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Alzheimer's disease one century later: the search for effective therapeutic targets continues

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Foreword

Each month several drug targets will be reviewed or a complete compilation of the most exciting therapeutic targets for a specific indication will be presented. Targets will be selected from DailyDrugNews.com, recent patent literature, conferences and journals. Trends in the use of these targets in drug discovery will enable the evaluation of their relevance and druggability.

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Abstract

Despite many years of intensive research efforts, there is still no effective therapy for the prevention and treatment of Alzheimer's disease (AD). However, the search for effective treatment strategies continues, with special attention focused on the identification of novel targets for drug development. This article discusses those targets that are currently under active investigation, as well as newly identified potential targets.

Introduction

Alzheimer's disease (AD) was first described over 100 years ago. It is a progressive and ultimately fatal degenerative brain disorder that primarily affects the elderly and is the most common cause of dementia and loss of global function in this population, followed by vascular dementia. AD affects the parts of the brain that control thought, memory and language. The disease is characterized by senile or neuritic plaques and neurofibrillary tangles in the brain, together with loss of nerve cells in the areas of the brain involved in memory and other mental abilities, cerebrovascular alterations and reduced levels of neurotransmitters. AD appears to disrupt normal thinking and memory by blocking the transmission of complex messages between brain cells. The search for effective agents to treat AD has become a research priority due to the marked increase in the geriatric population worldwide (1-3).

Since the late 1970s, researchers have presented numerous theories regarding the etiology of AD and many putative therapeutic strategies for its treatment have been described. However, despite intensive research, a safe and effective treatment for AD has not been identified and the 4.6 million individuals estimated to be diagnosed worldwide this year can only expect modest improvements with available therapies. The only agents approved by the FDA and currently available for the symptomatic treatment of AD include four acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, rivastigmine and tacrine) and one *N*-methyl-D-aspartate (NMDA) receptor antagonist (memantine). However, these therapies have no long-term efficacy and do not alter disease progression. AD is a multifaceted disease involving various cellular processes and therefore may require a multifaceted treatment approach. Thus, despite years of intensive research efforts, an effective AD therapy continues to elude researchers. The search for effective treatment strategies for AD continues, with special attention focused on the identification of novel targets for drug development. Those targets that are currently under active investigation are discussed below (see also Fig. 1) (4-6).

Targets

Acetylcholinesterase

Acetylcholinesterase (AChE; EC 3.1.1.7), also known as cholinesterase, is a member of a family of enzymes that catalyze the hydrolysis of acetylcholine (ACh). Patients with AD have marked loss of cholinergic neurons in the neocortex and hippocampus, areas associated with learning, memory, emotional responses and executive functioning. Blocking the enzyme that degrades ACh could enhance levels of the neurotransmitter sufficiently to compensate for its deficiency in patients with AD (7-10).

