INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterised by irreversible cognitive and physical deterioration. AD is the most common cause of dementia in the elderly population and its incidence doubles every five years between 65 and 85 years of age; it also represents a growing public health problem as life expectancy increases. The first case report of AD was published in 1907 by Alois Alzheimer (1), who described the presence of abnormal nerve cells containing tangles of fibres and neuritic plaques in the cerebral cortex of a woman who died at the age of 55 with progressive dementia. Much work has been done since then to characterise the neuropathological lesions typical of AD, such as neuritic plaques and neurofibrillary tangles (NFT). Alzheimer’s disease is morphologically characterised by abundant accumulation of β-amyloid in the form of senile plaques and abnormally phosphorylated tau protein in the form of NFT, resulting in a loss of neurons and diffuse brain atrophy. Neurofibrillary lesions have an intracellular localisation: they are found in the neuronal soma and in the apical dendrites as NFT. Ultrastructurally, these le-
sions are mainly made up of paired helical filaments (PHF) and straight filaments (SF). The major component of PHF is a multiple isoform phosphoprotein called “tau” protein. The function of tau is to participate in the formation of microtubules as an aid in the polymerisation of tubulin. In the NFT tau protein is present as a hyperphosphorylated form, and it is known that the phosphorylation of tau reduces its ability to bind and stabilise the microtubules. Another protein thought to be an integral component of the PHF of aged and AD brains is ubiquitin, revealed by immunocytochemistry in NFT and in senile plaque neurites of the AD brain. The appearance and development of NFT lesions are not casual, but follow a stereotyped pattern that allows the definition of six stages in the neuropathology of AD (2,3). Stages I and II involve the transentorhinal region: this phase of the disease is virtually free of symptoms. The first cognitive deficits appear during stages III and IV when the neurofibrillary lesions in the transentorhinal region are more severe and lesions begin to appear in the hippocampus and in some subcortical areas. Stages V and VI are characterised by a great increase in the density of these lesions in the already affected areas with an additional involvement of the higher cortical associative areas.

The formation and growth of senile plaques is believed to be a crucial event in the pathogenesis of AD (4). Neuritic plaques are compact spheroidal extracellular deposits mainly made up of filaments of a protein named β-amyloid (Aβ), surrounded by a variable number of dystrophic neurites. Activated microglial cells and reactive astrocytes are also found around the amyloid core of these plaques, also defined as mature plaques. A number of proteins have been found in close association with senile plaques, and these include complement cascade proteins, proteoglycans, cytokines and apolipoproteins. In addition to the mature plaques the brain of Alzheimer’s patients also shows the presence of numerous diffuse plaques that are made up of a β-amyloid protein deposit in amorphus form and are not associated with dystrophic neurites or activated glial cells. Thus, amyloid plaques are primarily made up of a compacted deposit consisting mainly of β-amyloid (Aβ), a 39-43 aminoacid hydrophobic peptide derived from a larger precursor protein called amyloid precursor protein (APP) (5). APP is an integral cell membrane glycoprotein made up of 697-770 residues, which is found in most cells throughout the human body, but most abundantly in the brain, and it is metabolised by several alternative pathways. In the secretory pathway, APP is cleaved extracellularly within the Aβ domain by α-secretase to generate soluble derivates of APP (sAPPα) that are secreted in the conditioned medium of cell cultures, human plasma and in the cerebrospinal fluid. This pathway prevents the formation of amyloidogenic fragments. Other enzymes, β- and γ-secretase, cleave APP on the N and C termini of Aβ, respectively, releasing the amyloidogenic peptide.

The treatment of AD continues to represent a major challenge since understanding of the events that lead to the selective neurodegeneration typical of Alzheimer’s brains is incomplete. Currently, attention is focused on study of the pharmacological modulation of APP metabolism, a modulation whose purpose is to reduce the formation of Aβ in the hope of reducing the formation of a potentially neurotoxic peptide.

The view that the cascade linked to excess of β-amyloid formation is the key to the pathogenesis of the disease (6) (Fig. 1) is reinforced by studies of familial cases (7) and by investigations of transgenic animals (8-10).

