terminus by cleavage at Glu11. The most common cleavage by α-secretase precludes Aβ formation **(fig002ggn)**.

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culture. Aβ is cleaved from βAPP by the successive actions of β- and γ-secretases (Fig. 2). Initially it was thought that Aβ was generated only under abnormal conditions, but in the early 1990s it was discovered that all cells normally secrete Aβ (Ref. 4).

Hypotheses for the pathogenesis of AD

Amyloid cascade hypothesis

The amyloid cascade hypothesis for AD received major support with the discoveries of autosomal dominant forms of early-onset familial AD (FAD) with specific pathogenic mutations in βAPP (Ref. 5). The presence of AD pathology with trisomy of chromosome 21 (Down's syndrome; DS), the chromosome where βAPP is located, had previously suggested such a genetic link, since an extra copy of βAPP is thought to increase amounts of Aβ. Subsequently it was found that genes encoding the presenilins 1 and 2, located on chromosomes 14 and 1, respectively, are associated with forms of early-onset autosomal dominant FAD, and also cause increased amounts of Aβ. Furthermore, a major genetic risk factor for the more-common, late-onset, 'sporadic' AD, is the apolipoprotein E (apoE) ε4 allele, which correlates with increased Aβ burden. Moreover, the generation of transgenic mice bearing human FAD mutations led to remarkable AD-like plaque pathology (Refs 6, 7). Thus, cumulative data supported the concept that Aβ is central to AD, and resulted in the hypothesis that all forms of AD might have increased Aβ as an underlying and unifying pathogenic mechanism (Ref. 8).

The current prevailing version of the 'amyloid cascade hypothesis' is based on the neurotoxic properties of Aβ (Ref. 9), and posits that increased secretion of Aβ leads to elevated extracellular levels of Aβ as SPs, which in turn are toxic to surrounding neurons. Aβ is generally described as a 40 or 42 amino acid peptide, with the shorter form more abundantly generated, but the longer, Aβ42 variant, which aggregates more readily, is more specifically linked to AD. Since the first plaques in AD and DS are composed of Aβ42 (Ref. 10), all forms of FAD cause an increase in the Aβ42 peptide (Ref. 8), and Aβ42 is particularly neurotoxic, it is Aβ42 that is thought to be central in AD pathogenesis. Interestingly, immunohistochemical studies indicate that the initial Aβ42 deposits appear to be composed of Aβ42 that is truncated at the N-terminus (Aβx–42) (Ref. 11). The β-site APP-cleaving enzyme (BACE), the recently discovered β-secretase, cleaves specifically at AβAsp1 and Glu11. AβGlu11 peptides were reported to be the most abundant Aβ species secreted by primary neurons (Ref. 12); intracellularly, Aβx–42 has been shown to be specifically elevated with FAD presenilin 1 mutations in transfected cell lines (Ref. 13); and Aβ11–42 might be especially elevated in the brains of patients with FAD presenilin 1 mutations (Refs 14, 15). Successive deletions of the N-terminus of Aβ increase the ability of highly insoluble β-pleated sheet formation (Ref. 16).

Currently, studies are attempting to define the subcellular site(s) and molecular mechanisms by which presenilins and apoE influence Aβ, and thereby AD. Cumulative studies indicate an important role for presenilin in the γ-cleavage of Aβ, with investigators increasingly viewing presenilin as the elusive γ-secretase (Ref. 17).