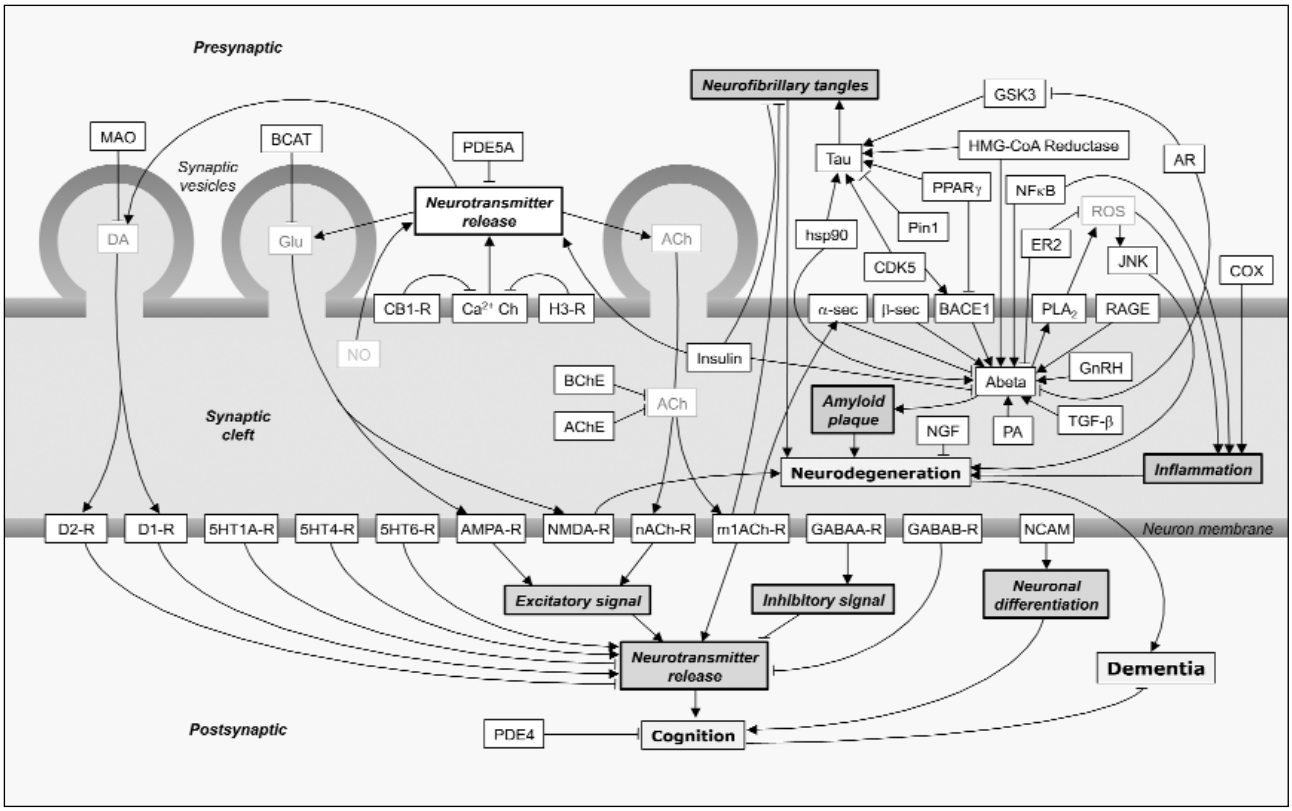

Fig. 1. Therapeutic targets for the treatment of Alzheimer's disease. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of Alzheimer's disease and their biological actions (arrow: positive effect; dash: negative effect). Abbreviations: 5HT1A-R: 5-HT_{1A} receptor; 5HT4-R: 5-HT_4 receptor; 5HT6-R: 5-HT_6 receptor; Abeta: β-amyloid peptide; ACh: acetylcholine; AChE: acetylcholinesterase; AMPA-R: AMPA receptor; AR: androgen receptor; BACE1: β-secretase; BCAT: branched-chain-amino-acid transaminase; BChE: butyrylcholinesterase; Ca^{2+} Ch: calcium channels (N-, P/Q-, R- and T-type); CB1-R: cannabinoid receptor type 1; CDK5: cyclin-dependent kinase 5; COX: cyclooxygenase; D1-R: dopamine receptor 1 subtype; D2-R: dopamine receptor 2 subtype; DA: dopamine; ER: estrogen receptor; GABAA-R: GABA receptor subtype A; GABAB-R: GABA receptor subtype B; α-sec: α-secretase; γ-sec: γ-secretase; Glu: glutamate; GnRH: gonadotropin-releasing hormone; GSK3: glycogen synthase kinase 3; H3-R: histamine H_3 receptor; hsp90: heat shock protein 90; JNK: c-Jun *N*-terminal kinase; M1mACh-R: muscarinic M_1 receptor; MAO: monoamine oxidase; nACh-R: nicotinic acetylcholine receptors; NFκB: nuclear factor κ B; NGF: nerve growth factor; NMDA-R: NMDA receptor; NO: nitric oxide; PA: plasminogen activator; PDE4: phosphodiesterase type 4; PDE5A: phosphodiesterase type 5A; Pin1: peptidylprolyl *cis-trans* isomerase; PLA_2: phospholipase A_2; PA: plasminogen activator; PPARγ: peroxisome proliferator-activated receptor γ; RAGE: receptor of advanced glycation end products; ROS: reactive oxygen species (free radicals); Tau: microtubule-associated protein tau; TGF-β: transforming growth factor-β.

AMPA receptor

The AMPA receptor is a non-NMDA-type ionotropic transmembrane receptor for the excitatory neurotransmitter glutamate that is involved in learning and memory; AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) is the synthetic ligand for this receptor. Studies have shown that changes in the number of synaptic AMPA receptors may be responsible for synaptic plasticity (*i.e.*, the neuronal mechanism required for learning and memory). AMPA receptor agonists could potentially help combat the memory loss seen in AD (11-13).

β-Amyloid

β-Amyloid (Aβ) is comprised of amyloidogenic 39-43-residue fragments of the amyloid precursor protein (APP) that are produced via β- and γ-secretase-mediated cleavage. $A\beta_{42}$ and $A\beta_{40}$ are produced when cleavage of APP occurs in the endoplasmic reticulum and trans-Golgi apparatus, respectively. Deposition and accumulation of Aβ in the brain constitute the major pathological features of AD; $A\beta_{40}$ is more concentrated in cerebrovascular plaques, while $A\beta_{42}$ is predominant in neuritic plaques. A small fraction of the total Aβ is in a soluble form, the levels of which correlate with the severity of AD. Aβ plaque deposition has been shown to occur in five distinct phases. Deposits first develop in the neocortex. In the second phase, additional allocortical brain regions are involved, and during the third phase deposits are encountered in the diencephalic nuclei, putamen, caudate nucleus, substantia innominata and the magnocellular cholinergic nuclei of the basal forebrain. Several brainstem nuclei become involved during the fourth stage. During the fifth

and final phase, plaque progression ultimately involves the cerebellum and additional brainstem nuclei. These regions are involved in sensory perception, motor command, spatial reasoning, conscious thought, language, emotion, motivation, memory and learning, all functions that decline with the progression of AD. Inhibition of APP or Aβ production (*i.e.*, by blocking the cleavage or production of APP), reductions in Aβ accumulation and/or increases in Aβ degradation, solubilization and clearance from the brain represent potentially effective approaches for the treatment of AD (7, 14).

Upstream targeting of Aβ, such as protease inhibition or modulation of APP or alteration of APP trafficking into α- or β-secretase compartments using statins, for example, has resulted in anti-AD efficacy. Downstream targeting of Aβ, such as enhancing its degradation using insulin-degrading enzyme or neprilysin or increasing brain clearance by immunization with native or modified Aβ forms, may also be effective. A more direct approach, however, involves targeting the actual toxicity of Aβ. Two major mechanisms responsible for Aβ toxicity have been identified. These include redox reactions associated with Aβ Cu/Zn binding sites (His6, 13/14, Tyr10 together with Met35 interaction) and lipid activity participating in the α/β conformation of the hydrophobic *C*-terminus. Preliminary results using agents targeting these mechanisms have indicated potential promise for this therapeutic approach (15).

Further investigation on Aβ indicated that reduced Aβ catabolism may be responsible for sporadic AD, while increased Aβ anabolism may cause familial AD. Experimental gene therapy using the gene encoding neprilysin, a candidate protein for $A\beta_{42}$ degradation *in vivo*, resulted in anti-AD effects. A role for the neuropeptide somatostatin in upregulating neprilysin activity was discovered, suggesting that somatostatin receptors may also represent an effective target for the prevention and treatment of AD (16).

Androgen receptor

The androgen receptor (AR) is a nuclear receptor that binds androgens (*e.g.,* testosterone, dihydrotestosterone, androstenedione), a class of sex hormones involved in the development and maintenance of the secondary male sex characteristics, sperm induction and sexual differentiation. Binding of these hormones to their receptor results in increased virility, libido and nitrogen, water retention and stimulation of skeletal growth. Testosterone depletion is a normal consequence of aging in men and is associated with senescent effects in androgen-responsive tissues, and may increase the risk for the development of AD. Testosterone has been shown to be an endogenous regulator of Aβ, modulating hyperphosphorylation of tau through glycogen synthase kinase-3 (GSK-3), and it has been demonstrated to possess both neurotrophic and neuroprotective activities. Moreover, an AR polymorphism consisting of a CAG repeat in exon 1 has been identified as a potential risk factor for AD in men (17-20).

BACE 1

See section on Secretases

BCAT

Branched-chain-amino-acid transaminase, or BCAT (EC 2.6.1.42), is the key enzyme catalyzing the reversible transfer of the amino group from a branched-chain amino acid (isoleucine, leucine or valine) to 2-oxoglutarate to form 2-oxo acid and the neurotransmitter glutamate. There are two isozymes: mitochondrial BCAT (BCATm), which is present in most tissues and thought to be involved in nitrogen metabolism, and cytosolic BCAT (BCATc), which is largely restricted to the CNS and is involved in glutamate synthesis. Excessive excitation by neurotransmitters, such as the excitatory amino acids glutamate and aspartate, at the NMDA receptor has been shown to cause degeneration and death of neurons. Thus, BCATc is a target for preventing neuronal loss from stroke, CNS trauma and neurodegenerative diseases such as AD, amyotrophic lateral sclerosis (ALS) and Huntington's disease (21-23).

Butyrylcholinesterase

Butyrylcholinesterase (BChE; EC 3.1.1.8) is a member of the cholinesterase family of enzymes that catalyze the hydrolysis of ACh. Butyrylcholine is a synthetic compound used purely to differentiate BChE from AChE in enzyme assays. Both enzymes catalyze the hydrolysis of ACh in humans. High levels of this enzyme are evident in the brains and cerebrospinal fluid (CSF) of patients with AD and this enzyme may therefore be involved in disease onset and progression. Inhibitors of this enzyme may represent a potential therapeutic approach to the treatment of AD (24-26).

Voltage-gated calcium channels

Voltage-gated calcium channels (L-, N-, P/Q-, R- and T-type) are pore-forming proteins present in cell membranes that control the flow of ions, thereby establishing the small voltage gradient that exists across the membrane of cells. These voltage-gated channels are formed as a complex of several different subunits and are prominent throughout the nervous system, where they are responsible for triggering the release of neurotransmitters. It has been suggested that modulation of intracellular calcium levels by voltage-gated calcium channels may be involved in neuronal death and cognitive deficits associated with AD, and L-type calcium channel modulators have been shown to enhance cognition in AD patients (27-29).

