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Review

Neuroplasticity in Alzheimer's Disease

Bruce Teter[1]* **and J. Wesson Ashford**[2]
[1]Department of Medicine, University of California Los Angeles, California and Veteran's Affairs–Greater Los Angeles Healthcare System, Sepulveda, California
[2]Departments of Psychiatry and Neurology, and the Sanders-Brown Center on Aging, University of Kentucky, Lexington, Kentucky and Veteran's Affairs Medical Center, Lexington, Kentucky

Ramon y Cajal proclaimed in 1928 that "once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers the nerve paths are something fixed, ended and immutable. Everything must die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree." (Ramon y Cajal, 1928). In large part, despite the extensive knowledge gained since then, the latter directive has not yet been achieved by 'modern' science. Although we know now that Ramon y Cajal's observation on CNS plasticity is largely true (for lower brain and primary cortical structures), there are mechanisms for recovery from CNS injury. These mechanisms, however, may contribute to the vulnerability to neurodegenerative disease. They may also be exploited therapeutically to help alleviate the suffering from neurodegenerative conditions. **Published 2002 Wiley-Liss, Inc.**†

Key words: neuroplasticity; Alzheimer's; genetics; apolipoprotein E; therapeutics; pharmacogenetics

Abbreviations: AB, amyloid β protein; ADDLs, AB-derived diffusible ligands; AD, Alzheimer's disease; apoE, apolipoprotein E (gene or protein); APP, amyloid precursor protein; ChAT, choline acetyl transferase; CNS, central nervous system; CREB, cAMP response element binding protein; DRG, dorsal root ganglion; E4, E3, apoE isotypes epsilon 4, epsilon 3; EC, entorhinal cortex; ECL, entorhinal cortex lesion; ERT, estrogen replacement therapy; GFAP, glial fibrillary acidic protein; GT1-1, hypothalamic cell line; HC, hippocampus; HDL, high density lipoprotein; HNE, hydroxy-nonenol; IML, inner molecular layer of the hippocampus; ko, gene knockout mice; LDLR, low density lipoprotein receptor; LRP, LDLR-related protein; LTP, long term potentiation; MAP, microtubule associated protein; NCAM, neural cell adhesion molecule; NF-κB, nuclear factor kappa B; NFT, neurofibrillary tangles; NGF, nerve growth factor; NOS, nitric oxide synthetase; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; NSE, neuron-specific enolase; OML, outer molecular layer; OHSC, organotypic hippocampal slice culture; PNS, peripheral nervous system; PS, presenilin; PSD-95, post-synaptic density protein; TNFα, tumor necrosis factor α; VLDL, very low-density lipoprotein

*Correspondence to: Bruce Teter, Dept. of Medicine, UCLA, VA Medical Center, MC151, 16111 Plummer St., Sepulveda, CA 91343.

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1. INTRODUCTION

Alzheimer's disease (AD) displays aspects of mechanisms related to all the major theories of aging: mitochondrial decline in energy production, deregulation of calcium homeostasis, ROS generation and accumulation of its damage products, immune/inflammation dysfunction, hormone deregulation, and loss of regenerative ability (Brewer, 2000). The information storage defect in AD is represented at all levels of systems functions: biological, psychological and sociological (Ashford et al., 1998a). All these factors and levels can be traced to basic mechanisms of memory storage and retrieval. The contribution of neuroplasticity to AD, as a compensatory response or a fundamental defect, is gaining recognition, from the original recognition of the implications of dystrophic neurites by Alzheimer and others to more recent evidence of plasticity at many levels (Fischer, 1907; Simchowicz, 1911; Scheibel and Tomiyasu, 1978; Scheibel, 1982). That AD is a fundamental defect in such mechanisms was first proposed in 1985 (Ashford and Jarvik, 1985) and has been recently reviewed (Neill, 1995; Mesulam, 2000; Arendt, 2001a,b). This common downstream target can explain how numerous genes and factors cause the same clinical and neuropathological phenotype.

AD is characterized by ongoing neurodegeneration, yet in AD and in normal aging neuronal loss is not a prerequisite for functional deficits (reviewed in Morrison and Hof, 1997; Mrak et al., 1997). Synaptic pathology is an early marker of both AD and aging (Greenough et al., 1978; Agnati et al., 1992; Martin et al., 1994). Is AD an inevitable consequence of aging-related processes, simply a faster deterioration of the capacity for plasticity? Even 'normal aging' can change its course at some point: enhanced dendritic growth in early aging (70s) is followed by regression of dendritic arbor in the oldest old (90s) (Flood et al., 1985). Plasticity in AD may be a process of compensatory, albeit futile sprouting in vulnerable neurons. In this scheme, mechanisms of plasticity and their physiological burden are overstimulated in AD, leading to secondary neurodegenerative effects, which then feed a vicious cycle of increasing plasticity burden (Mesulam, 2000; Joseph et al., 2001). The increasing burden of plasticity is initially an adaptive response that also includes upregulation of τ phosphorylation and APP turnover, with subsequent formation of neurofibrillary tangles (NFT) and amyloid plaques as consequences that eventually lead to neurodegenerative events including loss of synapses, axons, and dendrites, and eventually cell death (Mesulam, 2000). The two pathologic hallmarks of AD, neuritic plaques and NFT, could be both causative in memory deficits and result from more fundamental failures of memory, where positive feedback in vicious cycles could feed initially minor disturbances (Geddes et al., 1985). AD synaptic degeneration can also be viewed as an adaptive 'rescue program' in response to metabolic fuel deprivation, by pruning of the axonal tree to reduce energy-consuming neuronal activity, as suggested by the decrease in synaptic metabolic activity with age and in AD (Heininger, 2000). The vulnerability of neurons to the effects of such plasticity-elicited degeneration reflects their capacity for plasticity. A simplistic analogy is found in cancer, where cells with a predilection to divide are the most vulnerable to failure of mitogenic control. Failure of neuroplasticity ultimately unleashes the onset of clinical AD symptomology by disrupting the balance between degenerative and regenerative processes (reviewed in Mesulam, 2000; Arendt, 2001a).

It is remarkable that all genetic causes and risk factors of AD can impinge on neuroplasticity. Instead of causing AD, these genetic mutations can be viewed as interacting with ongoing, age-related impaired plasticity activity to accelerate the events that lead to its failure. Alternatively, they could initiate stress-related repair mechanisms that fail because of downstream defects in or blocks to plasticity. Are genetic factors in AD progeroid genes? For example, ApoE4 is associated with decreased longevity compared to E2 (Corder et al., 1994). What do genetic mutations tell about the distinction between AD and 'normal' aging? Do genetic mutations decrease the natural activity of the wild-type protein, or are they gain-of-function mutations that create altogether new activities? Only parallel analysis of wild-type and mutant forms address such questions. In addition, most of the genes and factors discussed here are pleiotropic and interact at various levels. Such interactions create many secondary, indirect effects that exponentially expand the complexity of AD etiology, and full coverage of these is beyond the scope of this review (extensively reviewed in Arendt, 2001a). Further, because most factors also show effects in neurodegeneration, the interactive relationship between neurodegeneration and the capacity for neuroplasticity adds yet more to this complexity (see Section 8).

2.1 NEUROPLASTICITY: AN OVERVIEW

Neuroplasticity is both a substrate of learning and memory and a mediator of responses to neuronal attrition and injury (compensatory plasticity). It is a continuous process in reaction to neuronal activity and neuron injury, death, and genesis, which involves modulation of structural and functional processes of axons, dendrites, and synapses. The varied structural elements that embody plasticity include LTP, synaptic efficacy, synaptic remodeling, synaptogenesis, neurite extension including axonal sprouting and dendritic remodeling, and neurogenesis and recruitment. In a broader sense, phenomenological processes that manifest plasticity are: synapses (electrical, biochemical, structural), neurite (axon, dendrite), neuron cell bodies, anterograde (toward distal neurites) and retrograde (from distal neurites) transport, cell interactions (neuron-glia), neural networks, and behavioral, psychological, and sociological activities.

The rules of synaptic strengthening postulated by Hebb (1949), which require a concerted activation of pre- and postsynaptic elements (see Sections 2.2, 8), subserve the phenomenon of LTP as a model of memory formation, and which is also associated with synapse dynamics including formation and removal of synapses and changes

in synapse morphology (Chang and Greenough, 1984; Toni et al., 1999; Martin et al., 2000) (see Section 2.2). Signals of plasticity include intraneuronal (anterograde and retrograde), interneuronal (transsynaptic and extra/parasynaptic) as well as intercellular signaling through glia (Cotman and Nieto-Sampedro, 1984; Neill, 1995). They include many molecules in the following families: extracellular matrix molecules, semaphorins/collapsins, immunoglobulins, myelin-associated inhibitors, tyrosine kinase receptors, netrins, neurotrophic factors, growth factors, inflammatory cytokines, and neurotransmitters; furthermore, many inhibitory molecules also come from the same classes (reviewed in Horner and Gage, 2000). Many mutant and transgenic mice have helped elucidate aspects of plasticity (reviewed in Chen and Tonegawa, 1997).

The adult central nervous system responds to injury with limited yet sometimes effective restoration of synaptic circuitry. Whether compensatory growth is widespread and whether it reverses cognitive deficits has been debated (Cotman et al., 1991; Poirier, 1994; Masliah et al., 1995b). Functional recovery requires that reactive synaptogenesis not exacerbate circuitry dysfunction, as has been proposed (Cotman et al., 1991; Masliah et al., 1991c). If reactive plasticity leads to aberrant misconnection by innervating the wrong target, there may be intrinsic, inhibitory or limiting mechanisms to attenuate such misguided synaptogenesis. Clearly, brain self-organization continuously balances synapse formation and removal as well as neurite sprouting and retraction, and in some conditions, inhibition of sprouting may actually be protective by sequestering dysfunctional neurons. Such inhibition of distal plasticity events could signal plasticity-related events in the perikaryon (Mesulam, 2000). Chronic stimulation, however, may become unsustainable resulting in a plasticity 'burden' that leads to degenerative events.