Because AD imposes a major burden on society, there is an urgent need for new treatments. Recent developments in basic research into AD have led to the production and clinical evaluation of a number of therapeutic agents for the disease, including cholinergic drugs,
neuropeptides and their derivates, oestrogen, antioxidants and free radical scavengers. While the ultimate goal is to prevent the progression of AD, the main objectives of treatment until then are to reduce the cognitive decline and to delay to some extent the progression of the disease. To date, however, only a few acetylcholine esterase inhibitors have shown clear evidence of therapeutic benefit.

**NEUROTOXICITY OF β-AMYLOID PEPTIDES**

An important feature of Aβ toxicity is that it requires the peptide to be present in the form of an amyloid aggregate. Amyloid fibrils consist of antiparallel β-plated sheets that bind Congo Red and display green birefringence when viewed in cross-polarised light. Aging of Aβ by incubation at 37°C for several days leads to the formation of stable oligomeric peptide aggregates, which contain a significantly increased portion of β-sheet structure. This conformational transition from random coil to β-sheet structure appears to be an important contributory factor to enhanced toxicity. Very recent results support this view and in addition show an involvement of the ubiquitin-proteasome system, which may be unpaired by protein aggregation (14), and of an altered putative Aβ-degradation peptidase (15). Within this context, Hashimoto et al. (16) have shown the existence of a rescue factor (humanin) that abolishes the neuronal cell death induced by familial AD genes and by Aβ.

These studies are consistent with the observation that neuronal degeneration in the AD brain is associated with the deposition of dense-core plaques, which contain aggregated fibrillar β-amyloid. Complementing histopathological results, which support a key role for Aβ in AD, there exist cell culture data showing that Aβ is neurotoxic and can increase neuronal vulnerability to insults related to the pathogenesis of AD including metabolic impairment and excitotoxicity (17). In addition, Aβ can induce elevations of intracellular free calcium concentrations (Ca^{2+}) (18), and of reactive oxygen species in neurons (19). In fact, several findings (20) support the hypothesis that altered processing of β-amyloid precursor protein contributes to a loss of neuronal calcium homeostasis and hence to neurofibrillary degeneration. These data suggest that a shift in APP processing in favour of increased production of β-amyloid and reduced release of sAPP destabilises intracellular Ca^{2+} and endangers neurons in two ways: increased levels of β-amyloid would make neurons more vulnerable to excitotoxicity (21) and reduced levels of sAPP would deprive neurons of a neuroprotective substance that can stabilise Ca^{2+}. Aβ can also induce lipid peroxidation in cells and thereby disrupt the function of membrane proteins involved in the transport of ions, gluta-

[Fig. 1 - Working hypothesis on AD pathogenesis and present and future drug targets (modified from ref. 6).]
Altered signal-transduction mechanisms can be directly involved in AD pathogenesis: the metabolic fate of APP is significantly regulated by events that involve the activation of second messengers. The alterations in neurotransmission in the AD brain seem to occur at multiple levels, and include modified receptor responses because of G-protein coupling, second messenger synthesis and protein kinase activation (22). Protein kinase C (PKC) is an important kinase, particularly in the brain where it regulates many aspects of neuronal plasticity, including transmitter release, receptor sensitivity and, at more integrated levels, long-term synaptic potentiation, learning and memory. One of the most consistent findings in AD brains is the alteration of this kinase. The level, activity and subcellular distribution of PKC have been found to be altered. Reduced PKC activity is consistently found in peripheral tissues from AD patients, suggesting that these alterations are not secondary to neuronal loss and may be directly involved in the pathogenesis of AD. PKC was the first signal-transduction-related molecule to be implicated in the regulation of APP metabolism. Extensive studies on regulated APP processing established that the Aβ amyloidogenic pathway and the α-secretase non amyloidogenic pathway were mutually exclusive in several experimental settings. The target of PKC phosphorylation is not the APP molecule itself, but either α-secretase or, more likely, a key cellular factor that targets APP to the α-secretase. Although PKC activity is thought to be central in these pathways, a number of them interact to form a complex signalling network in which at least four major kinase systems are involved (23).