Cannabinoid CB_1 receptor

The cannabinoid CB_1 receptor is a G-protein-coupled, 7-transmembrane-spanning receptor protein which, together with CB_2, has been identified as the receptor for

cannabinoids. CB_2 is highly expressed in immune cells, although its biological functions are still unclear. CB_1 is preferentially expressed in the brain, where it mediates the psychoactivity of cannabinoids. High levels of CB_1 receptors are found in the basal ganglia, hippocampus, cerebellum and cortical structures. CB_1 receptors are coupled through the $G_{i/o}$ family of proteins to signal transduction mechanisms that include inhibition of adenylyl cyclase and activation of mitogen-activated protein kinase (MAPK). Activation of presynaptic CB_1 receptors inhibits N-type Ca^{2+} channel activity, which in turn reduces excitatory neurotransmitter release to the synaptic cleft, thus allowing the excitatory signals to activate the postsynaptic cell. Senile plaques in AD express both CB_1 and CB_2 receptors. CB_1-positive neurons are present in high numbers in nondiseased brains but are greatly reduced in areas of microglial activation in AD brains. While CB_2 receptors are selectively overexpressed in neuritic plaque-associated glia in AD, the expression of CB_1 receptors remains unchanged. Cannabinoids have been speculated to exert neuroprotection against excitotoxicity and acute brain damage. Thus, cannabinoid receptor activation would protect hippocampal or granule cerebellar neurons from excitotoxicity and from hypoxia and glucose deprivation, and might prevent neurodegenerative progression in AD. On the other hand, CB_1 is implicated in learning and memory, and antagonism of this receptor may improve cognitive deficits in AD and other neurodegenerative diseases (30-33).

Cyclin-dependent kinase 5 (CDK5)

CDK5 is a kinase that is essential for normal development and is implicated in synaptic plasticity, learning and memory in the adult brain. To be activated, CDK5 must associate with its regulatory protein p35. CDK5 activity is also associated with neurodegenerative diseases and has been implicated in the phosphorylation of tau and neurofibrillary tangles and the production of Aβ. An increase in CDK5 activity has been observed in the brains of AD patients. In addition, enhanced CDK5 activity was observed in mice overexpressing p25, a truncated form of p35, which correlated with increased levels of the β-secretase BACE1. CDK5/p25 has been found to accumulate in AD brains and, unlike CDK5/p35, it is constitutively active, resulting in hyperphosphorylation of tau and neuronal death. Moreover, mutagenesis of a putative BACE CDK5 site decreased mature BACE levels. Results suggest potential efficacy for blood-brain barrier-penetrating agents that target CDK5 (34-37).

Cyclooxygenase

Cyclooxygenase (COX; EC 1.14.99.1), also known as prostaglandin endoperoxide synthase, catalyzes the two steps in prostaglandin (PG) synthesis, forming PG_2 and PGH_2 from arachidonic acid. The two major forms of the enzyme are COX-1 and COX-2. Recently, COX-3, a distinct COX-1 variant, and two smaller COX-1-derived proteins (partial COX-1 or PCOX-1 proteins), have been cloned and found to be expressed in canine cerebral cortex and other tissues; COX-3 was predominantly expressed in canine cerebral cortex and heart and was shown to be selectively inhibited by nonsteroidal antiinflammatory drugs (NSAIDs), suggesting the involvement of this isoform in pain and fever. COX-1 is constitutive and present in endothelium, stomach and kidney. It is involved in the maintenance of platelet and kidney function and is considered a housekeeper enzyme, maintaining homeostasis. COX-2 is not present at baseline but is inducible during inflammation by cytokines and endotoxins. It has been shown to play a role in the propagation of inflammatory cascades leading to disorders such as AD, rheumatoid arthritis and osteoarthritis, cancer, kidney disease and osteoporosis. Thus, inhibition of COX-2 may be effective in preventing the development and progression of AD (38, 39).

Dopamine receptors

Dopamine receptors are G-protein-coupled, 7-transmembrane-spanning receptor proteins which bind the neurotransmitter dopamine present in the CNS in basal ganglia. Dopamine is the precursor of norepinephrine and epinephrine and accounts for 90% of all catecholamines. The first two dopamine receptor subtypes identified were the D1 receptors, which stimulate the synthesis of cAMP, and D2 receptors, which inhibit cAMP synthesis. Dopamine D3 and D4 receptors, homologous to the D2 receptor, and the dopamine D5 receptor, homologous to the D1 receptor, were identified later. Activation of the D1 receptor and antagonism of the D2 receptor have been reported to be effective in the treatment of AD dementia (40-42).

Estrogen receptor

Estrogen is a general term used to refer to any naturally occurring or synthetic substance that has activity (*i.e.,* estrogenic) similar to that of the most potent naturally occurring estrogen 17β-estradiol. Estrogens are produced by the ovary, testis, placenta and adrenal cortex and by certain plants. The actions of these agents occur via two receptor subtypes, ERα and ERβ, and include stimulation of secondary sex characteristics, growth and maturation of long bones and control of the menstrual cycle. ERβ gene (*ESR2*) expression, although relatively low in the human forebrain, is most abundant in the hippocampal formation (primarily the subiculum), claustrum and cerebral cortex, suggesting that the receptor may play a role in cognition, memory and motor function. It has been reported that more women than men suffer from AD and *ESR2* variants are associated with an increased risk of AD in women. Moreover, agonism of these ERs has been shown to improve dementia in AD (43-49).

Fibroblast growth factor receptor 1 (FGFR1)

See section on Neural cell adhesion molecule

Free radicals

A free radical is a chemically active atom or molecular fragment which contains a charge due to an excess or deficient number of electrons. These highly reactive atoms receive or release electrons to achieve a more stable configuration, a process that can damage large molecules within cells. Free radicals have been implicated in more than 50 diseases, including AD, stroke, asthma, Crohn's disease and Parkinson's disease. Oxidative stress is important in the pathogenesis of AD and reactive oxygen species (ROS) have been implicated in the cellular damage seen in neurodegenerative disorders. ROS can react with cellular macromolecules through oxidation and can cause the cells to undergo inflammation, necrosis or apoptosis. Agents inhibiting oxidative stress and free radical production may be beneficial in AD (50-53).

GABA receptors

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the brain and spinal cord and acts via $GABA_A$, $GABA_B$ and $GABA_C$ receptors. $GABA_A$ receptors are widely distributed throughout the CNS. They are ionotropic and can be activated by several different compounds. These receptors are suggested to be involved in the modulation of vigilance, anxiety, muscle tension, epileptogenic activity and memory functions. Enhancement of $GABA_A$ receptor-mediated fast synaptic inhibition may be effective in improving cognition. $GABA_B$ receptors are widely distributed throughout the CNS and in peripheral autonomic terminals and are metabotropic, distinguishing them from ionotropic $GABA_A$ receptors. $GABA_B$ receptors are coupled to G-proteins and their activation causes a decrease in Ca^{2+} and an increase in K^+ in the membrane. $GABA_B$-induced changes in Ca^{2+} conductance are thought to be associated with P/Q- and N-type, and possibly L-type, Ca^{2+} channels and with several different types of K^+ channels. GABA transmission has been shown to be disrupted in patients with AD and $GABA_A$ and $GABA_B$ receptor modulators may be effective in improving cognitive performance (54-56).