2.2 Synapses

The balance between dynamic stabilization and destabilization of synapses may provide the basis for failure of plasticity with age and disease. Aspects of LTP are mediated by rapid generation of new spines, presumably guided by actin-mediated shape changes (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999; reviewed in Luscher et al., 2000). The shape of dendrites, as well as cell survival, can be modified by neurotrophins (McAllister et al., 1999; reviewed in Huang and Reichardt, 2001). The cytoskeleton also mediates aspects of signal transduction, as shown by microtubule involvement with effector molecules in the hedgehog, Wnt, JNK, and ERK pathways (reviewed in Gundersen and Cook, 1999). Actin controls the generation and motility of growth cones, spines and dendrites. F-actin assembly at the leading edge of growth cones is regulated by many factors, especially those of the substrate (Suter and Forscher, 1998; Hynes, 1999) and by small receptor-activated GTPases including rac, rho and Cdc42 (Lanier and Gertler, 2000). Dendritic spines are enriched in actin (reviewed in Matus, 1999). Not only are they highly motile structures covered with presynaptic structures, they may coordinate with the postsynaptic complex, moving together, mechanically stabilizing the synapse (Barres and Smith, 2001). Synapse formation during development may be a collaborative process involving growth of a presynaptic element on a site where a postsynaptic spine is either present or ready to form (Horner, 1993) (see Section 9.1). Further, the cadherin/catenin systems play an important role in the recognition between presynaptic growth cones and its postsynaptic dendritic target (Brose, 1999). Subsequent actions of immediate early genes like Narp, Arc, and synaptotagmin recruit and localize synaptic protein components. Arc stimulates both activity and plasticity of synapses and is modulated by the insulin receptor signal cascade. The cellular sorting, directional transport, and specific accumulation of axonal and dendritic components (including certain mRNAs) (Schuman, 1999; Winckler et al., 1999; Wells et al., 2000) are affected by AD-related pathology like NFTs (see Section 6) and APP (see Section 5.2).

Interestingly, mRNAs for GAP-43 and Arc have been found in growth cones, and NR1 and Arc in dendrites, implicating the important need for their activities at these sites and their synapse-specific regulation (Crino and Eberwine, 1996; Gazzaley et al., 1997; reviewed in Huang, 1999; Martin et al., 2000; Campenot and Eng, 2000; Steward and Schuman, 2001). Translation-dependent synapse formation can occur even in the absence of cell bodies (Schacher and Wu, 2002).

Presynaptic markers include GAP-43, SNAP25, syntaxin, synaptotagmin, synaptoporin, synaptophysin, and the synapsins. GAP-43 is highly expressed in neural development, axon regeneration and neuritic sprouting (Neve et al., 1988; Masliah et al., 1991a ; de la Monte et al., 1995; Benowitz and Routtenberg, 1997). Postsynaptic markers include MAP-2, PSD-95, NR1, spinophillin, and dendritic actin (reviewed in McEwen, 2001).

2.3 Adhesion Molecules

Optimal cell adhesion is required for synaptic plasticity (Schubert, 1991). Presynaptic differentiation is triggered by molecules associated with the synaptic basal lamina (reviewed in McGowan and Marinkovich, 2000). Adhesion molecules also communicate directly with signaling cascades regulating cell proliferation and differentiation, like FAK and MAP cascade, which are also implicated in AD (Shirazi and Wood, 1993; Zhang et al., 1994; Gartner et al., 1999). L1 and PSA-NCAM are associated with regenerating hippocampal axons (Aubert et al., 1998; Seki and Rutishauser, 1998; Ronn et al., 1999; Weidner et al., 1999). NCAM-I, a marker of plasticity (Ronn et al., 1998), is increased in hippocampal regions, but in a disorganized way in more AD-affected hippocampal areas (Mikkonen et al., 1999). Proteolytic disassembly of the extracellular matrix is regulated by MMP-9 during dendritic remodeling in the adult hippocampus (Szklarczyk et al., 2002). Laminin stimulates neurite outgrowth (Baron-Van Evercooren et al., 1982), is reorganized with estradiol-induced neurite outgrowth (Rozovsky et al., 2002), is found around plaques in AD brain (McKee et al., 1991; Murtomaki et al., 1992), and its mRNA and protein

are elevated in AD brain. Laminin interacts with many factors and systems reviewed here (see Sections 3.3, 3.4, 5.3, 5.4, 6, 8, 9.3).

2.4 Glia: Astrocytes and Microglia

Astrocytes and microglia play critical roles in CNS response to and recovery from injury (Gage et al., 1988; Frederickson, 1992; Norenberg, 1994; Chao et al., 1996; Bechmann and Nitsch, 1997; Rabchevsky, 2002). Astrocytes have been shown to play important roles in nutrient supply, waste removal, and axonal guidance. More recent work reveals that astrocytes play a more active role in neuronal activity, including regulating ion flux currents, energy production, neurotransmitter release, and synaptogenesis. The latter includes the activity of glia cell apposition to synapses and the regulation of synapse elimination by ensheathment (known as glial swelling) (reviewed in Laming et al., 2000). Ultrastructurally, this is seen as close apposition of GFAP-positive processes (astrocyte end-feet) that undergo rearrangement associated with changes in GFAP expression and localization. This has been observed not only in the hypothalamus during estrus cycle-dependent synaptogenesis, but also in hippocampus and visual cortex, and may mediate the astrocyte control of synapse number in the developing cerebellum (Lino et al., 2001). Age-related increases in GFAP as an astrocyte activation marker, involved in astrocytic morphologic changes in responses to injury and stress (Nichols et al., 1993; David et al., 1997), may adversely affect their support of synaptogenesis (Vernadakis, 1996); indeed, repression of GFAP is associated with estradiol-induced neurite outgrowth (Rozovsky et al., 2002). Astrocytes can couple directly to neurons and directly regulate synaptic activity (Alvarez-Maubecin et al., 2000). Neurons signal to astrocyte through neuronally-derived glial growth factors (GGF) (Verdi et al., 1996). Glia (astrocytes, microglia and oligodendrocytes) secrete growth-promoting factors like neurotrophins (NT-3) and cytokines, and show age-dependent changes in this activity (Sievers et al., 1995; reviewed in Goldberg and Barres, 2000). Other possible mediators and modulators include S100b (Whitaker-Azmitia et al., 1997), taurine, PS-NCAM, tenascin, NT-3, and cytokines. Glia mediate many effects of estrogen on plasticity (Garcia-Segura et al., 2001) (see Section 9), and are major producers of apoE lipoprotein particles (see Section 2.4, 4).

Glia also play roles in failure of plasticity (reviewed in Lemke, 2001). When activated, microglia and astrocytes secrete potent inhibitors of neurite outgrowth (Snow et al., 1990; McKeon et al., 1991; Canning et al., 1996). White matter actively inhibits axon outgrowth through secretion of inhibitory proteins like myelin protein IN-1, proteoglycans, semaphorins and slit proteins; however, responsiveness of neurons to this kind of inhibition can depend on their ability to survive (Davies et al., 1997) (see Section 8). These may contribute to or mimic the astrocyte-induced physiological 'stop' signal to growth cone progression (Reier et al., 1983; Liuzzi and Lasek, 1987).

2.5 Age

Age diminishes many aspects of plasticity including LTP induction and maintenance, compensatory synaptogenesis after injury, and reactive synaptogenesis in response to complex experience (Scheff et al., 1980; Mori, 1993; Lanahan et al., 1997). The interplay of many factors contributes to decreased synaptoplastic potential in the aging brain, with resulting delay of axonal sprouting and less effective formation of new connections to replace those lost (McWilliams and Lynch, 1984; Anderson et al., 1986). The capacity of neurons to elaborate neurites is reduced with age but is not lost completely (Brewer, 2000; Brewer et al., 2001). The failure of granule cell axon sprouting is inherent in the age of the sprouting neuron, not the age of its targets (Li et al., 1995). Ca^{2+} homeostasis is disrupted with aging and can contribute to disrupted neuronal plasticity (Mattson et al., 1992; Teyler et al., 1994; Ghosh and Greenberg, 1995; Foster and Norris, 1997; O'Neill et al., 2001).

Is this age-related loss in plasticity capacity due to reduced intrinsic neuronal capacity, reduced stimulation, or increased inhibition, which can be the same as reduced stimulation in terms of neuronal permissiveness or responsiveness (Tuttle and O'Leary, 1998)? It seems all three are involved, and future experimental directions will focus on determining whether boosting the extrinsic signaling can ameliorate the reduction in intrinsic growth ability (Aubert et al., 1995; Neumann and Woolf, 1999; Cai et al., 1999; reviewed in Goldberg and Barres, 2000). The decreased capacity for plasticity with age might represent a continuous process of which AD is an inevitable endpoint, although there are many differences between normal aging and AD that support AD as a partly age-independent disease (see Section 1).

3. ALZHEIMER'S DISEASE

3.1 Temporal and Spatial Course

AD pathology progresses over a typical spatial and temporal course of events, with the sequential involvement of basal forebrain, entorhinal cortex, hippocampus, amygdala, and association cortices (Braak and Braak, 1991, 1997). This sequence of events can be understood from a perspective of the functional network through which these areas associate. AD-vulnerable regions like hippocampus and amygdala are related by ancient projections of the olfactory bulb. The entorhinal cortex sits at the evolutionary crossroads between the highly plastic olfactory system, with its distributed representation of information, and the archi-cortex (hippocampus), paleocortex (amygdala), and neocortex (see Section 3.6). These evolutionary relationships may underlie the neural network of initiating and propagating processes in AD (Ashford et al., 1998a).

AD pathology affects CNS regions involved in higher brain functions that are synaptically (structurally and functionally) plastic, and involved in acquisition of new epigenetic information. The limbic system has perhaps the highest potential for neuroplasticity compared to

other parts of the cerebral cortex (indicated by high level expression of GAP-43, particularly in the entorhinal-hippocampal pathway (see Section 3.6)) (Neve et al., 1988; Lin et al., 1992). Plasticity-related dendritic remodeling (length and branching) is most extensive in limbic and paralimbic regions (entorhinal-hippocampal), less in association cortices, and undetectable in primary sensory and motor areas (Arendt et al., 1998a). The lifelong increased neuroplasticity burden and chronic upregulation of plasticity-related cellular activities of the limbic system could increase its vulnerability to NFT formation. Degeneration in limbic structures could then spread to adjacent limbic and paralimbic neurons in reciprocally connected association cortices to increase their plasticity burden. This would induce reactive synaptogenesis to replace the synapses provided originally by the degenerating axons of NFT-bearing neurons and induce dendritic remodeling to receive synapses once associated with the dendritic trees of adjacent degenerating neurons. If these reactive neurons cannot respond to the challenge of this increased plasticity burden due to barriers to plasticity, they too might then be subjected to similar τ events and subsequent NFT formation with cytoskeletal disruption.