Direct activation of PKC by phorbol esters can induce an increase in sAPPα release and a reduction in the formation and release of Aβ. Many inhibitors of PKC activity (staurosporine and bisindolylmaleimide, among others) are able to block the effect of PKC on APP metabolism. Protein kinase A (PKA), which, in certain conditions, may activate sAPPα and thus induce its release from cells, more consistently seems to antagonise the effect of PKC activation. The use of inhibitors of tyrosine kinases, such as genistein, has demonstrated that unspecified tyrosine kinases appear to be activated and involved in sAPPα release independently of their activation downstream of PKC. It has also been shown that the effect of PKC on APP processing is mediated, at least in part, by other kinase systems. The intervention of a mitogen-activated protein kinase (MAPK) cascade in the process has been suggested by the observation that the MAPK inhibitor PD98059 blocked the phorbol-ester-mediated release of sAPPα in different cellular systems (24,25). Among the second messengers, the role played by Ca2+ in AD is extremely important. It is a cofactor for the activation of PKC and tyrosine kinases. Ca2+ ions flow through receptor-activated channels and are released by internal stores following the binding of Ins(1,4,5)P3 to its receptor. IP3, together with diacylglycerol, the other molecule generated by the hydrolysis of phosphoinositides (PI) after receptor activation, serves as second messenger either for the mobilisation of calcium from internal stores, or for the activation of PKC. Also, these systems have been found to be altered in the AD brain, with the observation of a reduction of PI in the brain of AD patients. These alterations, together with altered calcium homeostasis, have been implicated in the triggering of calcium-dependent cytoskeleton-disrupting mechanisms, leading to a disruption of neuronal structure.

In summary, a complex network of second messengers is involved in the regulation of APP metabolism, a network that is defective in
the AD brain but at the same time open to pharmacological modulation.

ACETYLCHOLINESTERASE-AMYLOID-β-PEPTIDE INTERACTION

A consistent feature of AD is the degeneration of cholinergic neurons originating in the nucleus basalis of Meynert, the vertical diagonal band and the septal nucleus and projecting to the cerebral cortex and the hippocampus. Acetylcholine concentration is reduced in the AD brain, and this reduction is accompanied by a reduction in its synthesis and a deficiency of the high-affinity uptake of choline. A consistent and important alteration of the cholinergic system in the AD brain is the dramatic deficit of choline acetyltransferase (ChAT) activity, which is reduced by 50%-85% in the cortex and hippocampus of the brains of severe AD patients. ChAT is regarded as the best marker of cholinergic terminals, and its reduction in AD is secondary to selective cholinergic neurodegeneration. This cholinergic change is believed to represent the neurochemical event that leads to AD symptoms (26,27). Acetylcholinesterase (AChE) is the enzyme involved in the hydrolysis of the neurotransmitter acetylcholine in the central nervous system of mammals (28). Most of the cortical AChE activity present in the AD brain was found to be associated with neuritic plaques (29), in which it colocalised with Aβ deposits, including both the preamyloid diffuse deposits and the mature senile plaques (30). The diffuse deposition of AChE together with Aβ is particularly interesting because it represents an early step in the development of the senile plaques; it has been suggested that AChE, an enzyme that is localised on the presynaptic nerve terminal and also secreted as a soluble form (31), may be present together with the soluble Aβ at a very early stage of amyloid plaque formation. In vitro AChE modulates amyloid formation by inducing a conformational change in Aβ (32); in fact, AChE is able to accelerate the aggregation of Aβ into amyloid fibrils. The effect is independent of the source and structural polymorphism of the enzyme, is not affected by an active inhibitor, and is diminished by a peripheral site blocker. The domain of AChE involved in the acceleration of amyloid formation is related to a hydrophobic environment close to the peripheral anionic binding site of the catalytic subunit of the enzyme (33,34).

Hence, biochemical, physical and morphological data strongly suggest that an amyloid-AChE complex is formed when AChE accelerates the assembly of Aβ peptides. The formation of an Aβ-AChE complex in vitro is consistent with the fact that AChE has been identified within Aβ deposits, mature senile plaques and cerebral blood vessels (35). Aβ-AChE complexes increase the neurotoxicity of Alzheimer’s fibrils (36). In fact, data showing that the Aβ-AChE complex presented a stronger cytotoxic effect than Aβ fibrils alone, in both PC12 cells and primary retina cells, indicate that the incorporation of AChE into amyloid fibrils changes their cytotoxic properties.

NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS AND ALZHEIMER’S DISEASE

Neuronal nicotinic acetylcholine receptors (nAChRs) are known to be involved in various important neurophysiological processes, such as learning and memory, analgesia, anxiety and convulsions (37-39). A significant loss of nAChRs is found in the Alzheimer brain, and was initially described in autopsy brain tissue (40). Extensive research over the last decade has established that brain nAChRs are a structurally and functionally different group of ligand gated cation channels, which are associated with numerous transmitter systems for which they have a modulatory function (41). The majority of receptors with a high affinity for agonists (nico-
tine, methyl carbamyl choline, cytisine, epibatidine) are composed of $\alpha_4$ and $\alpha_2$ subunits, but other subunits (for example $\alpha_3$ and $\alpha_6$) may play a role in specific brain pathways (42,43), and modify receptor pharmacology. Alpha-bungarotoxin binds to homomeric $\alpha_7$ containing receptors, which are characterized by a low sensitivity to agonists, a relatively high Ca$^{2+}$ conductance and a CNS distribution distinct from that of nAChRs with high affinity for agonists in the human brain. Identification of the major loss in cholinergic innervation of the cerebral cortex in AD was followed by investigations into the possible involvement of cholinergic receptors in AD. Reductions in nAChRs were observed at autopsy in a number of neocortical areas and the hippocampus of patients with AD, in the majority of studies compared to age-matched controls (44,45). A significant reduction in $^{125}$I$\alpha$-bungarotoxin binding to a separate subtype of nAChRs was also reported in temporal, but not frontal cortex in AD (46). The introduction of quantitative immunohistochemical investigations in the field of AD research, led to the first evidence that the loss of nAChR $\alpha$-subunit protein was not related to a neuronal cell loss but rather to a decreased expression of nAChR protein in AD cortical neurons. Hence, Wevers et al. (47) were able to show a significant reduction of neurons that express the $\alpha_4$ and the $\alpha_7$ subunit protein of the nAChR in the human frontal cortex in AD. However, this reduction was not accompanied by a concomitant reduction in the number of cortical neurons in AD patients. In addition, a lower reduction of cortical neurons expressing $\alpha_7$ subunit protein in the frontal cortex of AD patients has been observed. In conclusion, exposure of telencephalic neurons to $\beta$-amyloid has revealed a massive reduction of $\alpha_4$-expressing neurons, while those showing immunoreactivity for the $\alpha_7$ subunit are less affected. This finding points to a possible impact of $\beta$-amyloid on the protein expression of the nAChR $\alpha_4$ subunit in neurons, and constitutes the first evidence that the well-known cholinceptive dysfunction in AD may be related to the impact of $\beta$-amyloid on nAChR synthesis.

PHARMACOLOGICAL TREATMENT OF ALZHEIMER’S DISEASE WITHIN THE CONTEXT OF PATHOGENETIC MECHANISMS

It is well-known that deficits in the cholinergic system of the brain contribute to loss of cognitive function in AD, and a number of therapeutic strategies have been developed intended to compensate for these deficits. The most successful strategy has been the use of cholinesterase (ChE) inhibitors, four of which (tacrine, donepezil, rivastigmine and galantamine) are presently in clinical use (48). Although the main action of ChE inhibitors is to inhibit degradation of Ach, other interesting targets may be important and contribute to the clinical efficacy seen in AD patients treated with ChE inhibitors (49). Presently, cholinesterase (ChE) inhibitors are the drugs of choice in the treatment of AD. Following the introduction in the 1980s of a first generation of non-specific drugs such as physostigmine and tacrine, a second generation of more suitable compounds was developed in the 1990s. The latter drugs are clinically more efficacious and produce less severe side-effects at effective doses: in fact, they are able to avoid the production of toxicity symptoms including effects of excessive CNS cholinergic activation such as hallucinations, delusions, a high stress level and motor agitation. A considerable amount of basic knowledge related to the cholinergic system anatomy, biochemistry, physiology, pharmacology and molecular biology has been accumulated during the last 50 years of intensive fundamental research in the field of acetylcholine (ACh) and contributed to the therapeutic success of ChE inhibitors. Physostigmine was the first active compound to be isolated as a natural product and used in ther-
apy. Its clinical use in 1877 preceded by almost half a century the discovery, in 1914, of ACh as a brain neurotransmitter (50). The use of physostigmine provided experimental support for the demonstration of ACh as an active ester and for the postulation of an enzyme contributing to its inactivation. ChEs were isolated from the mammalian brain and purified in 1932. The introduction of ChE inhibitors as anti-dementia drugs represent the most recent neuropharmacological application of these agents in neurology and psychiatry. The first ChE inhibitor to be used against AD was physostigmine administered in various modes (51,52); this was followed by oral tacrine. Subsequently, metrifonate and galantamine (53) were tested orally. ChE inhibitors, particularly second generation ones, not only save ACh from degradation, but are also able to enhance the release of non-amyloidogenic-soluble derivates of APP from the cortex, both in vitro and in vivo (54-56). This effect might concomitantly decrease secretion of potentially amyloidogenic Aβ peptides and exert neuroprotection because ChE inhibitors improve memory deficits and cognitive decline in some AD patients.