GSK-3

This enzyme was originally identified as the kinase responsible for phosphorylating and inhibiting glycogen synthase, the rate-limiting enzyme in glycogen biosynthesis. α And β isoforms have been identified which have similar biochemical properties. GSK-3β is thought to be involved in signaling that controls energy metabolism, embryonic development and cell proliferation in adult tissues, and inhibition of this isoform has been shown to attenuate apoptotic signals. Tau is a known substrate of GSK-3 and tau hyperphosphorylation is an event occurring early in neurodegenerative conditions such as AD. Administration of a selective GSK-3β inhibitor in a murine model of AD resulted in reduced tau phosphorylation and a reversal in microtubule deficiency in the brain. Moreover, GSK-3β inhibitors have been suggested to promote axon regeneration after neuronal injury (57-62).

Gonadotropin-releasing hormone

The decapeptide hormone gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone [LHRH]) is produced and released by the hypothalamus to control reproductive function via modulation of the synthesis and release of the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Neuronal receptors have been identified for LH and GnRH throughout the limbic system on several cell types and their expression is regulated through hormonal feedback loops. In particular, a high concentration of LH receptors is present in the hippocampus, which is aggressively targeted by AD. Studies have shown that LH may mediate neurodegenerative changes and play a role in promoting amyloidogenic processing of APP. Significantly increased levels of LH have been observed in serum and pyramidal neurons of patients with AD, and preclinical studies showed that cognitive performance was increased and Aβ deposition was decreased in aged transgenic mice carrying an APP mutation treated with a GnRH agonist. Moreover, there is a reduced incidence of neurodegenerative disease in patients treated with GnRH agonists for prostate cancer and increases in LH levels during menopause and andropause due to dysregulation of the hypothalamic-pituitary-gonadal axis may be responsible for inducing neurodegeneration. GnRH analogues may therefore be an effective strategy to prevent the onset and progression of AD (63-65).

Heat shock proteins

Heat shock proteins (HSPs) are highly conserved stress proteins present in prokaryotic and eukaryotic cells and bacteria which increase thermal tolerance. Some forms stabilize proteins in abnormal configurations by playing a role in protein folding and unfolding and in the assembly of oligomeric complexes, while others act as molecular chaperones. HSPs are characterized in the following major subclasses: HSP90, HSP70, HSP60 and small HSPs. HSPs (*e.g.,* HSP72, HSP73) have been shown to be significantly upregulated in the AD brain and preclinical studies have reported that HSP60, HSP70 and HSP90, both alone and in combination, provide differential protection against intracellular Aβ stress through the maintenance of mitochondrial oxidative phosphorylation and functionality of tricarboxylic acid cycle enzymes. When combined, these three HSPs decrease free radical burden, maintain ATP generation, suppress cytochrome *c* release and inhibit caspase-9 activation, all important mediators of Aβ-induced neuronal dysfunction and death. In addition, HSP90 and HSP70 have been implicated in the development of AD. HSP70, for example, was shown to be involved in regulating tau ubiquitination, degradation and aggregation, and administration of an HSP90

inhibitor rapidly and selectively degraded aberrant hyperphosphorylated tau in a mouse model of tauopathy. Targeting HSPs could therefore be effective in suppressing Aβ aggregation and the formation of neurofibrillary tangles (66-71).

Histamine H_3 receptor

The histamine H_3 receptor is a G-protein-coupled receptor that, in contrast to histamine H_1, H_2 and H_4 receptors, is predominantly expressed in the CNS. Due to their location, it has been speculated that H_3 receptors mediate various CNS functions by modulating brain histaminergic tone, and possibly through interactions with H_1 and H_2 receptors. H_3 receptors have been shown to act as autoreceptors in presynaptic neurons controlling histamine turnover, and also as heteroreceptors in dopamine-, serotonin-, norepinephrine-, GABA- and ACh-containing neurons. H_3 receptors are thought to play a role in memory formation and pharmacological blockade of central H_3 receptors has been shown to enhance cognition in rodents. Thus, H_3 receptor antagonists may be effective in the treatment of cognitive dysfunction in AD (72).

HMG-CoA reductase

HMG-CoA reductase (EC 1.1.1.88) is a key enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis. There is evidence that tangle-bearing cells in AD have high levels of free cholesterol as compared to adjacent tangle-free nerve cells. In addition, cellular cholesterol homeostasis has been shown to be involved in several pathological events occurring in the brain of patients with AD. Studies have demonstrated that processing of APP and tau phosphorylation can be modulated by pronounced alterations in cellular cholesterol levels (73-77).

Insulin

Insulin is a polypeptide hormone secreted by pancreatic β-cells that promotes the uptake and metabolism of glucose by cells, prevents the release of glucose by the liver, promotes the uptake of amino acids by muscle cells (*i.e.,* protein synthesis) and inhibits the breakdown and release of fats. Insulin release is triggered by growth hormone (GH; somatotropin), glucagon and glucose, and insulin and insulin signaling are important for neuronal survival. There is also evidence for the involvement of insulin in the pathogenesis of AD. AD is associated with peripheral and central insulin abnormalities and cognitive capacities are often impaired in patients with diabetes. Studies in mice deficient in the neuronal insulin receptor demonstrated increased tau phosphorylation and reduced brain growth. Direct injection of streptozotocin in the brains of rat pups resulted in blockade of brain insulin synthesis and induction of AD-like symptoms. *Post mortem* studies have revealed reduced expression of insulin and insulin-like growth factor (IGF) genes and their corresponding receptors in the brain tissue of AD patients. Moreover, in these patients, membrane-bound insulin-degrading enzyme levels were proportionate with an increase in $A\beta_{42}$. Insulin resistance and dysregulation of the degradation of neurotoxic amyloid and insulin appear to be at the core linking AD and diabetes. The functions and expression of insulysin, an enzyme involved in the degradation of neurotoxic amyloid peptides and insulin, are usually impaired or reduced in AD and diabetes. Moreover, direct delivery of insulin (intranasal) to the brain of patients with early-stage AD was shown to improve memory and other functions (78-81).

c-Jun N-terminal kinases

The c-Jun *N*-terminal kinases (JNKs) are a group of enzymes also known as stress-activated protein kinases, or SAPKs, belonging to the mitogen-activated protein kinase (MAPK) family, which modulate the expression of genes controlling immune responses, proliferation and cell death. They are activated by exposure of cells to cytokines and environmental stress. Genetic deletion of JNK1 or JNK2 results in disruption of the regulation of $CD4^+$ cell differentiation to Th1 or Th2 subsets and may represent a new therapeutic approach for modulating Th1 and Th2 diseases. The JNK signaling pathway has also been implicated in neuronal death and may therefore be an important target for the treatment of AD (82-84).