Unanswered questions

Although the amyloid cascade hypothesis is currently the most prevalent hypothesis for AD, it leaves many questions about AD pathogenesis unanswered, including the following ones. How does aging influence the disease? What causes the anatomical selectivity of AD? Does, and by what mechanism, Aβ influence tau? What are the normal functions of βAPP and potentially Aβ? What is the specific mechanism whereby Aβ leads to neuronal dysfunction and cell death? Modified versions of the amyloid hypothesis are emerging, including those that view Aβ deposits as more peripheral to the pathogenesis of AD. Although β-pleated Aβ has been shown to be more toxic to neurons than non-fibrillar forms are, studies in transgenic AD mice with elevated Aβ are increasingly reporting abnormalities before SPs and NFTs develop, including the early presence of markers for oxidative stress (Ref. 18) or inflammation (Ref. 19). Transgenic AD mice appear to exhibit behavioural, synaptic and physiological abnormalities preceding overt SP pathology (Refs 20, 21, 22, 23). In addition, recent Aβ42 ELISA (enzyme-linked immunosorbent assay) studies of postmortem human brain indicate increases in total Aβ42 before SP and NFT formation in mild cognitive dysfunction (Ref. 24), and suggest that soluble Aβ42 specifically correlates with cognitive dysfunction in AD (Ref. 25). Thus, some proponents of the amyloid hypothesis are amending the original scenario to include the possibility that extracellular, pre-

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amyloid Aβ protofibrils might play a direct role in AD pathology (Ref. 26).

Some investigators are currently also investigating whether intracellular, rather than extracellular, Aβ42 plays a direct pathogenic role in AD (Refs 27, 28, 29, 30). This view is supported by the following: first, the ratio of Aβ42 to Aβ40 within neurons is markedly higher than that of secreted Aβ (Refs 28, 29, 30); second, FAD mutations also cause elevations in intracellular Aβ (Refs 13, 31); third, Aβ42 increases with time in culture (aging) within neuronal NT2 cells (Ref. 32); and fourth, Aβ42 shows a particular increase within AD-vulnerable neurons of the human brain early in the course of classic SP and NFT pathology (Ref. 30; see Figure 3 for a schematic diagram of the current understanding of the subcellular sites of Aβ). These intraneuronal increases in Aβ42 levels might reflect increased Aβ42 generation for subsequent secretion and extracellular neurotoxicity, although the fact that similar increases are markedly less apparent for the more abundantly secreted Aβ40 seems to argue against this scenario. Interestingly, in vitro studies, including a study using a hippocampal slice model, indicated that AD-vulnerable neurons preferentially internalise exogenous Aβ42 (Ref. 33), supporting the view that intraneuronal Aβ42 might, at least in part, be extracellularly derived. Thus, the proposal that Aβ42 might play a direct role in neuronal dysfunction from within neurons is currently under consideration, but requires further experimental support (see 'Further reading, resources and contacts' for additional information).

Cardiovascular and cholesterol hypotheses

Converging epidemiological and biological evidence have also implicated cardiovascular factors in the development of AD. Risk factors for atherosclerosis, such as hypertension, high cholesterol, diabetes mellitus and especially apoE ε4 genotype, increase the risk of developing AD (Ref. 34). Furthermore, cholesterol depletion or treatment of cells in vitro leads to alterations of Aβ levels (Refs 35, 36, 37), rabbits fed a high-cholesterol diet develop AD-like pathology of SPs and NFTs (Ref. 38), and transgenic AD mice fed with a high-cholesterol diet develop earlier Aβ plaque pathology (Ref. 39). Moreover, intake of cholesterol-lowering statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) has been reported in retrospective studies to be associated with a lower prevalence of probable AD (Ref. 40). On a molecular level, the critical Aβ γ-cleavage occurs within the lipid bilayer, and the site of APP cleavage can be influenced by the thickness and fluidity of the membrane (Ref. 41). The 'critical threshold cerebral hypoperfusion' hypothesis for AD suggests that atherosclerosis causes chronically decreased brain perfusion and damage particularly to AD-vulnerable brain areas (Refs 42, 43). This could provide a mechanism for the anatomical selectivity of AD pathology.

Oxidative stress

Oxidative stress and alterations in energy metabolism with aging have increasingly been found to play a role in a variety of age-related diseases, including neurodegenerative diseases (Ref. 44). Free radicals are produced as by-products of oxidative metabolism and can cause oxidative damage to proteins, lipids and nucleic acids, which might be relevant to AD pathogenesis. Supplementation with the antioxidant vitamin E has been associated with reduced disease progression in AD (Ref. 45). Altered oxidative metabolism has been reported in AD postmortem brain (Ref. 46) and also within AD-vulnerable neurons even preceding the formation of NFTs (Ref. 18). Studies of cultured primary neurons revealed increases especially in intracellular Aβ42 upon oxidative stress (i.e. hydrogen peroxide treatment), and protection against this with concomitant antioxidant treatment (Ref. 47).