Cholinergic activities may therefore be involved in the regulation of APP metabolism (23) (interaction with Aβ toxicity, aggregation and APP release) even though it is not known whether this effect is also exerted in vivo in the patient.

Besides the established AChE-I therapy several other pharmacological interventions have been attempted in AD, mostly giving modest clinical results (57). These interventions have been frequently based on the epidemiological identification of risk or protective factors. Within this context oestrogens, antiinflammatory drugs, antioxidants and, more recently statins, have been proposed for AD pharmacotherapy. It is interesting to explore how these interventions fit within the mainstream pathogenetic hypothesis of AD. For example, oestrogens have been shown to stimulate choline acetyltransferase (ChAT) activity (58), take part in the nerve growth factor signalling pathway, maintain synapses, increase the cerebral blood flow, increase nicotinic acetylcholine receptor expression, stimulate the non-amyloidogenic pathway of APP degradation (59), as well as reduce formation of Aβ in vitro (60). Oestrogens may also cause antioxidant and anti-inflammatory activity and thus decrease cerebral amyloid deposition. These functions could, theoretically, decrease the cognitive decline and delay the onset of AD. In fact, oestrogens have been demonstrated to protect against Aβ-induced toxicity in different cell lines (59,61,62), but the mechanism underlying this effect has not been clarified in detail. However, in spite of epidemiological data on postmenopausal women, the results on oestrogen active treatment in AD are still inconclusive.

Steroids, in general, have a significant effect on the activity of membrane-associated enzymes and processes. Given that APP is an integral cell membrane glycoprotein and that all of the enzymes regulating its metabolism are probably membrane-associated or integral membrane proteins, it is likely that functional cellular membranes are crucial to APP metabolism. Consistent with the hypothesis that the levels of cholesterol in the membrane can influence the metabolic processing of APP (63,64), reducing the cellular cholesterol levels has been shown to inhibit the formation of Aβ, in cultured hippocampal neurones (65). These data suggest the involvement of membrane cholesterol in the regulation of APP metabolism. Recently, starting from the notion that cholesterol may modulate APP metabolism (64), it has been suggested that statins may control the expression of α-secretase (66,67).

Epidemiological research has also been conducted to find a connection between the effects of antioxidant substances (such as vitamin E and C) and the risks associated with the development of dementia. In fact, the increase in oxidative stress, particularly that occurring
with aging, may be one of factors contributing to the neuronal death that occurs following ischemic/hypoxic insult and also in neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases (68). For example, the age-related increase in cellular oxidative stress and impairment of energy metabolism results in the disruption of neuronal calcium homeostasis and increased vulnerability of neurons to excitotoxicity and apoptosis (69). In addition, oxidative damage, caused by the action of free radicals, may initiate and promote the progression of a number of chronic diseases including cancer, cardiovascular diseases and inflammation. Oxidative stress in cells can result either from an increase in the levels of reactive oxygen species (70) or from a reduction of the natural cell antioxidant capacities (71). Of the free radicals, the hydroxyl radical is one of the most aggressive found in living beings reacting, at a diffusion controlled rate, with molecules such as DNA, lipids, proteins and carbohydrates (72). So, it has been described that AD histopathological cortical lesions are caused by oxidising stress and by accumulation of free radicals leading to a lipoperoxidation that causes lesions of neuronal membranes (73,74). Besides the clinical trials using antioxidant drugs such as vitamin E, selegeline, Gingko extracts, idebenone (57), one emerging aspect is that of dietary antioxidants. In humans, antioxidant protection against toxic intermediates may indeed be heavily influenced by nutrition (75) and it is noteworthy that there has been considerable interest in the possibility that antioxidants of plant origin may reduce the risk of chronic conditions such as cancer and cardiovascular disease as well as age-related degenerative brain disorders (76). The presence in fruits and vegetables of antioxidant compounds is now considered to be of great nutritional importance because they are believed to inhibit, both in chemical systems and in vivo, the action of free radicals and thus prevent their deleterious effects (77,78).