Monoamine oxidase

Monoamine oxidase, or MAO, is a flavin-containing oxidoreductase (EC 1.4.3.4) involved in the catabolism of the neurotransmitters serotonin, norepinephrine and dopamine (MAO-A) and dietary amines such as phenylethylamine (MAO-B), which are important for maintaining normal brain status of dopamine. Both MAO-A and MAO-B in the brain have been implicated in the etiology of AD, where MAO-B is elevated in plaque-associated glia and elevated neuronal MAO-A is associated with increases in neurotoxic metabolites and neuron loss. Selective inhibition of brain MAO-A and MAO-B has been shown to significantly increase levels of dopamine, norepinephrine and serotonin in the striatum and hippocampus and improve cognition in aged rhesus monkeys. It has been suggested that iron accumulation may contribute to the oxidative stress-induced apoptosis reported in AD and Parkinson's disease, which results in increased glial hydrogen peroxide and subsequent activation of MAO activity. The increased MAO activity can generate reactive hydroxyl radicals from the interaction of iron and hydrogen peroxide. Thus, inhibition of these enzymes may be effective in preventing the progression of AD (85-87).

Muscarinic acetylcholine M_1 receptor

The muscarinic acetylcholine M_1 receptor is one of five subtypes of membrane-bound G-protein-coupled, 7-transmembrane-spanning acetylcholine receptor

(AChR) proteins that have been identified and found to be predominantly expressed within the parasympathetic nervous system, which exerts inhibitory and excitatory control over central and peripheral tissues and plays a role in physiological functions, such as heart rate, arousal, cognition, learning, hippocampus-based memory, short-term memory, sensory processing and motor control. This class of AChR is activated by ACh and the highly toxic exogenous alkaloid muscarine, thus distinguishing them from the unrelated nicotinic AChRs (nAChRs), which respond to nicotine but not muscarine. Activation of the stimulatory M_1 receptor results in mobilization of intracellular calcium and may link Aβ accumulation, tau hyperphosphorylation and paired helical filaments with loss of cholinergic function, causing cognitive impairment. The M_1 receptor is relatively spared in AD and is known to play a role in hippocampus-based memory, learning and short-term memory. M_1 receptor agonists have been shown to improve cognition and modify disease properties (*e.g.,* decrease brain Aβ) in animal models. However, these agonists lack M_1 selectivity and are thus associated with adverse events limiting their clinical use. A muscarinic agonist was shown to increase secreted APP and decrease Aβ and tau hyperphosphorylation *in vitro,* and improve cognition, cholinergic markers and tau hyperphosphorylation *in vivo* (88-90).

Nerve growth factor

Nerve growth factor, or NGF, is a protein (MW approx. 26,000) that controls the development and maintenance of sympathetic postganglionic neurons and may be involved in the development of sensory ganglion cells and the stimulation of nucleic acid and protein synthesis. Dysfunction of NGF and its high- (TrkA) and low-affinity (p75NTR) receptors may be responsible for the selective degeneration of the nucleus basalis (NB) cholinergic cortical projection neurons in end-stage AD. Preclinical studies using rodents showed that conjunctivally administered NGF reaches the CNS and prevents degeneration of the NGF-receptive neurons involved in AD and Parkinson's disease. Anti-NGF transgenic mice (AD 11) are an animal model of AD in which NGF depletion results in cholinergic deficits and progressive AD-like neurodegeneration. In addition, proNGF, which cannot bind to TrkA receptors, has been shown to elicit neuronal apoptosis via the low-affinity p75NTR and high levels of proNGF are seen in the NB of AD patients. Low levels of brain-derived neutrophic factor (BDNF) in the NB, on the other hand, are associated with improvement in AD. A phase I trial conducted in patients with mild AD showed that NGF gene therapy significantly improved the rate of cognitive decline, increased cortical 18-fluorodeoxyglucose and may have stimulated growth responses to NGF (91-94).

Neural cell adhesion molecule

Neural cell adhesion molecule (NCAM) is a homophilic binding glycoprotein that is a member of the immunoglobulin (Ig) superfamily. It is expressed on the surface of neurons, glia and skeletal muscle and is implicated in the modulation of cell-cell adhesion, neurite outgrowth, synaptic plasticity, learning and memory. It is composed of five Ig homology modules (IgI-IgV) and two fibronectin type III homology modules (F3,I and F3,III), and signals via direct interaction with the FGFR. There are 20-30 distinct isoforms of NCAM, with 3 major forms (180-, 140- and 120-kDa) expressed in the nervous system: NCAM-180 and NCAM-140 on neurons and NCAM-140 and NCAM-120 on glial cells. NCAM has been shown to induce neuronal differentiation, stimulate axonal outgrowth and fasciculation, and modulate synaptic activity. Levels of soluble fragments of NCAM are increased in sera and CSF of patients with AD and other neurodegenerative disorders, suggesting abnormal processing and/or shedding of the glycoprotein. NCAM mimetics which would activate FGFR1 could stimulate neurite extension, enhance presynaptic function and promote synapse formation, thus enhancing cognitive processes and affording neuroprotection in neurodegenerative diseases such as AD (95-98).

Nicotinic acetylcholine receptors

The nicotinic acetylcholine receptors (nAChRs) are a class of AChRs that are activated by ACh and the alkaloid nicotine (which imitates the effects of ACh), thereby distinguishing them from the unrelated muscarinic AChRs. The receptors are linked to ion channels in the cell membrane and are divided into two subclasses: the ganglionic nicotinic receptors found in the central and peripheral nervous systems and the neuromuscular nicotinic receptor found in neuromuscular junctions of somatic muscles. Activation of the neuronal receptors through ligand binding causes depolarization of the plasma membrane, resulting in excitation of the neurons in presynaptic nAChRs and calcium entry in postsynaptic nAChRs, thus inducing neurotransmitter release and long-term potentiation (LTP) through gene regulation. There are several types of neuronal nAChRs that vary according to the arrangement of the homologous subunits around the central ion channel. They have been implicated in memory and treatment with nicotinic agonists has been shown to ameliorate learning and memory impairment. Moreover, chronic transdermal nicotine treatment of subjects with age-associated memory impairment resulted in sustained improvement in clinical symptoms and patients with AD have been found to have downregulated nAChRs and NMDA receptors in the brain. Thus, activation of nicotinic receptors or agents that block the inhibition of nAChRs may be effective as a treatment for AD (99, 100).

Nitric oxide

Nitric oxide (NO) is a small, membrane-permeable molecule involved in cellular signaling. It is formed by the enzyme nitric oxide synthase (NOS) from the amino acid arginine and it mediates activation of soluble guanylyl

cyclase, which, when activated, produces the second messenger cGMP in the brain. In the brain, NO regulates the release of neurotransmitters and plays an important neuroprotective role. Small molecules that mimic the biological activity of NO would bypass cholinergic receptor activation and might therefore be effective in treating and/or preventing dementia in AD. NO mimetics may possess cGMP-dependent and -independent activity and may operate via multiple signaling pathways which increase survival of neurons subjected to stress. They may also stimulate cognition-enabling pathways to circumvent dementia in diseases such as AD. On the other hand, NO production by astrocytes has been suggested to contribute to neurodegenerative processes and NOS isoforms have been linked to the pathogenesis of AD. Moreover, platelet NO is significantly increased in patients with AD (101-103).