In AD there is extensive loss of cholinergic input into the hippocampus (reviewed in Francis et al., 1999). Cholinergic neurotransmission plays an essential role in reactive and experience-induced synaptic reorganization (Baskerville et al., 1997; Kilgard and Merzenich, 1998; Zhu and Waite, 1998), and induces production of neurotrophic secreted APP (Nitsch et al., 1992) (see Sections 5.3, 10.3). Cortical cholinergic depletion in AD (Geula and Mesulam, 1999) arises from loss of neurons that project from nucleus basalis of Meynert, a limbic structure that retains high plasticity in late adulthood (Arendt et al., 1995) and contains some of the first neurons to show NFT pathology (Mesulam, 1996).

3.2 Development, Differentiation Recapitulation

Mechanisms of plasticity in adults overlap those used in brain maturation in early development (Cotman et al., 1990; Eriksson et al., 1998; Wheal et al., 1998). Regions with the highest degree of structural plasticity are those that take the longest to mature during childhood (Braak and Braak, 1996) and are the same regions most vulnerable in AD (reviewed in Arendt, 2001b). Although many regions undergo critical periods of intense plasticity, many become relatively quiescent at maturity and the regions that retain high levels of plasticity correlate with AD vulnerability (Ashford et al., 1995, 2000; Alexander et al., 2002). This may allow for the evolutionary acquisition of higher brain functions; regions vulnerable in AD share a common evolutionary foundation in the massive enlargement of the association cortices and functionally linked regions (Rapoport, 1990; Neill, 1995) (see Section 3.1).

The differential susceptibility of AD-specific regions and neurons may be related to the degree of retained capacity for plastic remodeling (Arendt et al., 1998a). In vivo, synaptogenesis rates decline with developmental age (Gall et al., 1979) and there is recapitulation of developmental gene expression responses in adult lesion and aging, including AD (Kondo et al., 1996; Styren et al., 1999). The *Nun Study* indicates that the risk of AD can be determined as early as 20years of age, implicating genetic and developmental factors (Ashford and Mortimer, 2002). If such mechanisms controlling developmental plasticity are defective and are later reactivated (in aging, or AD, or pre-AD), they would contribute to ineffective plasticity responses and exacerbate the plasticity burden of aging and AD.

It has been hypothesized that a 'labile state of differentiation' of neurons allows for neuroplasticity after development but also renders these neurons vulnerable to degenerative effects (Arendt, 2000, 2001a,b). In AD, the differentiation control may be in some way disrupted, involving expression or re-expression of genes (dedifferentiation) that contribute to making new neuronal connections in regenerative plasticity, i.e., genes involved in both growth cones and synaptic connections (Pfenninger et al., 1991) (see Sections 3.1, 3.3), as a necessary component of the ability to maintain a high degree of plasticity throughout life. This retention of plasticity potential leads to or may require re-expression of developmentally regulated genes, alteration of posttranslational modifications and imbalance of gene products, and re-activation of cell cycle genes such as cyclin B and E, as observed in neurons in healthy, elderly individuals (Nagy et al., 1997; Smith et al., 1999) and in phospho-τ-expressing neurons (Nagy et al., 1997). This confounds irreversible block of entry into the cell cycle of the neuron, a situation that may trigger cell death (Heintz, 1993) (see Sections 8.2, 8.3). For example, developmentally regulated genes like MAP1B-P, involved in axon growth (Gordon-Weeks and Fischer, 2000; Mack et al., 2000), are downregulated postnatally but remains active in regions of plasticity (Nothias et al., 1996). Its distribution parallels PSA-NCAM, involved in neurite growth and synaptogenesis (Seki and Arai, 1993; Muller et al., 1996; Cremer et al., 1997). The capacities for plasticity may depend on specific kinases, high levels of neurofilaments, and τ isoforms (Myoken et al., 1990; Hof and Morrison, 1994; Bahr and Vicente, 1998; Delacourte et al., 1998; Esclaire et al., 1998; Morrison et al., 1998), some of which also mark neurons destined for degeneration in AD (see Section 8).

3.3 Synaptic Loss

Synaptic loss is an early event in AD and is a structural correlate of cognitive dysfunction (Gonatas et al., 1967; Gibson, 1983; Davies et al., 1987; Bertoni-Freddari et al., 1989; Hamos et al., 1989; Scheff et al., 1990; Weiler et al., 1990; Brunelli et al., 1991; Terry et al., 1991; Honer et al., 1992; Lassmann et al., 1992, 1993; Zhan et al., 1993; Martin et al., 1994; Masliah et al., 1994, 1995a; Dickson et al., 1995; Heinonen et al., 1995; DeKosky et al., 1996; Sze et al., 1997; Cotman and Anderson, 2000; Mattson et al., 2001; reviewed in Arendt, 2001a). Memory loss in AD may result from synaptic dysfunction that precedes large-scale neurodegeneration, where the synapse-to-neuron ratio is decreased by about 50% (Cullen et al., 1997; Lambert

et al., 1998; Chapman et al., 1999; Hsia et al., 1999; Chen G et al., 2000; Tezuka et al., 2001; reviewed in Arendt, 2001a). Synapse and dendrite loss in AD exceeds that seen with normal aging (reviewed in Terry et al., 1994; Anderton et al., 1998). Synaptic degeneration, like early AD, progresses slowly at first, perhaps reflecting attempts for compensatory plasticity, and as such could be initially reversible, but eventually becomes irreversible due to marked synapse loss (Rapoport, 1999).

In early AD, a number of growth-associated proteins are upregulated, which may reflect attempts to stimulate plasticity, including GAP-43, MARCKS, spectrin, heparansulfate, laminin (see Sections 2.3, 6), NCAM, various cytokines and neurotrophic factors including NGF (see Section 10.4), bFGF, EGF, IL-1, Il-2, IL-6, IGF-1, IGF-2, PDGF, HGF/SF, and several growth factor receptors (reviewed in Arendt, 2001b: see Section 3.2). Deregulation of proteins involved in structural plasticity of axons and dendrites (Jorgensen et al., 1990; Hatanpaa et al., 1999; Lubec et al., 1999; Mikkonen et al., 1999) and computational studies (Horn et al., 1996; Hasselmo, 1997) indicate a failure of plasticity mechanisms, and support a disruption of synapse turnover as a primary mechanism in AD (Arendt, 2001b) (see Section 3.2). For example, synapsin IIa mRNA is downregulated in early AD, as detected by gene chip microarray analysis (Ho et al., 2001; Pasinetti, 2001). Synaptic remodeling in AD brain is detected also by elevation in the NCAM/SNAP-25 ratio (Jorgensen et al., 1990, 1997; Jorgensen, 1993, 1995). Although these structural and biochemical changes in AD provide understanding of aspects of plasticity, their relation to the properties of LTP in relation to AD are poorly understood (Dawson et al., 1992; Farooqui and Horrocks, 1994; Nalbantoglu et al., 1997).

3.4 Axonal and Dendritic Remodeling

Extracts of AD brain increase axonal branching of neurons grown on laminin (Kittur et al., 1992; Jorgensen, 1993), and AD brain and CSF extracts sustain neuron growth and survival (Uchida et al., 1988; Uchida and Tomonaga, 1989; Pauwels et al., 1993; Erickson et al., 1994). Axonal and dendritic remodeling in AD show restricted regional and temporal localization (Arendt et al., 1995, 1997, 1998a). Neocortex and hippocampus exhibit increased sprouting and synaptogenesis in AD (Grady et al., 1989; Masliah et al., 1991a,c; Jobst et al., 1994). Sprouting of commissural and associational fiber axons in AD is indicated by expansion of kainic acid receptor distribution that matches that seen in entorhinal cortex lesions (see Section 3.6); hippocampal sprouting of septal afferents is indicated by the pattern of AchE innervation in the perforant path terminal zone (Geddes et al., 1985; Gertz et al., 1987; Hyman et al., 1987; Masliah et al., 1991c) (see Section 3.6). In AD, axon length correlates with dementia severity suggesting regressive axonal events may be more relevant than dendritic attrition or neuron loss (Anderson, 1996). This is consistent with degeneration of presynaptic termini that then leads to secondary transneuronal degeneration of postsynaptic dendrites (Su et al., 1997).

Dendritic extent in the hippocampus can increase with age itself, possibly a compensatory response to loss of synaptic connections (Flood and Coleman, 1990). This may not be sustainable, however, because enhanced dendritic growth in the early aging (70s) is followed by regression of dendritic arbor in the oldest old (90s) (Flood et al., 1985). Neocortex and hippocampus in AD also show massive somatodendritic sprouting (Ihara, 1988; Jorgensen et al., 1997), which may reflect unsuccessful remodeling in response to presynaptic or axonal damage (Scott, 1993). Such somatodendritic sprouts, which have filopodium-like structures resembling growth cones, contain τ and MAP2, which recapitulates their codistribution in neurite sprouting during development (reviewed in Arendt, 2001a). These dendritic changes therefore may be secondary to deafferentation, signal transduction failures, or cytoskeletal abnormalities (Anderton et al., 1998). As in aging, dendritic sprouting in AD may not be sustainable, as dendritic extent can decline (Flood and Coleman, 1990), particularly dendrites of hippocampal granule cells (Einstein et al., 1994). Some neuropil threads (curly fibers) show preferential development at dendritic branch points, suggesting that blocking dendritic transport could lead to dendrite pruning, and the loss of associated synapses (Ashford et al., 1998b).

3.5 Aberrant Sprouting and Dystrophic Neurites as Dendritic Sprouting

Neuronal sprouting in AD can be aberrant based on its localization, morphology, cytoskeletal composition (Arendt et al., 1986, 1998b; Arendt and Zvegintseva, 1987; McKee et al., 1989; Ferrer et al., 1990; Phinney et al., 1999), and synaptic protein expression (Geddes et al., 1985; Ihara, 1988). Aberrant sprouting can be an early feature of AD (Ihara, 1988), preceding detectable tangle formation and extensive neuron loss (Su et al., 1993; Arendt et al., 1998b), and therefore might represent a fundamental defect in AD rather than an overt response to ongoing degeneration (Geddes et al., 1991; Cotman et al., 1993; Masliah et al., 1993a,b). Abnormal neurite growth might be associated with the elevation of NGF receptors (Ernfors et al., 1990; Mufson and Kordower, 1992) that precedes neurofibrillary degeneration (Arendt, 1993). APP transgenic mice also show behavioral and synaptic changes before plaque formation (Holcomb et al., 1998; Hsia et al., 1999; Moechars et al., 1999; Chen G et al., 2000) (see Section 5). Transgenic mice expressing APP show increased hippocampal synaptophysin that correlates with impaired learning and memory (King and Arendash, 2002).