In recent years many new antioxidants have been sought from natural sources, especially from edible or medicinal plants (79-81). Among the vegetable extracts, artichoke extracts have been shown to be protective against hydroperoxide-induced oxidative stress in cultured rat hepatocytes (82). Moreover, with relevance particularly to the Mediterranean diet, studies have been conducted showing components of olive oil, such as hydroxytyrosol, to be highly protective against peroxynitrite-dependent DNA damage in vitro (83). Overall, many methods are currently being explored in order to obtain successful screening of plant extracts. It also seems interesting that melatonin, a hormone that has been suggested to play a role in the aging process and that possesses antioxidant properties, has been reported to protect against Aβ neurotoxicity and lipid peroxidation in vitro. Whether antioxidants or melatonin decrease the incidence of AD is important from a therapeutic viewpoint and should be confirmed in the near future by clinical trials designed for this purpose.

These approaches may give full insight into the therapeutic potential of these extracts and open up new therapeutic fields that can be further explored (84).

In AD, the immune response seems to be altered (6,85-87). In an AD brain there are some proteins typical of acute inflammation and components from the immune system even though classic signs of inflammation, such as neutrophil invasion and oedema are not present. Such alterations, found in the brains of AD patients brains, but not in samples taken from age-matched healthy controls, include a larger number of receptors for immunoglobulins and for the complement, an increased microglial expression of the histocompatibility major complex, a larger production of cytokines, and infiltrations of T lymphocytes in tissues. Furthermore, neurofibrillary plaques and tangles are also surrounded by complement proteins, while inhibitors of this system are present in damaged neurons and in their processes.
From an immunohistochemical point of view microglia is phenotypically correlated with monocytes the phagocytic role of which is substituted in brain tissues by microglia. In AD reactive microglia are present near degenerating neurons, where they participate in their destruction, by phagocytosis, and surround the plaques. Particularly in AD, microglia constitute an expression of a series of important markers of the immune function, such as major histocompatibility antigens of class I and II that favour interactions with T lymphocytes.

It seems that the complement system too (88), which is made up of a series of proteins known as phagocytosis and cell death mediators, participate in these reactive processes.

On the basis of these observations, indicating the existence of a connection between the chronic inflammatory processes and the common AD processes in an affected brain, it has been suggested that antinflammatory treatments could slow down the course of the disease. Although research has been conducted and plenty of valuable literature published (89), providing direct evidence (on brain tissue) that inflammatory cascades involving COX-II are activated by AD (90,91), there continues to be a lack of direct clinical data. The only intervention trial, using prednisone, gave substantially negative results (92), probably because the right stage of intervention or prevention has still to be identified.

CONCLUDING REMARKS

AD is one of the most devastating disorders of elderly humans. Over the past decade, efforts to disclose the aetiology and the neuropathological and neurochemical mechanisms involved in the disease, as well as the relevant genetic causal and susceptibility factors, have been stepped up (93), but still there is no cure. Extensive research activities have stimulated the development of new treatment strategies in AD, and the ChE inhibitors, constituting symptomatic transmitter therapy, have entered clinical use. All current and near-future therapies treat symptoms or slow the disease, at best. More advanced therapies in the future could prevent the aggregation of Aβ into amyloid; free radical scavengers might be effective in achieving this purpose. In view of the hypothesis that the polymer type of Aβ aggregates more easily, inhibiting polymer formation may be beneficial. It is these advances that hold the promise for the development of newer causal therapies in AD.

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