NMDA receptor

The NMDA receptor is a subtype of glutamate receptor that binds the excitotoxic amino acid NMDA. Activation of the NMDA receptor results in opening of an associated ion channel pore, allowing inflow of Na^+, K^+ and Ca^{2+}, of which the latter is thought to play a critical role in synaptic plasticity. The receptor mediates LTP of the signaling involved in learning, memory and cognition, but it has also been implicated in causing the cell damage observed in AD, as well as Parkinson's and Huntington's diseases. Although some studies report that the NMDA receptor is downregulated in the brains of patients with AD and effective treatment would include potentiation of the NMDA receptor, others assert that the activity of this receptor is actually upregulated in AD brains and excitotoxicity plays a critical and detrimental role in chronic neurodegenerative disorders. Synaptic overactivity results in excessive glutamate release, thus overstimulating postsynaptic cell membrane receptors (*i.e.,* the NMDA receptor), which upon activation, open associated ion channel pores and increase ion influx. The consequence is neuronal cell injury and death. Antagonism of the NMDA receptor may therefore be effective in preventing neurodegeneration in AD (104-108).

Nuclear factor-κB

Nuclear factor-κB (NF-κB) is a nuclear transcription factor and intracellular mediator of the inflammatory cascade involved in the generation of certain adhesion molecules (*e.g.,* ICAM-1, VCAM-1), inducible nitric oxide synthase (iNOS), COX-2, cytokines (*e.g.,* IL-1β, IL-2, TNF-α, IL-6, interferon gamma) and chemokines (IL-8). Other genes which are regulated by NF-κB include those encoding the IL-2 receptor, the IL-12 p40 subunit and c-myc. NF-κB has been implicated in the control of cell proliferation and apoptosis and may participate in long-term memory formation. Moreover, NF-κB signaling in microglia is essential for the Aβ-induced neuronal death that causes AD. Thus, the transcription factor represents a potential target for anti-AD therapy (109-111).

Peroxisome proliferator-activated receptor γ

The peroxisome proliferator-activated receptor γ, or PPARγ, is a ligand-activated nuclear transcription factor that is a member of the nuclear receptor superfamily, which also includes about 70 steroid, retinoid, thyroid hormone or vitamin D receptors (*e.g.,* RAR [retinoic acid receptor], RXR [retinoid X receptor], TR [thyroid hormone receptor], NGF1B, LXR [liver X receptor], PPAR). Three PPAR subtypes have been identified: PPARα, PPARβ/δ and PPARγ. They are activated by endogenous fatty acids or fatty acid derivatives. Once activated via the endogenous ligand prostaglandin J_2, they heterodimerize with the RXR and bind to response elements on DNA, resulting in regulation of transcription. Their function is further modified by co-activators and co-repressors. Studies have shown that PPARγ could be a repressor of BACE1 and may therefore play a major role in modulating Aβ generation. Activation of the PPARγ subtype may be effective in treating AD dementia. It has been suggested that PPARγ agonists may increase insulin sensitivity in the brain and therefore effectively improve AD symptoms (112-114).

PDE4

The phosphodiesterase (EC 3.1.4) type 4 (PDE4) isozyme degrades cAMP and cGMP, thereby modulating signal transduction mediated by these second messengers. PDE4 is characterized by high affinity for cAMP and poor affinity for cGMP. Four PDE4 isoforms have been identified (A, B, C and D) and are abundant in immunocompetent cells, where an increase in cAMP leads to inhibition of the synthesis and release of proinflammatory mediators, cytokines and ROS. Research suggests that PDE4 inhibitors may be effective treatment strategies for inflammatory diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD) and multiple sclerosis. Moreover, PDE4 inhibitors may also represent a novel therapy for the treatment of AD, which involves neuroinflammation. PDE4 inhibitors have been shown to counteract deficits in long-term memory in preclinical models and they also exert neuroprotective, neuroregenerative and antiinflammatory activities, which would all be beneficial in the treatment of AD (115-117).

PDE5

The PDE5 isozyme has relatively high affinity for cGMP and hydrolyzes cAMP poorly. Glutamatergic NMDA-mediated synaptic transmission may play an important role in synaptic plasticity, which is required for learning and memory. PDE5 interrupts glutamate-mediated neurotransmission by rapidly converting cGMP to the inactive 5'-GMP. Inhibition of this enzyme would attenuate the degradation of cGMP and thus facilitate further release of neurotransmitter. This mechanism may improve different kinds of learning and memory and protect against neurodegeneration (118, 119).

Pin1

Pin1 is a peptidylprolyl *cis-trans* isomerase (PPIase) that isomerizes only phosphorylated Ser/Thr-Pro peptide bonds and regulates several phases of the cell cycle, including G1/S, G2/M and DNA replication checkpoints. It is overexpressed in many human cancers and depletion of this enzyme induces apoptosis in tumor cells. Its expression is also inversely correlated with predicted neuronal vulnerability and neurofibrillary degeneration in AD. Pin1 knockout mice exhibit AD-like symptoms, including motor and behavioral deficits, hyperphosphorylated tau, tau filaments and neuronal degeneration. Pin1 binds to and restores the function of hyperphosphorylated tau isolated from the brains of AD patients. Sequestration of Pin1 into tau filaments could cause its depletion in the nucleus, leading to apoptosis of neurons with hyperphosphorylated tau filaments. It has also been suggested that Pin1 has effects on APP processing and Aβ production, such that when Pin1 activity is increased Aβ levels are low and when Pin1 activity is reduced Aβ levels increase and AD develops. Thus, targeting Pin1 may be an effective anti-AD therapy (123-127).

Phospholipase A_2

Phospholipase A_2 (PLA_2) is a member of the phospholipase family of enzymes that hydrolyze the ester bonds in phospholipids. This group includes two types of enzymes: the aliphatic esterases that release fatty acids and include PLA_1 (EC 3.1.1.32), PLA_2 (EC 3.1.1.4) and PLB (EC 3.1.1.5), and phosphodiesterases such as phospholipase C (EC 3.1.4.3) and D (EC 3.1.4.4) that release diacyl glycerol and phosphatidic acid, respectively. PLA_2 is present in all mammalian tissues and has been implicated in inflammatory responses due to its ability to release arachidonic acid (AA). Mitochondrial dysfunction, including loss of membrane potential and increased ROS production in astrocytes, coupled with impaired ATP production, are speculated to play important roles in the pathophysiology of AD. The cystolic and calcium-independent PLA_2s, $cPLA_2$ and $iPLA_2$, have been shown to mediate Aβ peptide-induced mitochondrial dysfunction in AD brains. Targeting PLA_2 may therefore influence the progression of AD (120-122).