Dystrophic neurites (mainly dendritic) within or near plaques (Gonatas et al., 1967; Probst et al., 1983; Benzing et al., 1993; Su et al., 1993), as a consistent component of AD pathology, were originally regarded as aberrant sprouts by Alzheimer and others (Fischer, 1907; Simchowicz, 1911; Scheibel and Tomiyasu, 1978). This is supported by Golgi (Scheibel and Tomiyasu, 1978; Ferrer et al., 1983, 1990; Arendt et al., 1986; Ihara, 1988),

ultrastructure (Paula-Barbosa et al., 1980), and association of GAP-43, MARCKS, spectrin, and synaptic, axonal, and cytoskeletal proteins (Geddes et al., 1985, 1986, 1990; Masliah et al., 1989, 1990, 1991a,Masliah et al.,b,d, 1992, 1993a; Cotman et al., 1990; Kosik, 1991; Saitoh et al., 1993; Phinney et al., 1999) (see Section 5.4). Abnormally dilated synaptic terminals, indicative of a compensatory response, are found in both aged and demented brains (Braak and Braak, 1988; DeKosky and Scheff, 1990; Ferrer et al., 1990) (see Section 5.4).

Mega neurites, which represent a specific subpopulation of dystrophic neurites (>10 μM diameter), are often associated with plaques, contain synaptophysin, hyperphosphorylated PHF-τ, GAP-43, and are modified by sialic acid addition and glycosylation. These characteristics suggest that they are abnormal neuritic sprouts of atrophic dendritic structures (Espinosa et al., 2001). Such modifications may represent early events in neurofibrillary degeneration mediated by microtubule depolymerization at the growth cone and adhesion interactions (Araujo et al., 1997).

3.6 Entorhinal Cortex, Hippocampal Pathway, and Lesion Models

In AD, the entorhinal cortex (EC) shows extensive loss of neurons (Hyman et al., 1984; Geddes et al., 1985) and neuronal cytoskeletal disruption (McKee et al., 1991) whereas the hippocampal region that receives EC innervation (the molecular layer) shows plaque-independent granule cell dendritic pathology (Einstein et al., 1994) and loss of synaptophysin immunoreactivity (Heinonen et al., 1995). In response to these degenerative effects, some patients show regenerative changes in the dentate gyrus (Geddes et al., 1985; Arendt et al., 1998a) and apoE4 patients are impaired in this compared to apoE3 (Arendt et al., 1997; reviewed in Arendt, 2001b). Aged human brain shows increased granule cell axon sprouting, suggesting that the molecular layer might be partially deafferented with age (Cassell and Brown, 1984). The dendritic spine density of granule cells is reduced in AD only in distal segments, possibly indicating sprouting of undamaged proximal segments.

In mice and rats, the entorhinal cortex lesion (ECL) is a well-established model of synaptic plasticity (Poirier et al., 1991a,b; Masliah et al., 1995d, 1996; Danik and Poirier, 1998) and behavioral correlates (Miwa and Ueki, 1996; Good and Honey, 1997; Hardman et al., 1997). ECL-induced deafferentation of the EC input models aspects of AD, albeit in an acute model, and has been used to show age-dependent reduction in sprouting in response to ECL (Scheff et al., 1980). The major neuron type that undergoes sprouting is the granule cell of the dentate gyrus, whose dendritic field is the target of EC innervation. Granule cell axons, so-called mossy fibers, sprout and are detected by Timm's stain (for vesicular zinc) (Danscher, 1981; Gaarskjaer, 1986), or other markers of neurite sprouting GAP-43, synaptophysin; these latter markers also detect sprouting of commissural/associational fibers (Cotman et al., 1991). The ECL paradigm recapitulates developmental gene expression responses seen in adult lesion models, aging, and AD (Kondo et al., 1996; Styren et al., 1999) (see Section 3.2). Such similarities to developmental events include expression of synapsin I, eNCAM, and fetal ALZ-50 reactive clone 1 (FAC1) (reviewed in Bulinski et al., 1998; Styren et al., 1999) and partial similarity to changes in dendritic structure, microtubule (MAP2) metabolism, intermediate filament expression (nestin, vimentin), trkB expression, and glutamate and GABA receptor expression.

Organotypic hippocampal slice culture (OHSC) is a semi-simplified yet physiologically and neuro-organo-relevant in vitro system of postnatal hippocampal tissue, widely regarded as a bridge between in vivo and in vitro models, powerful in elucidating mechanisms of complex and necessarily emergent CNS phenomena (Zimmer et al., 1999). OHSCs are typically derived from early postnatal rodents although adult OHSC methods are now available (Temple and Malouf, 2000; Xiang et al., 2000). OHSCs continue to develop and retain organotypic features of the intact hippocampus (Bruce et al., 1995), including development of the mossy fiber pathway that arises from dentate granule cells and projects to the CA3 pyramidal cells (Zimmer and Gahwiler, 1987; Sutula et al., 1989), as well as other synaptic development phenomenon that parallel those observed in vivo (Buchs et al., 1993; Muller et al., 1993; Stoppini et al., 1993).

OHSC is an in vitro model of deafferentation-induced hippocampal neuron sprouting that replicates aspects of ECL. In addition to C/A connections (Frotscher, 1992), the preparation of OHSC transects the perforant path and thereby removes the major extrinsic innervation by the entorhinal cortex (EC) to the granule cell dendritic field in the OML, as well as the commissural projection to the IML. Like ECL in vivo, this deafferentation stimulates sprouting of granule cell mossy axon collaterals into the dentate molecular layer, where they are not normally found in abundance (Gaarskjaer, 1986; Sekiguchi et al., 1996). There they make aberrant synapses (Rudling and Angelin, 1993) with dendrites of the deafferented granule cells that are electrophysiologically functional (Wong and Moss, 1992). Granule cell axon sprouting is altered by intrinsic neural excitability in the absence of cell death (Stringer et al., 1997) (see Sections 3.1, 3.4, 4.2, 8.1).

3.7 Cholesterol in the CNS and AD

Metabolism of cholesterol in the brain and cross-talk with peripheral lipid metabolism (reviewed in Dietschy and Turley, 2001; Rapoport, 2001) is an emerging consideration for AD etiology and possible therapeutic targets (Roses and Saunders, 1997; Vance et al., 2000). Levels of cholesterol in the brain are critical for synapse formation and maintenance and recent studies identify cholesterol as a limiting factor in synaptogenesis (reviewed in Koudinov and Koudinova, 2001). Reduced cholesterol may place a limit on plastic processes thus reducing the tendency to develop AD. An issue for very long axons is the ability to supply sufficient cholesterol for rapid axonal growth, especially in regeneration. What proportion of axonal mem-

brane phospholipid is synthesized in situ in axons compared to that made in cell bodies and transported to axons? (reviewed in Vance et al., 2000).

AD brain contains less cholesterol, perhaps because of enhanced efflux of derivatized cholesterol from the brain (Koudinov and Koudinova, 2001). This contributes to AD-related alterations in membrane composition (Bertoni-Freddari, 1988; Majocha et al., 1989; Svennerholm and Gottfries, 1994; Gottfries et al., 1996), membrane fluidity (Scott et al., 1994; Fernandes et al., 1999; Zubenko et al., 1999), and lipid bilayer structure and dynamics (Mason et al., 1992; Mulder et al., 1998) (see Section 4.4). Cholesterol also influences the phosphorylation status of τ (Distl and Meske, 2000; Fan et al., 2001; Koudinov and Koudinova, 2001; Ohm et al., 2001), MAP2 phosphorylation in the context of dendrite outgrowth (Fan et al., 2002), and amyloid metabolism (including AB production) and its related membrane fluidity effects (Hartmann, 2001; Buxbaum et al., 2002; Ji et al., 2002; Runz et al., 2002; Wahrle et al., 2002) (see Section 5).

Statins, as inhibitors of cholesterol synthesis, may reduce the prevalence of AD (Jick et al., 2000; Wolozin et al., 2000; Buxbaum et al., 2002; Rockwood et al., 2002; Yaffe et al., 2002), possibly by reducing cholesterol turnover in the brain (Locatelli et al., 2002). Axonal growth ceases when cholesterol synthesis is inhibited by pravastatin and could be reactivated by addition of cholesterol to either cell bodies or distal axons (Posse de Chaves et al., 1997). LTP is inhibited by cholesterol biosynthesis inhibitors (Matthies et al., 1997) and LTP induction is associated with pathway-specific increases in lipid production (Koudinov and Koudinova, 2001). An important contribution of glia is their production of apoE-bound lipoprotein particles to deliver rate-limiting cholesterol to neurons, stimulating both synaptogenesis and stable maintenance of synapses, as measured by synapsin and synaptophysin (Kosik, 1992; Pfrieger and Barres, 1997; Barres and Smith, 2001; Mauch et al., 2001; Ullian et al., 2001) (see Section 4.4). Possible mechanisms include cholesterol as a limiting factor in the structural demands of synaptogenesis including membrane formation, synaptic vesicle formation, and clustering of postsynaptic receptors (Gimpl et al., 1997; Martens et al., 2000; Thiele et al., 2000; Bruses et al., 2001; Lang et al., 2001), activation of synaptogenesis by cholesterol signaling through the apoE receptor LRP (see Section 4.1), or other pathways such as hedgehog, Wnt, and reelin (Herz, 2001a; Rice et al., 2001). Future goals should include determining whether these cellular effects can be generalized to synaptogenesis during learning and memory, whether astrocyte-derived cholesterol is a limiting factor in vivo (see Section 2.4), and evaluating the differential effects apoE isotypes in these phenomena.

4.1 APOLIPOPROTEIN E

Apolipoprotein E (apoE) is a component of several classes of lipoproteins regulating lipid metabolism and redistribution (Mahley and Huang, 1999; LaDu et al., 2000; Mahley and Rall, 2000). ApoE isotype E4 is a risk factor for familial and late-onset AD, showing increased risk particularly in the 60–80 year age group (Breitner et al., 1999), and earlier age of onset (Roses et al., 1995; Blacker et al., 1997; Meyer, 1998) ApoE4 influences the risk of AD through pleiotropic effects on both the pathology of AD and the environmental and developmental factors influencing its etiologies (reviewed in Teter, 2000; Teter et al., 2002). This pleiotropy obscures the mechanism for apoE4, and may involve a balance or interaction between neurodegenerative (Poirier, 1994; Buttini et al., 1999; reviewed in Teter et al., 2002) and neuroregenerative effects (see Section 8). The major epidemiological effect of E4 in AD is to promote an earlier age of onset than E3, typically by ~5 years but as much as 15 years (reviewed in Hyman et al., 1996; Blacker et al., 1997; Meyer, 1998; Mesulam, 1999; Arendt, 2001b; Ashford and Mortimer, 2002). Because AD is characterized by ongoing neurodegeneration, accelerated clinical onset could be caused by defects in apoE-related compensatory mechanisms that repair circuitry (reviewed in Mesulam, 1999; Teter, 2000; Arendt, 2001a) This is only one of several mechanisms that could delay the onset of AD.