Inflammation/immune response

Retrospective epidemiological studies have suggested that intake of anti-inflammatory medications is protective against the development of AD (Ref. 48). Inflammatory processes occur in the brain in AD, including gliosis and recruitment of microglia to sites of AD pathology. Interestingly, markers of inflammation have been shown even to precede Aβ deposits in transgenic FAD mutant βAPP mice (Ref. 19). Although inflammatory processes are general features of most types of brain disease, a role for inflammatory processes received support from recent reports indicating protection against and reversal of Aβ plaque deposition in transgenic FAD mutant βAPP mice immunised with Aβ (Ref. 49): intravenous infusion of Aβ led to reductions in Aβ plaques. Interestingly, the results with Aβ vaccination

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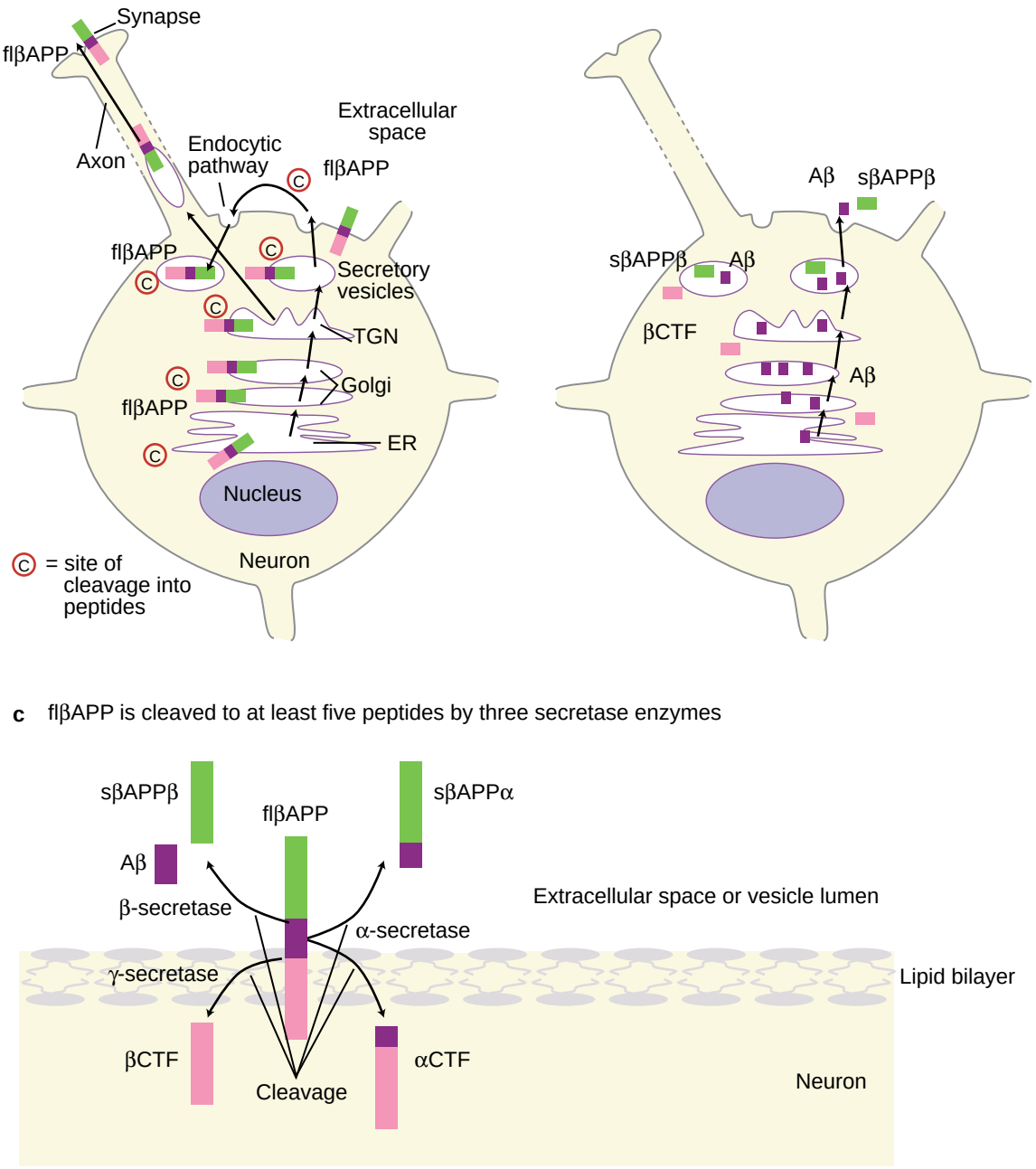