Plasminogen activators

Plasminogen activators (PAs) are secreted serine proteases which convert the inactive single-chain proenzyme plasminogen to active plasmin, a fibrinolytic enzyme with Aβ-degrading capacity that consists of two peptide chains linked by disulfide bonds. There are two types of PA: tissue-type PA (tPA; 55 kD) and urokinase-type PA (uPA; 70 kDa). tPA plays a significant role in the blood coagulation cascade and it is also the predominant PA in the brain, where it is expressed in the hippocampus, hypothalamus, cerebellum and amygdala. A variant in the gene encoding for uPA (*PLAU*) is suspected to be involved in the pathogenesis of AD and in the age at onset of the disease. Evidence suggests that the brain tPA/plasminogen cascade is required for normal matrix degradation during neuronal development and in LTP, memory and motor learning, which all require synaptic plasticity. Plasmin can enhance APP-α cleavage and Aβ degradation, and brain plasmin levels in AD patients are significantly decreased. It is therefore speculated that defects in the plasminogen system play a major role in the pathology of AD and enhancement of plasmin activity through specific PAs may be effective in the treatment of AD. tPA may also mediate plasmin-independent processes, including activation of microglia, stimulation of mossy fiber outgrowths and enhancement of NMDA receptor-mediated signaling. However, some of these plasmin-independent effects may be neurotoxic. Aβ increases the expression of both tPA and uPA, and increased concentrations of tPA have been localized in brain areas of AD patients exhibiting high levels of Aβ and tau phosphorylation. It has been reported that tPA activates the extracellular-regulated kinase ERK1/2 in hippocampal neurons via modulation of the NMDA receptor, G-proteins and protein kinase C (PKC) and is independent of catalysis. The result is activation of GSK-3β, which subsequently leads to aberrant tau phosphorylation, microtubule destabilization and apoptosis. Thus, in cases when tPA exerts plasmin-independent neurotoxic effects, PA inhibitors may be effective in the treatment of AD (128-134).

RAGE

The receptor for advanced glycation end products, or RAGE, is a multiligand member of the Ig superfamily that is expressed as a cell-surface molecule and is composed of three Ig-like regions, a transmembrane domain and a highly charged short cytosolic tail required for post-RAGE signaling. The receptor recognizes families of ligands and not a single protein. Its ligands include advanced glycation end products (AGEs), the Aβ protein, the S100/calgranulin family of proinflammatory cytokine-like mediators, β-integrin Mac-1 and high mobility group protein B1 (HMGB1). The receptor has been implicated in vascular disease, rheumatoid arthritis and neurodegeneration, and low levels of the secreted isoform, soluble RAGE (sRAGE), which is a truncated form of the receptor composed of the extracellular ligand-binding domain and lacking the cytosolic and transmembrane domains, are considered a possible risk factor for atherosclerosis, rheumatoid arthritis and AD. Upon ligand binding, RAGE activates NF-κB, leading to an inflammatory response. The *RAGE* gene is itself a target for NF-κB, and thus large amounts of Aβ may establish a positive feedback cycle leading to chronic inflammation. Treatment with sRAGE effectively suppressed the development of cerebral β-amyloidosis in a mouse model of AD. Moreover, patients with AD are reported to have lower levels of sRAGE as compared to normal subjects and subjects with vascular dementia. Thus, modulation of RAGE may be effective in altering the progression of AD (135-137).

Secretases

α-, β- and γ-Secretases are proteolytic enzymes that catalyze the sequential cleavage of membrane-bound amyloid precursor protein (APP) into three fragments. Activation of the nonamyloidogenic pathway involves α-secretase-mediated cleavage of APP releasing a large soluble *N*-terminal fragment (APPs-α) and the 10 kD membrane-bound *C*-terminal fragment (C83). The amyloidogenic pathway involves APP cleavage via β-secretase (BACE) at the *C*-terminus between residue 671 and 672 which releases a 100 kD soluble *N*-terminal fragment (APPs-β) and a membrane-bound 12 kD *C*-terminal fragment (C99). Both C99 and C83 are substrates for the multi-subunit protease complex γ-secretase which catalyzes the final processing step. γ-Secretases cleave C99 and C83 fragments within their transmembrane domain, resulting in release of the insoluble peptide Aβ ($A\beta_{40}$ or $A\beta_{42}$) and AICD (amyloid precursor protein intracellular domain) and the secretion of nonpathogenic p3 peptide and AICD, respectively. Thus, inhibition of β- and γ-secretases and activation of α-secretase are possible approaches for reducing Aβ burden in the brain and thereby slowing the progression of AD (2, 138-140).

Identification of effective β-secretase inhibitors has proven difficult. However, significant progress has been made in development of these agents. Improvements include reductions in size of inhibitors to increase blood-brain barrier and cellular penetration, better selectivity, reductions in conformational options and reductions in peptide character (141).

α-Secretase is also a potential therapeutic target for the treatment of AD since soluble APPs-α released from APP by α-secretase has been shown to be neurotrophic and neuroprotective. ADAM-10, ADAM-17 (TACE) and ADAM-9, three members of the ADAM (a disintegrin and metalloprotease) family of proteases, have been identified as possible α-secretases. Studies have shown that amyloid plaque formation and hippocampal defects were prevented with ADAM-10 treatment in a mouse AD model. In addition, retinoic acid, identified as an inducer of human ADAM-10 promoter activity, upregulated ADAM-10 and its APP substrate and increased secretion of their extracellular domains in a human neuroblastoma cell line; a related APP-like-protein 2 (APLP2) was also upregulated with treatment. Thus, induction of α-secretase activity may be effective in the treatment of AD to reduce Aβ production and its associated neurotoxicity (142-147).

Serotonin (5-HT) Receptors

In the CNS, serotonin (5-hydroxytryptamine, 5-HT) is a biogenic amine neurotransmitter synthesized in neurons of the raphe nucleus in the brainstem and present in high concentrations in the hypothalamus and basal ganglia. The serotonergic system innervates almost all areas of the brain and spinal cord. 5-HT is involved in a wide variety of behaviors, including affective state, sleep-wakefulness, feeding behavior, sexual behavior, temperature regulation, circadian rhythmicity, locomotion, neuroendocrine secretion, pain, hallucinogenesis and memory. 5-HT is also present in peripheral tissues and is evident in carcinoid tumors. It is a potent vasoconstrictor released from platelets to inhibit gastric secretion and stimulate smooth muscle. 5-HT acts via several receptors belonging to the class of phosphoinositide-specific phospholipase C (PLC)-linked receptors. The $5\text{-}HT_{1A}$, $5\text{-}HT_4$ and $5\text{-}HT_6$ receptor subtypes have all been implicated in the pathogenesis of AD and agents targeting them may be effective in the treatment of the disease (40, 148-150).