A great deal of evidence implicates a role for apoE in AD-associated plasticity (Poirier, 1994; Masliah et al., 1995d, 1996), possibly through its isoform-specific functions in cholesterol and phospholipid metabolism and membrane lipid recycling and trafficking, which facilitate neuronal sprouting (Mahley, 1988). ApoE plays a role in both PNS and CNS synaptic remodeling (Poirier et al., 1993a; Poirier, 1994; Laskowitz et al., 1998) although apoE deficiency does not compromise PNS regeneration, perhaps by compensatory overproduction of another apolipoprotein (Popko et al., 1993), it seems to be essential in the CNS (Poirier et al., 1993a; Masliah et al., 1995b). Evolutionary perspectives of apoE allele frequencies are consistent with roles in diet and lipid metabolism (Corbo and Scacchi, 1999).

Differential intracellular trafficking may underlie apoE isotype effects on plasticity. ApoE isotypes localize differentially and accumulate in neurons and astrocytes (Xu et al., 1998). ApoE isotypes may be sorted into late endosomes, escaping lysosomal hydrolysis, where they can then differentially mediate intracellular process like stimulating neurite outgrowth (Mahley and Rall, 2000). E4 may not be able to escape the endocytic pathway to interact with τ or contribute other functions (Hardy et al., 1998; Tesseur et al., 2000).

Many of the activities of apoE are dependent on receptor-mediated events, involving any of a number of low-and high-affinity receptors, including the LDL receptor family of lipoprotein receptors (reviewed in Herz, 2001a), like LRP and HSPG. Several of the neurite outgrowth-promoting properties of apoE isotypes have been shown to be dependent on LRP, both in vitro (Table I) and in vivo (Veinbergs et al., 2001). LRP decreases with age (Kang et al., 2000; Herz, 2001a) and is implicated in AD (Rebeck et al., 1993), with LRP and VLDL polymor-

TABLE I. ApoE4 is Defective in Supporting Neurite Sprouting In Vitro

apoE source	Neurite source	apoE4 effect (apoE3 stimulates)	Depends on	References
Pure	DRG and 1° cortical neuron	Inhibit	Lipoprotein, apoE levels	Handelmann et al., 1992; Nathan et al., 1994; Nathan et al., 2002
Pure	N2A	Inhibit	β-VLDL, LDLR/LRP	Nathan et al., 1994; Nathan et al., 1995
Transfected N2A low expressing	N2A	Inhibit	β-VLDL, HSPG/LRP	Bellosta et al., 1995
Transfected N2A high expressing	N2A	Neutral		De Mattos et al., 1998
Pure	GT1-1 (a HT line)	Neutral	β-VLDL, LRP	Holtzman et al., 1995b
Human plasma HDL, CSF lipoproteins	GT1-1 (a HT line)	Neutral	LRP	Fagan et al., 1996
GFAP transgenic astrocyte	1° HC neuron	Neutral	LRP	Sun et al., 1998
Pure (no lipid) + laminin	1° HC neuron	Stimulates (=E3)		Huang et al., 1995
Transfected HEK cells	1° HC neuron	Stimulates (=E3)		Puttfarcken et al., 1997
Human APOE transgenic OHSC	Granule neurons	Stimulates (=58% E3)		Teter et al., 1999b
		"Inhibits" by dose	apoE levels	Teter et al., 2002

phisms increasing AD risk (Kang et al., 1997; Helbecque et al., 1998). LRP is implicated in LTP in OHSC (Zhou et al., 2000). LRP signaling roles may modulate synaptic plasticity because it interacts with NMDA receptors via the multivalent scaffold protein PSD-95 in postsynaptic membranes, among many possible mechanisms (Gotthardt et al., 2000; reviewed in Herz, 2001a,b; Herz and Strickland, 2001). LRP may mediate the effect of E4 but not E3 stimulating the ERK cascade and CREB (Ohkubo et al., 2001). ApoE isotypes show other signaling-dependent effects (reviewed in Ohm et al., 2001).

ApoE expression is increased in early postnatal development (Muller et al., 1997), which correlates with the onset of synaptic development. ApoE is upregulated by estrogen and in association with estrogen-stimulated, apoE-dependent plasticity (Tam et al., 1986; Stone et al., 1997; Srivastava et al., 1997), and in glia (primarily astrocytes) in regions that undergo estrus cycle-dependent synaptic remodeling (Stone et al., 1997) (see Section 4.11). ApoE mRNA is upregulated in AD (Poirier, 1994) and in the entorhinal cortex lesion model (Poirier et al., 1991a; McRae et al., 1997). Besides effects of apoE levels on plaque development (Bales et al., 1997), levels of expression of the apoE protein have a profound effect on the isotype-specific activity in supporting compensatory sprouting in vitro and in lesion responses and behavior effects in vivo (see Section 4.10). The dose-responsiveness of isotype-specific activities also bears on the therapeutic implications of altering apoE expression levels (see Section 4.12).

4.2 ApoE-Dependent Sprouting (reviewed in Teter, 2000; Teter et al., 2002)

4.3 Alzheimer's Disease. There is epidemiologic evidence for failure of plasticity in E4 patients with Alzheimer's disease. For example, in later stages of AD, E4 brains show reduced dendritic remodeling of pyramidal and subcortical neurons in addition to more severe degeneration. ApoE E4 copy number also affects the relationship between (and possible coupling between) neuronal loss and dendritic growth (see Section 8), with E4/E4 showing no relationship, and shows a shift toward proximal branching (Arendt et al., 1997; 1998a; reviewed in Arendt, 2001b). Interestingly, basal dendrites do not consolidate LTP unlike apical dendrites (Arai et al., 1994a) (see Sections 3.4, 3.6, 4.9 for proximal branching effects).

4.4 Sprouting mechanisms and the lipid metabolism model. The role of apoE in stimulating neuronal regeneration has received much support. E4 consistently shows defects (reviewed in Poirier, 1994, 1995; Danik and Poirier, 1998; Holtzman and Fagan, 1998; Laskowitz et al., 1998; Kerr and Kraus, 1998); unfortunately, no studies have examined the relative capacity of E2 to support neurite sprouting. A well-established mechanism involves the role of apoE in lipid metabolism. Among the many activities that apoE has demonstrated that could account for its CNS effects (see Sections 4.1, 4.4), its definitive role in cholesterol and phospholipid scavenging, metabolism, and transport has defined its role in CNS and PNS plasticity after injury (Masliah et al., 1995d, 1996). The central model of this latter role has been described (Boyles et al., 1989; Poirier et al., 1993a, 1994; Laskowitz et al., 1998) where glia phagocytosing degenerating terminals esterify cholesterol from scavenged membrane lipid, repackage it with apoE as a lipoprotein particle and deliver it to neurons to supply cholesterol for neurite growth via their apoE receptors, LDLR or LRP. Aspects of this mechanism were demonstrated originally in the PNS (Boyles et al., 1989; Saada et al., 1995). Recently, apoE and the cholesterol it carries was identified as the glial factor that stimulates new synapse formation in cultured neurons (Mauch et al., 2001; Ullian et al., 2001).

Besides lipid metabolism, isotype-specific effects could be mediated by specific association with lipoprotein particles, inter- and intracellular apoE trafficking, and oxidative effects of apoE. The defective ability of E4 to support neurite sprouting could involve the isotype- and cell type-specific differential localization and accumulation of apoE (see Section 4.1). Stimulation of neurite outgrowth by E3 in vitro is associated with greater neuronal apoE accumulation (Nathan et al., 1994) and E3 extends along neurites more than E4 (Nathan et al., 1995). Studies have shown that apoE isotypes experimentally directed to cytoplasmic compartmentalization exhibited the E4 defect in sprouting of N2A cells; that the carboxy terminus determined intracellular distribution whereas the amino terminus mediated neurite sprouting suggests that the E4 defect may be due to differential cytoplasmic compartmentalization (Huang et al., 1999).

ApoE could play a role in lipid metabolism through its oxidative effects (see Section 10.2). ApoE-dependent effects on oxidative stress could modulate its ability to support neurite sprouting and could account for synaptic disruption observed in apoE-ko mice. Lipid peroxidation toxicity could inhibit sprouting by the inability to efflux such toxins. In humans, E4 genotype shows higher plasma lipid peroxide that correlates with apoE levels (Smith et al., 1998) and higher lipid peroxidation in brain (Ramassamy et al., 2000). The lack of apoE in the apoE-ko mice results in oxidative stress in the periphery and CNS, e.g., increased CNS F2-isoprostanes (Montine et al., 1999; Pratico et al., 1999), which are suppressed in the plasma by vitamin E (Pratico et al., 1998). Vitamin E ameliorates cognitive deficits in apoE-ko mice (Veinbergs et al., 2000); apoE-ko animals demonstrate increased susceptibility to oxidative stress conditions including global ischemia where neuronal damage correlates with 4-HNE (Horsburgh et al., 1999). Lack of apoE, however, (in apoE-ko mice) was found to increase CNS lipid peroxidation without neurodegenerative or synaptic changes, perhaps because of an oxidative magnitude issue (Montine et al., 1999) (see Section 10.2).

4.5 Model systems

4.6 ApoE-knockout mice. Studies of the apoE-ko mouse (Piedrahita et al., 1992) reveal insight into functions of apoE, peripherally and centrally. Although neuropathologically normal, apoE-ko mice show numerous CNS defects including impaired memory and learning deficits, some of which are age-dependent (Gordon et al., 1995; Masliah et al., 1995b,c, 1996; Krzywkowski et al., 1997, 1999; Veinbergs et al., 1997; Veinbergs and Masliah, 1999; Keller et al., 2000; Bi et al., 2001), changes in cholinergic responses (Gordon et al., 1995), age-related disruption in the dendritic cytoskeleton, and reduced synaptophysin and MAP2 in the hippocampus (Masliah et al., 1995a; Veinbergs and Masliah, 1999; reviewed in Masliah et al., 1996;). Some effects, however, may be strain-dependent (Gandy et al., 1995; Masliah et al., 1996). ApoE-ko mice also demonstrate deficits in response to injury, including cerebral ischemia (Connolly et al., 1996; Laskowitz et al., 1997), and impaired synaptic regeneration (recovery of synaptophysin to entorhinal cortex deafferentation) (Masliah et al., 1995b; Chen Y et al., 1997; Laskowitz et al., 1997; Fagan et al., 1998) (see Section 3.6). Neurotrophic compounds like cerebrolysin that ameliorate behavioral and neurodegenerative changes in apoE-ko mice are associated with upregulation of GAP-43 (Masliah et al., 1999). Some evidence suggests, however, that synapse formation in development is normal in apoE-ko mice, and humans who lack apoE are apparently cognitively normal (Feussner et al., 1996), suggesting the existence of redundant pathways replacing some apoE functions. It may be that in the aging brain these redundant pathways are ineffective, increasing the reliance on apoE activity for plasticity. Loss of synaptic and dendritic density seen separately with age or with absence of apoE expression are synergistic in aged apoE-ko mice (Masliah et al., 1995d).