Possible cellular trafficking of β-amyloid (Aβ)

Figure 3. Possible cellular trafficking of β-amyloid (Aβ) (*see next page for legend*) **(fig003ggn).**

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Figure 3. Possible cellular trafficking of β-amyloid (Aβ). (a) In the cell body of a neuron, full-length β-amyloid precursor protein holoprotein (flβAPP) is generated in the endoplasmic reticulum (ER), transported through the Golgi complex, and carried in post-trans Golgi network (post-TGN) secretory vesicles to the plasma membrane. Most flβAPP resides in the Golgi complex, but some is also transported from the cell body down axons by fast axonal transport and reportedly is contained in multivesicular bodies of synaptic preparations. (b) A subset of flβAPP molecules are cleaved during export. A minority of Aβ peptides are generated in the ER, but the majority are generated in the Golgi complex, from where most Aβ peptides are packaged into post-TGN vesicles destined for secretion into the extracellular space. Soluble α-cleaved βAPP (sβAPPα) is also generated in post-TGN vesicles and/or at the plasma membrane, from where it is secreted into the extracellular space. Aβ is also thought to be generated in the endocytic pathway following internalisation of βAPP from the plasma membrane. (c) Cleavage of flβAPP by β- and γ-secretases during trafficking gives rise to Aβ, soluble βAPP (sβAPPβ) and β C-terminal fragment (βCTF); α-secretase cleavage generates sβAPPα and α C-terminal fragment (αCTF). The precise sites of generation and trafficking of specific Aβ peptides are an active area of research in the field **(fig003ggn)**.

suggest that immune/inflammatory mechanisms might be protective for AD, since immunisation presumably leads to activation of the immune system and clearance of Aβ by microglia.

Hormones

Gonadal hormones

Numerous retrospective epidemiological studies have suggested a protective role for estrogen replacement therapy (ERT) in the development of AD in postmenopausal women (Refs 48, 50). However, recent prospective studies have not shown benefits for ERT when given to women with early-to-moderate AD (Refs 51, 52), although ERT might be able to prevent or delay the development of the disease if initiated early enough. Emerging neurobiological research suggests that estrogen plays important roles in the brain. Treatment with 17β-estradiol reduces the secretion of Aβ peptides by primary neurons (Ref. 53) and levels of Aβ in brains of guinea pigs (Ref. 54). More recently, studies indicate that levels of bio-available testosterone also decline in both men and women with age, and testosterone has also been demonstrated to reduce Aβ secretion by neurons (Ref. 37).

Insulin

Epidemiological studies indicate that diabetes mellitus is a risk factor for the development of AD (Ref. 55), and insulin appears important for learning and memory (Ref. 56). Insulin was shown to inhibit the pathological phosphorylation of the microtubule-associated protein tau, which is the principal component of NFTs (Ref. 57), and to stimulate the secretion of soluble βAPP (Ref. 58). Studies on aging in the roundworm *Caenorhabditis elegans* have found that an insulin-like receptor has the most important influence on lifespan (Ref. 59). Furthermore, it was also serendipitously found that the major insulin-degrading enzyme, IDE, is the most effective protease at degrading Aβ (Ref. 60). Interestingly, treatment of cultured neurons with insulin not only competitively inhibits extracellular Aβ degradation by IDE, but also reduces the intracellular pool of Aβ while stimulating Aβ secretion (Ref. 61).