Transforming growth factor

Transforming growth factor-β (TGF-β) is a member of a large family of pleiotropic homodimer cytokines which includes the TGF-β1, TGF-β2 and TGF-β3 isoforms. They are secreted by many different cell types, including B- and T-cells, macrophages, platelets, neurons and glial cells, and signaling is mediated via a high-affinity transmembrane receptor complex consisting of TGF-β receptor type I (activin receptor-like kinase 5, or ALK5) and TGF-β receptor type II receptor (TβRII) serine/threonine kinase receptor subunits. In addition to activities such as suppression of immune responses (via downregulation of antigen-presenting cells [APCs] and inhibition of B- and T-cell proliferation), enhancement of extracellular matrix protein production and mediation of cell growth, differentiation and embryonic development, TGF-β isoforms also act synergistically with neurotrophins to exert neuroprotective effects. In AD, TGF-β levels are increased in human brain tissue, although brain TβRII expression and serum TGF-β levels are reduced, and evidence suggests that TGF-β may have both beneficial and detrimental effects in this disease. TGF-β1 overproduction by astrocytes has been associated with a decrease in overall Aβ accumulation in human APP transgenic mice, and stimulation of Aβ phagocytosis in rats. In contrast, TGF-β1 overproduction has also been implicated in the development of cerebral amyloid angiopathy associated with AD. Neuronal TGF-β signaling via Smad transcription factors has been demonstrated to be impaired in AD, and reductions in neuronal TGF-β signaling increased age-dependent neurodegeneration and AD-like disease in a mouse model of AD. Thus, enhancement of TGF-β signaling may effectively decrease neurodegeneration in AD (151-154).

Conclusions

Intensive research efforts in the search for effective AD therapies have not yielded an effective long-term therapeutic strategy for the treatment of AD. However, new targets are emerging every day, some of which are indicated in Table I. These novel targets represent promise for a future effective AD therapy.

Table I: Targets being pursued for Alzheimer's disease (from Prous Science Integrity®).

Target	Product/Patent	Source	Phase
Acetylcholinesterase	Donepezil hydrochloride	Eisai	L-1997
	Huperzine A	Neuro-Hitech	II
AMPA receptor	CX-717	Cortex	II
β-Amyloid	Bapineuzumab	Wyeth Pharmaceuticals/Elan	II
	Tramiprosate	Neurochem	III
	HE-0420	Hunter-Fleming	I
	Posiphen™	TorreyPines Therapeutics	I
	AZD-103/ELND-005	Transition Therapeutics/ Ellipsis Neurotherapeutics/ Elan	I
Androgen receptor	PHT-1	IRM	Biological testing
Butyrylcholinesterase	Tacrine hydrochloride	Pfizer	L-1993
	Rivastigmine tartrate	Novartis	L-1997
	Galantamine hydrobromide	Sanochemia	L-1995
Calcium channels	Idebenone	Takeda	L-1986
	MEM-1003	Memory Pharmaceuticals	II
Cannabinoid CB_1 receptor	AVE-1625	sanofi-aventis	II
Cyclin-dependent kinase 5 (CDK5)	IDRS-35	Inje University	Biological testing
	WO 2006004507	AstraZeneca	Biological testing
Cyclooxygenase	Curcumin	Chinese University of Hong Kong	I/II
Estrogen receptor	Alfatradiol (MX-4509)	Migenix	I
Fibroblast growth factor receptor 1 (FGFR1)	FGL-L	Enkam	I
$GABA_A$ receptor	Radequinil	Dainippon Sumitomo Pharma	II
	EHT-0202	ExonHit Therapeutics	I
GSK-3 (glycogen synthase kinase-3)	AZD-1080	AstraZeneca	I
	NP-031112	NeuroPharma	I
Gonadotropin-releasing hormone (GnRH)	VP-4896 (leuprolide acetate implant)	Durect/Voyager	III
Histamine H_3 receptor	GSK-189254	GlaxoSmithKline	I
HMG-CoA reductase	WO 1995006470	Merck & Co.	Biological testing
	WO 2003039542	Merck & Co.	Biological testing
	WO 2004028456	Merck & Co.	Biological testing
	WO 2003094909	eNOS Pharm	Biological testing
	WO 2005115371	Univ. Rene Descartes	Biological testing
	WO 2005115980	Pfizer	Biological testing
	WO 2005105738	Pfizer	Biological testing
	WO 2005099823	Pfizer	Biological testing
	WO 2005026116	Pfizer	Biological testing
	WO 2000028981	Nymox	Biological testing
	WO 2005123068	TorreyPines Therapeutics	Biological testing
Insulin	Intranasal insulin implant	National Institute on Aging	II
c-Jun *N*-terminal kinase (JNK)	WO 2006083673	Abbott	Biological testing
	WO 2002081475	Eisai	Biological testing/ Preclinical
Monoamine oxidase (MAO)	Rasagiline mesilate	Teva	II
Muscarinic acetylcholine receptor	NGX-267	TorreyPines Therapeutics	I
Neurotrophic factor	AL-108	Allon Therapeutics	II
	T-817MA	Toyama	I
	Paliroden	sanofi-aventis	II
Nicotinic acetylcholine receptor	Ispronicline (AZD-3480)	AstraZeneca/Targacept	II
Nitric oxide (NO)	CR-3394	Rottapharm	Preclinical
NMDA receptor	Neramexane hydrochloride	Merz/Forest	III
	Memantine hydrochloride	Merz/Lundbeck	L-2002

Continuation

Table I (Cont.): Targets being pursued for Alzheimer's disease (from Prous Science Integrity®).

Target	Product/Patent	Source	Phase
Nuclear factor-κB (NF-κB)	Tarenflurbil	Myriad Genetics	III
Peroxisome proliferator-activated receptor (PPAR)	Rosiglitazone maleate	GlaxoSmithKline	III
PDE4	MEM-1414	Memory Pharmaceuticals	I
	AVE-8112	sanofi-aventis	I
	EHT-0202	ExonHit Therapeutics	I
	MK-0952	Merck & Co.	Biological testing
PDE5	JP 2006117647	Kyorin	Biological testing
	WO 2005049616	Pfizer	Biological testing
	WO 2005089766	Altana Pharma (Nycomed)	Biological testing
Pin1	WO 2004087720	Pfizer	Biological testing
	WO 2005063259	Jerini	Biological testing
	WO 2004026815	Jerini	Biological testing
Phospholipase A_2 (PLA_2)	WO 2007008690	Dexel Univ. Coll. Med.	Biological testing
	WO 2004069797	Merckle	Biological testing
	WO 2002000257	Shionogi	Biological testing
Plasminogen activator	PAZ-417	Wyeth Pharmaceuticals	I
RAGE (receptor for advanced glycation end products)	TTP-488/PF-4494700	TransTech Pharma/Pfizer	II
Secretases	Begacestat	Wyeth Pharmaceuticals	I
	NGX-555	TorreyPines Therapeutics	Preclinical
	CTS-21166	CoMentis	I
Serotonin (5-HT) receptors	Xaliproden hydrochloride	sanofi-aventis	III
	Lecozotan hydrochloride	Wyeth Pharmaceuticals	II/III
	PRX-03140	Epix Pharmaceuticals/ GlaxoSmithKline	II
	742457	GlaxoSmithKline	II
	MEM-3454	Memory Pharmaceuticals	I
	SAM-315	Wyeth Pharmaceuticals	I
Transforming growth factor-β (TGF-β)	WO 2005103028	In2Gen/SK Chem./Ewha womans Univ.	Biological testing

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