4.7 Human apoE isotype transgenics. Several lines of transgenic mice have been developed that express the human apoE isotypes under the transcriptional control of various promoters: the natural human apoE promoter (*human apoE*); the astrocyte-specific GFAP promoter (*GFAP*); the neuron-specific NSE promoter (*NSE*); and recently, the natural mouse apoE promoter (*mouse apoE*), so-called knock-in mice. Clearly, each has strengths and limitations experimentally and in their relevance to AD. For example, the *GFAP* transgenic mice have provided what is considered a natural source of lipoprotein particles as synthesized by astrocytes. E3 produced by primary astrocyte cultures from transgenic mice (*GFAP*) is better than E4 at promoting neurite outgrowth in primary cultured neurons (Sun et al., 1998, Table I). This is also an advantage of the *human apoE* transgenic mice (see Section 3.6); transgenic line also expresses apoE in vivo with cellular specificity like that seen in humans (Xu et al., 1996, 1998, 1999) (see Section 4.1). Sprouting responses and synaptic disruptions in hippocampal pyramidal neurons of aged apoE-ko mice (GAP-43, MAP-2) and behavioral deficits are better ameliorated by E3 than E4 transgene (*human apoE*) expression (Veinbergs et al., 1999). Similar results were obtained by infusion of apoE isotypes directly into the brain of apoE-ko mice (Masliah et al., 1997). Behavioral and structural alterations are seen in female E4 but not E3 transgenic mice (*NSE*) (see Section 4.11). E4 transgenic mice (*human ApoE*) are unable to compensate for age-related neuronal loss by synaptic remodeling of the residual neurons (Hoffman and Chernak, 1994; Cambon et al., 2000). E4 transgenic mice (*NSE*) show less synaptophysin (a presynaptic marker) and MAP-2 (a dendritic marker) and behavioral deficits (Buttini et al., 1999; Raber et al., 1998, 2000, 2002). The effects of neuronal expression of human ApoE on sprouting have not been addressed adequately.

4.8 In vitro sprouting systems. The mechanisms by which apoE facilitates neuronal sprouting have been studied extensively in vitro. In most studies, E4 was defective in supporting neurite sprouting (Table I). In

these studies, the apoE source varied between pure (recombinant) protein, lipoprotein particles produced by transfected neurons or liver cells (HEK-293), particles produced by transgenic astrocytes (GFAP promoter-driven), or by a balanced production by all CNS cells (human ApoE transgenics). Neurite sprouting was measured in neuron cell lines N2A or GT1-1 (a hypothalamic line), primary hippocampal neurons, or hippocampal granule neuron mossy fibers in OHSC (see Section 3.6). In all these studies, E3 stimulated sprouting, whereas E4 showed an inhibitory effect, no effect, or weakly stimulatory effects on sprouting, always less than (or equal to) E3 (reviewed in Teter, 2000).

Important findings include consideration of the lipidation state of the apoE isoforms to reveal isoform-specific activities. For example, pure E4 inhibits N2A sprouting only when reconstituted with b-VLDL or with other lipid sources (also required for the defect in N2A-expressed apoE4) (Nathan et al., 1994, 1995; Bellosta et al., 1995; Holtzman et al., 1995b), and apoE isoforms expressed in lipoprotein particles by transfected HEK cells do not reveal the E4 defect (Puttfarcken et al., 1997) whereas those produced by transgenic astrocytes do (Sun et al., 1998). The lipidation state of apoE is a critical issue yet to be resolved fully because not all apoE isotype-specific effects, including sprouting, depend on lipidation (reviewed in Nathan et al., 1994, 2002; Jordan et al., 1998; Teter, 2000).

Possible mechanisms of isotype-specific sprouting include isotype-specific effects on lipid efflux (see Sections 3.7, 4.9); apoE cellular accumulation (Ji et al., 1998) (see Section 4.1), microtubule depolymerization and destabilization (Nathan et al., 1995; Pitas, 1996; Roses et al., 1996; Pitas et al., 1998), and neurotoxicity (Marques et al., 1996; reviewed in Teter, 2000; Teter et al., 2002). Several studies show a dependence of E3-stimulated sprouting on the LRP receptor or the HSPG/LRP receptor system (Table I) (Bellosta et al., 1995; Holtzman et al., 1995b; Nathan et al., 1995; Fagan et al., 1996; Sun et al., 1998). Interestingly, exogenous E3 does not rescue the E4 defect in stimulating sprouting (Nathan et al., 1994; Holtzman et al., 1995b).

4.9 Isotype-dependent granule cell mossy fiber sprouting. In early development and in OHSC in vitro (see Section 3.6), the early postnatal development of the granule cell mossy fiber system (Gaarskjaer, 1986; Slomianka and Geneser, 1997) parallels the large increase in apoE expression at this time (Muller et al., 1997). Mossy fiber sprouting in OHSC is found to be regionally dependent on apoE expression, where only dorsal dentate granule cells fail to sprout in apoE-ko OHSC (Teter et al., 1999a). These studies indicate that apoE-dependent spouting is region-specific, perhaps reflecting a developmental age-dependent difference in the capability of the granule cells to react to deafferentation. Aspects of this region-specific, apoE-dependent sprouting have been demonstrated independently in adult animals, where apoE-ko mice show deficient sprouting in response to ECL (Masliah et al., 1995b; Stone et al., 1998) (see Section 4.11).

Granule cell sprouting in OHSC derived from E3 and E4 transgenics (*human ApoE*) showed that E4 induced sprouting to a level only 50% of that induced by E3 (Teter et al., 1999b). This E4 defect in sprouting was demonstrated recently in vivo using the same transgenic mice and the ECL paradigm, where compensatory sprouting measured by GAP-43 and synaptophysin immunoreactivity did not recover as effectively in E4 as in E3, nor did morphometric measures of sprouting extent (White et al., 2001). ApoE4 transgenic mice (*NSE*) also show poorer recovery from other lesion paradigms, such as excitotoxic injury (Buttini et al., 2000). The reduced distal mossy fiber sprouting measured in E4 OHSC (outer molecular layer sprouting) may be explained by effects on neurite branching. The effect of apoE4 on proximal neurite branching in AD (see Section 4.3) is also seen in sprouting responses in vitro (Nathan et al., 1995).

4.10 ApoE gain-of-function defect in sprouting. Although E4 reduced sprouting activity in most studies, several studies indicate that the E4 activity in the inhibition of neurite sprouting actually represents a gain-of-negative function. First, Nathan et al. (1994) found that dorsal root ganglion (DRG) neurons, Neuro2A cells (Bellosta et al., 1995), and primary cortical neurons (Nathan et al., 2002) extend neurites in the presence of E3, but decreased neurite extension with E4 is dose-dependent. Importantly, E4 inhibition dominates over E3 stimulation, an effect seen in other in vitro systems (Holtzman et al., 1995b) and in bigenic mice (Nathan et al., 1995; Buttini et al., 2000) (see below). Second, in the OHSC model of denervation-induced fiber sprouting (see Section 4.9), transgenic (*human apoE*) expression of E4 is not only defective in supporting neurite sprouting compared to E3, but increased expression of E4 (by doubling the transgene copy number) inhibited sprouting whereas increasing E3 expression stimulated sprouting (Teter et al., 2002). The apparent gain-of-negative activity of apoE4 could be a form of toxicity (reviewed in Teter, 2000; Teter et al., 2002) that, at higher expression levels, dominates its weak sprouting activity. This could be relevant at the apoE levels measured in OHSC media because similar levels are found in human CSF and brain (2–6 μg/ml) (Hesse et al., 2000). Two studies show in vivo evidence consistent with E4 dominant negative inhibition of neurite sprouting. First, in the loss of synaptic markers (synaptophysin, MAP2 and neurofilament) in response to kainate lesioning, whereas E4 transgenics (*NSE*) show reduced synaptophysin that is equal to apoE-ko mice, doubling the gene dose causes even greater reductions; notably, the E4 effect dominates over E3 (Buttini et al., 2000). Second, E4-specifc cognitive impairments in these same mice (*NSE*) are not present in nontransgenic apoE-ko littermates (this "gain of function" is in comparison to apoE-ko, not a dose response of E4) (Raber et al., 1998, 2000; reviewed in Teter et al., 2002).

4.11 ApoE, Gender, Estrogen (see Section 9). Gender has an impact on ApoE4 effects, further increasing AD risk and diminishing ERT treatment response in post-

menopausal women (Corder et al., 1993; Poirier et al., 1993b; Farrer et al., 1995, 1997; Schneider and Farlow, 1997; Yaffe et al., 1997, 2000; Bretsky et al., 1999). These results from human studies are paralleled to some extent by results from studies of transgenic animals.

In OHSC, granule cell sprouting is regionally dependent on apoE expression (see Section 4.6). Although sprouting in wild-type, apoE-expressing OHSC is stimulated by physiological levels of estrogen, an effect that is blocked by both progesterone and tamoxifen, as seen in purified neuron cultures (Chawen et al., 1992; Woolley and McEwen, 1993), estrogen does not stimulate sprouting in apoE-ko OHSC, showing that neuronal sprouting is increased by estrogen in the same hippocampal region where sprouting is dependent on apoE. Likewise, whereas apoE-ko animals show compromised compensatory sprouting in response to ECL lesion in vivo (Masliah et al., 1995a; Masliah et al., 1996; Anderson et al., 1998; Stone et al., 1998), estrogen replacement in ovariectomized mice stimulates sprouting only in wild-type but not apoE-ko mice (Stone et al., 1998). Like the region-specific apoE dependency of estrogen-stimulated granule cell sprouting in OHSC, granule cells in the dorsal region are sensitive specifically to estrogen-stimulated increases in spine density (Miranda et al., 1999). Sprouting may be stimulated by estrogen through upregulation of apoE expression (see Section 4.1). Upregulation of apoE synthesis in glia (primarily astrocytes) occurs in CNS regions that undergo estrus cycle-dependent synaptic remodeling (Stone et al., 1997). Estrogen and apoE may therefore interact in their modulation of both AD risk and CNS plasticity. This is consistent with a postmenopausal decline in peripheral apoE levels (Kushwaha et al., 1991; Muesing et al., 1992). Other possible mechanisms of apoE and estrogen interaction include estrogen receptor polymorphism (Mattila et al., 2000) and oxidation (Inestrosa et al., 1998) (see Section 10.2).