Neuroplasticity hypothesis

The neuroplasticity hypothesis for AD focuses on disturbances of connectivity in AD, and regards Aβ, tau and apoE as factors that are able to perturb processes that facilitate neuroplasticity (synaptic turnover and upkeep) (Ref. 62; see also 'Further reading, resources and contacts'). Support for this hypothesis is provided by the lack of association between SPs and cognitive dysfunction compared with the closer association of synaptic loss and cognitive decline in AD. Failure in plasticity is considered to be an age-related phenomenon, to which the limbic and paralimbic cortices are particularly vulnerable. More-detailed neurobiological and molecular mechanisms in support of a role of neuroplasticity in AD are required.

Other hypotheses

Many other hypotheses have been proposed for the pathogenesis of AD. Roles for activation of apoptosis and altered calcium influx (i.e. by presenilin mutations) in AD have been suggested (Ref. 63). Another hypothesis stresses the importance of βAPP, beyond its role in Aβ generation, suggesting that physiological roles of βAPP are altered with AD pathogenesis and lead to neuronal dysfunction and AD (Ref. 64). The cholinergic hypothesis has been a leading hypothesis for AD, based on evidence that the

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neurotransmitter acetylcholine is especially depleted in AD brain, and the importance of the cholinergic system in learning and memory (Ref. 65). Currently, acetylcholinesterase inhibitors are the only class of medications approved for AD, having been shown in multiple studies to provide statistically significant, although only modest, benefits in behavioural and cognitive parameters in patients with AD. It is thought that neurotrophic factors might have a therapeutic role for AD, based on past studies showing that basal forebrain cholinergic neurons that express nerve growth factor receptor are especially damaged by AD and that these neurons can be rescued upon axotomy by administration of nerve growth factor in experimental animals (Ref. 66).

Conclusion

Today, we understand significantly more about the AD disease process and even have modest treatments available for patients afflicted with AD, including cholinesterase inhibitors and antioxidants. Over the past two decades, Aβ has increasingly taken centre stage in attempts to develop a unifying hypothesis for the molecular underpinnings of this complex disease. With the continued unravelling of the molecular events involved in AD pathogenesis, especially the elucidation of the proteases involved in Aβ generation, there is guarded optimism in the field that newer and more-effective, biologically based therapies will be developed in the near future that might delay the onset or even retard the progression of the disease. Inhibitors of the β- and/or γ-secretases and Aβ immunotherapy are currently leading therapeutic contenders. Recent evidence indicates that in contrast to presenilin knockouts, BACE knockout mice develop normally, making inhibition of BACE an exciting direction for AD therapy (Refs 67, 68). With time, the significance of elements of the various current hypotheses for AD will become apparent, as a more complete picture of the molecular and cellular neuropathology of AD emerges.

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Further reading, resources and contacts

Websites for Alzheimer's disease

The Alzheimer Research Forum website is the leading scientific resource for emerging research developments in Alzheimer's disease, and includes sections on clinical trials and Alzheimer's disease patents.

http://www.alzforum.org

The Alzheimer's Association (the leading US Alzheimer's disease foundation) website.

http://www.alz.org/

The Neurosciences section of About includes a summary of the history of Alzheimer's disease.

http://neuroscience.about.com/library/weekly/aa112999Alz.htm

Alzheimer's Disease International provides an global perspective on the disease.

http://www.alz.co.uk

Recent online discussions on Alzheimer's disease controversies

Discussion regarding intracellular versus extracellular β-amyloid.

http://www.alzforum.org/members/forums/journal/iab/index.html

Discussion of neuroplasticity hypothesis.

http://www.alzforum.org/members/forums/interview/mesulam.html

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Features associated with this article

Figures

Figure 1. Typical senile plaques observed in a hippocampus affected by Alzheimer's disease (fig001ggn).
Figure 2. Schematic diagram of the β-amyloid precursor protein (βAPP) (fig002ggn).
Figure 3. Possible cellular trafficking of β-amyloid (Aβ) (fig003ggn).

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