Only female E4 transgenic mice (*NSE*) develop age-related progressive impairments in spatial learning and memory in the water maze and nonspatial novel object recognition memory (Raber et al., 1998; 2000, reviewed in Teter et al., 2002). These cognitive impairments are independent of the cellular source of apoE as they are observed in mice expressing E4 in neurons (*NSE* transgenics) and in astrocytes (*GFAP* transgenics) (see Section 4.7). The findings that the detrimental effects of E4 are greater in female than in male transgenic mice is consistent with the epidemiological interaction of apoE4 and female gender on increased risk to develop AD.

4.12 ApoE Therapeutic Implications: Drug Interactions and Pharmacogenetics

ApoE4 plays a major role in the risk and onset of AD for ~50% of AD cases in the United States (Ashford and Mortimer, 2002); therefore, therapies that target the mechanism of increased risk for apoE4 and reduced risk for apoE3 and E2 would greatly impact AD prevalence. Possible targets include apoE expression levels and regulation, apoE protein structure or gene replacement, and primary targets or secondary effects of apoE activity. The protein structural determinants of apoE4 are known (Weisgraber, 2001); with further understanding of how structure modulates various apoE activities, this avenue holds promise for drugs that convert the E4 protein to a structure that resembles E3 or E2. Gene replacement may capitalize on emerging stem cell technology, or using cell precursors in the bone marrow that can cross the blood brain barrier and differentiate into a variety of CNS cell types (see Section 10.5).

Reducing the expression of the human apoE4 gene could reduce apoE4-related risk, however, the relevance of apoE gain- and loss-of-function effects are not well understood. Further, human apoE gene regulation is very poorly understood, particularly with respect to effects of current and candidate therapeutic drugs. Estrogen is known to regulate apoE expression, and this may mediate, at least in part, the effect of estrogen replacement therapy (ERT) in improving the cognitive deficits in postmenopausal women with AD and the poorer response of apoE4 women (see Section 4.11). These effects of the efficacy of ERT in AD will be better understood with results from several clinical trials currently in progress (WHIMS and others) as apoE genotype is monitored routinely.

Other therapeutic drugs show apoE isotype-dependent effects that may interact with primary targets or secondary effects of apoE activity (reviewed in Poirier, 1999). Tacrine (an anti-cholinesterase) therapy has lower efficacy in E4 (Poirier et al., 1995) and in women with E4, no effect by genotype in men (Farlow et al., 1998), and lower efficacy in E4 women on combination tacrine plus ERT (Schneider and Farlow, 1997). There are indications, however, that apoE genotype may affect only longer-term tacrine therapy (MacGowan et al., 1998). The efficacy of a noradrenergic and vasopressinergic activity facilitator is also higher in E4 (Richard et al., 1997). Citicoline, an intermediate of lipid and acetylcholine biosynthesis that increases cerebral blood flow, shows greater efficacy with E4 (Alvarez et al., 1999). Growth hormone therapy is poor in E4 (Johannsson et al., 1995), possibly involving the mechanisms of GH regulation of plasma ApoE levels (Sjoberg et al., 1994). Other drugs that could modulate apoE expression include therapeutic agents that target oxidative mechanisms, such as vitamin E, selegiline (Sano et al., 1997b), and *Ginkgo biloba* extract (EGb 761) (Le Bars et al., 1997) (see Sections 4.4, 10.2), anti-inflammatory drugs like NSAIDs that could impact apoE expression through glial responses to inflammation (see Section 10.3), and statins that modulate cholesterol levels and may thereby regulate apoE expression (see Section 3.7).

The gain-of-negative function of E4 could have important clinical implications for the pharmacogenomic efficacy of therapeutic drugs that impact or target apoE expression (Poirier, 1999; Saunders et al., 2000) to the extent that E4-defective sprouting contributes to neuroregenerative events in neurodegenerative conditions (or, for that matter, any toxic activity of E4 that prevents neuroregeneration or promotes neurodegeneration). A drug that increases apoE expression might show efficacy in

E3 but not in E4, and may even exacerbate the E4 condition, whereas the opposite is predicted for E4 defects that are simple loss-of-functions. As in the ERT trials, it will be important to evaluate apoE genotype effects in trials of other drugs that can modulate apoE expression. With the implementation of pharmacogenetic approaches to therapeutic drug design and with testing and efficacious matching of treatment protocol to the genetic polymorphism fingerprint of the patient, understanding of genetic influences on neurodegenerative disease will see rational therapeutic application.

Therapeutic strategies must also consider both when and how the drug target contributes to disease etiology. For example, the apoE4 phenotype of accelerating the age of onset requires prevention strategies and may not respond to drugs designed to slow disease progression. The pleiotropic effects of apoE and its isotypes raise the strong possibility that the isotypes differ in the mechanism by which they contribute to AD etiology. Although apoE has emerged as the strongest genetic risk factor for sporadic AD and is implicated in other neurodegenerative diseases, many other genes are also implicated. Identification of these genes (Tanzi, 1999) has been slow methodologically, but the availability of human genomic sequence to reveal other polymorphisms linked to AD will help pharmacogenetic drug design.

5.1 APP AND AB

Other than production of AB, the functions of APP relevant to AD etiology include neuronal development, synaptogenesis, synaptic plasticity, and cell signaling (Luo et al., 1992; Moya et al., 1994; Mucke et al., 1994; Muller et al., 1994; Roch et al., 1994; Qiu et al., 1995; reviewed in Neve et al., 2000, 2001; Neve, 2001; Arendt, 2001a). APP and PS are expressed at higher levels in neurons in regions most affected in AD: hippocampal CA fields, amygdala subregions, and neocortex (Lee et al., 1996). APP gene expression and processing is regulated by NF-κB as an injury-responsive cytokine/neurotrophic factor (Mattson and Camandola, 2001; Weggen et al., 2001) (see Section 10.3). Injury and denervation that induces plasticity also upregulate APP (Banati et al., 1993; Wallace et al., 1993; Beeson et al., 1994; Chauvet et al., 1997), as does cholinergic innervation (Nitsch et al., 1995) (see Section 3.1). APP interacts with substrate adhesion in many ways, including association with adhesion patch components, integrins, transglutaminase, glycosaminoglycans, and collagen (reviewed in Arendt, 2001a).

5.2 APP Trophic Effects and Axonal Transport

The superfamily of amyloid precursor proteins (APP, APLP1,2) is associated with axonal outgrowth in several neural systems (Ohta et al., 1993; Arai et al., 1994b; Moya et al., 1994; Thinakaran et al., 1995; Lyckman et al., 1998) and neurite outgrowth that is APP isoform-dependent (Milward et al., 1992; Qiu et al., 1995). APP is secreted from neurons in response to electrical activity and induces neurite outgrowth, synaptogenesis, and LTP (Roch et al., 1994; Huber et al., 1997; Ishida et al., 1997; Mattson, 1997). Transgenic mice expressing various forms of APP exhibit both degenerative and regenerative changes that depend on age and APP genotype. Transgenic mice expressing APP show increased synaptophysin (King and Arendash, 2002), even at low levels of APP (Mucke et al., 1994), and secreted APP promotes dendrite outgrowth at pM concentrations (Mattson, 1994). APP transgenic mice undergo synaptic, electrophysiologic, and behavioral changes before plaque formation and in the absence of overt neurodegeneration (Hsia et al., 1999; Mucke et al., 2000), although some models do show plaque-associated neuron loss (Calhoun et al., 1998). APP transgenic mice have increased numbers of synapses (Mucke et al., 1994) and increased cortical neuron number before plaque formation (Bondolfi et al., 2002) (see Section 3.5). APP may enhance proliferation of neural stem cells (Ohsawa et al., 1999) (see Section 10.5). In contrast, degenerative changes are expressed in older animals, perhaps reflecting accumulated AB/amyloid or soluble AB toxicity (see Section 5.4).

Members of the APP superfamily of proteins are transported by and play a role in the fast anterograde transport system (Koo et al., 1990; Sisodia et al., 1993); they also accumulate in presynaptic membranes. Axonal pathology is reflected by diminished axonal transport (Geinisman et al., 1977). This may involve the role of APP in chaperoning NCAM and sialic acid to the presynapse. Aging is associated with decreased axonal transport, which may be caused by AB (Kasa et al., 2000). The insulin receptor signaling cascade also affects APP trafficking. Reduction in axonal transport (anterograde) would deplete APP at the presynapse and cause accumulation in other cell compartments where AB production may be favored (Golde et al., 1992). Conversely, reducing APP proteolysis to AB is predicted to lead to trophic APP accumulation at the presynapse (see Sections 3.4, 5.3).

5.3 APP Processing Balance

The processing of APP by α secretase produces soluble/secreted APP that promotes new synapse formation. Decreasing the amount of functional APP or shifting toward β secretase products could contribute to failure of plasticity and elimination of synapses. This situation could be induced by mutations that inhibit any of these trophic activities of APP, or by mutations or other factors that shift the APP processing balance to produce nonfunctional fragments. Mutations in APP and other situations that shift the processing balance away from secreted APP toward AB42 would interfere with APP-induced plasticity. Transgenic mice expressing such mutated APP show decreased synaptic and dendritic density in the hippocampus, impaired LTP, decreased compensatory synaptogenesis in response to injury, and impaired spatial memory (Games et al., 1995; Masliah et al., 1995b; Chapman et al., 1999). Conceivably, any event that promotes AB deposition could do so by shifting the processing toward more AB production (albeit, ignoring clearance effects). With age, the processing of APP also shifts away from producing the neurotrophic secreted APP form (Palmert et al., 1990; van Gool et al., 1994). APP metabolism is also influenced by

laminin (Monning et al., 1995; Narindrasorasak et al., 1995; Bronfman et al., 1996), cholesterol (Jick et al., 2000; Refolo et al., 2000; Wolozin, 2001), and NSAIDs (see Section 10.3). APP-knockout mice show loss of presynaptic markers, reduced CA1 dendritic length, impaired LTP and cognitive performance, and reduced axon and dendrite growth in vitro (reviewed in Arendt, 2001a).

5.4 Amyloid-β and Amyloid Plaques

A major issue facing the amyloid hypothesis of AD is the relative contributions of the various forms of AB, the peptide released from β secretase-processed APP. AB forms a continuum of aggregation species: monomeric AB, soluble AB, ADDLs, insoluble AB, diffuse amyloid, compact amyloid, and neuritic amyloid, the latter two being the pathologic and diagnostic hallmarks of AD. Independent of fibril or plaque formation, however, AB can alter membrane potential and firing, synaptic transmission, synaptic plasticity, and learning (Cullen et al., 1997; Lambert et al., 1998; Hartley et al., 1999; Chen G et al., 2000; Chen QS et al., 2000; Chapman et al., 2001). AB, especially AB1–42, shows neurotoxic, neurite-inhibiting, and LTP-inhibiting properties (Freir et al., 2001; Dewachter et al., 2002). Soluble AB and AB oligomers inhibit LTP but not LDP, resulting in a 'neuroplasticity imbalance' in the competition for synaptic stabilization (Cullen et al., 1997; Wang et al., 2002), as occurs in development (Constantine-Paton, 1990). Oligomeric, but not monomeric AB inhibits LTP in vivo (Lambert et al., 1998; Walsh et al., 2002).

Negative effects of AB on plasticity are also revealed in studies of vaccination/immunization in mouse models. Active immunization reduces both brain AB/amyloid burden and cognitive impairments in APP transgenic mice (Janus et al., 2000; Morgan et al., 2000). Recent studies using the passive immunization approach in APP transgenic mice also indicate such a correlation, but importantly, very rapid behavioral effects are achieved (within days), even without changing global AB levels in the brain (Dodart et al., 2002). Perhaps relatively minor compartments of AB that inhibit learning are reduced rapidly by peripheral immunization, which is consistent with reports that soluble AB is a better correlate of memory impairment (Lue et al., 1999; McLean et al., 1999; Koistinaho et al., 2001). Clinical immunization for AB, despite an early setback, remains a potential therapeutic strategy.

These neurotoxic effects of AB may act to destroy synapses that are no longer required or are underutilized. In contrast to these neurotoxic effects, however, low concentrations of AB can show neurotrophic effects (Calabrese, 2001), and laminin and AB act synergistically in stimulating neurite outgrowth (Koo et al., 1993). Low levels of AB can modulate the activity of the transcription factor CREB (Sato et al., 1997), a factor necessary for neuronal plasticity (Segal and Murphy, 1998; Silva et al., 1998). AB may play a functional role in membrane lipid dynamics (Muller et al., 2001; Chochina et al., 2001). AB enhances the transport, uptake, and oxidative metabolism of lipids, acting much like an apolipoprotein (Wood et al., 1999), a process that takes place in the ER/trans Golgi and endolysosomal pathways, which are also utilized by apoE (Jensen et al., 1994). The possible equilibrium between plaque-bound AB and soluble AB is not understood. Plaques could be a localized source of soluble AB which, when released, could impact plasticity responses, and contribute to the plaque-association of dystrophic neurites, growth-promoting factors, and synaptic proteins (SNAP-25, synaptophysin, synaptotagmin, chromogranins, NT75, spectrin), as reviewed by Arendt (2001a) (see Section 3.5). Numerous growth-promoting factors associated with plaques could contribute to stimulated sprouting, such as S100b, bFGF, HGF, PDGF, Trk receptors, proteoglycans, EGF-R, ICAM, integrins, collagen, laminin (reviewed in Arendt, 2001a). Other plaque constituents like perlecan, agrin, and laminin could also contribute to localized sprouting responses (Phinney et al., 1999).

6. TAU

Tau is a member of the MAP family (reviewed in Maccioni and Cambiazo, 1995). Aggregated, hyperphosphorylated τ forms neurofibrillary tangles (NFT), the intracellular pathological hallmark of AD (reviewed in Lovestone and Reynolds 1997; Lovestone et al., 2001). Its expression and phosphorylation is associated with increased neuroplasticity in vivo and in vitro (Busciglio et al., 1987; Viereck et al., 1989; Trojanowski et al., 1993; Brion et al., 1994; Black et al., 1996; Lovestone and Reynolds, 1997). Hyperphosphorylation may also cause deleterious effects on plasticity, however, and may underlie its role in the etiology of AD (Maccioni and Cambiazo, 1995; Mandelkow et al., 1995). Tau modulates cytoskeletal and microtubule dynamics that contribute to growth cone migration and collateral branching (Gallo and Letourneau, 1999). Tau plays a major role in the outgrowth of neurites and axonal development (Maccioni and Cambiazo, 1995). NFT-bearing hippocampal neurons show more extensive dendritic trees, suggesting a concurrent or previous induction of reactive plasticity (Gertz et al., 1990) (see Section 3.4). NFT-bearing neurons contain numerous growth-associated proteins (reviewed in Arendt, 2001a). Antisense to tau mRNA suppresses neurite formation in B103 cells (Lambert et al., 1995). Tau overexpression by PC12 cells induces neurite extension, and NGF-induced extension is associated with large upregulation of τ (Drubin et al., 1985; Esmaeli-Azad et al., 1994).

The equilibrium between τ phosphorylation and dephosphorylation modulates the stability of the cytoskeleton and thereby the axonal morphology. Tau is phosphorylated by several kinases including GSK3b and Cdk5, and broken down by several phosphatases including A and B. Breakdown of this equilibrium causes structural and conformational changes in τ, thus affecting binding with tubulin and the capacity to promote microtubule assembly (Mandelkow et al., 1995; von Bergen et al., 2000). This may promote NFT, particularly in limbic structures (see Section 3.1), leading to cytoskeletal dysfunction. Dentate granule cell mossy fiber axons that undergo deafferentation-induced sprouting (see Sections 3.6, 4.6) display

excessive τ phosphorylation (Koudinov and Koudinova, 2001). It is not clear whether neurofibrillary-induced neurodegeneration is a later event in AD or whether its pathology simply cannot be detected in early AD (see Sections 3.4, 3.5).

Tau can link trophic signaling with cytoskeletal rearrangements involved with dendritic sprouting (see Sections 8.2, 8.3). The protein kinase Cdk5 and its neuron-specific activator p35 are essential molecules for neuronal migration and regulate axonal extension through phosphorylation of MAPs including τ (Pigino et al., 1997; Paglini et al., 1998). The formation of a stable Cdk5/p35 complex in hippocampal neurons (Alvarez et al., 1999) may lead to constitutive activation of the protein kinase with a consequent increase in τ phosphorylation. The complex concentrates at the leading edge of the growth cone (Pigino et al., 1997). Laminin stimulates p35 expression, increasing its redistribution to the growth cone (Ramirez et al., 1999), contributing to the axon-outgrowth activity of laminin (Paglini et al., 1998). Cdk5 may link τ hyperphosphorylation and AB (Alvarez et al., 1999; Maccioni et al., 2001). Therefore, the Cdk5 system may provide an important regulatory link between extracellular signals like laminin and the intracellular organization of MAPs and other cytoskeletal proteins involved in axon elongation (Maccioni et al., 2001). Cdk5 interacting proteins include τ, synapsin, CK1, b- and g-catenins, N-cadherins, Rac GTPase and Pak1 (which impacts actin cytoskeleton dynamics) (reviewed in Maccioni et al., 2001) (see Sections 3.4, 8.2).

7. PRESENILINS

PS-1 is necessary for normal neurogenesis and survival (Shen et al., 1997; Wong et al., 1997) and localizes to synaptic membranes and neurite growth cones. Presenilins are involved in intracellular trafficking, developmental signaling pathways, and Ca^{2+} homeostasis (Shen et al., 1997; Wong et al., 1997; Naruse et al., 1998; Nishimura et al., 1999). Ca^{2+} dysregulation could underlie effects of PS-1 on LTP: wild-type PS-1 underexpression impairs LTP in mice (Morton et al., 2002) and rats (Dewachter et al., 2002), mutant PS-1 alters LTP (Parent et al., 1999; Zaman et al., 2000); however, mutant but not wild-type PS-1 and mutant PS-2 facilitate weak-stimulation LTP in brain slices (Schneider et al., 2001). Mutant PS-1 may interfere with metabolism of β- and γ-catenin, which are involved in synapse formation and stabilization (Zhang et al., 1998; Kang et al., 1999) and cell adhesion (Noll et al., 2000) (see Section 6). Wild-type PS-1 stimulates whereas mutant PS1 inhibits NGF-induced neurite outgrowth (Furukawa et al., 1998; Dowjat et al., 1999; reviewed in Arendt, 2001a). PS-1 cleaves Notch, which inhibits neurite outgrowth (Berezovska et al., 1999; Sestan et al., 1999; Figueroa et al., 2002). Presenilins are also considered as a therapeutic target for AD (Golde and Younkin, 2001), however, the negative secondary effects of inhibiting presenilin need further investigation (Dewachter et al., 2002).

8. NEURODEGENERATION AND NEUROREGENERATION INTERACTIONS

8.1 Degeneration-Regeneration Cross Talk and Combinatorial Signaling

The same trophic signals that control survival can also promote neurite outgrowth (Campenot, 1994; Meyer-Franke et al., 1995). This could allow for a mechanism whereby simply promoting survival stimulates plasticity (Goldberg and Barres, 2000). Trophic responsiveness can be dependent on continuous trophic stimulation, where competition for limited target-derived trophic factors can ultimately decide cell fate, and thus it is possible that continuous availability of trophic stimulation could be limiting for plasticity mechanisms as well (Goldberg and Barres, 2000).

Neurons do not extend axons by default but must be signaled specifically to do so (Goldberg and Barres, 2000). Promotion of plasticity requires both presentation of an extrinsic stimulus and the intrinsic responsiveness of the neuron, which includes states that can be induced transcriptionally (Smith and Skene, 1997). Responsiveness of neurons to intrinsic and extrinsic signals that promote plasticity may come from combinatorial signaling, e.g., simultaneous presentation of electrical activity and growth factors, like BDNF. (McAllister et al., 1996; (reviewed in Goldberg and Barres, 2000). Electrically and biochemically active neurites would therefore survive and grow in response to trophic stimulation; for example, granule cell axon sprouting can result from alteration of the intrinsic neural excitability in the absence of cell death (Stringer et al., 1997). Thus, reduced neuronal activity would reduce its responsiveness to stimulation of plasticity.

Many factors influence both neuronal death and neurite sprouting, for example, c-Jun and GAP-43 (Herdegen et al., 1997; Gagliardini et al., 2000; Wehrle et al., 2001), and neurotrophins that promote neurite growth (Levi-Montalcini, 1987; Campenot, 1994; Meyer-Franke et al., 1995; Henderson, 1996). Other factors include substrate molecules like laminins, although this may be insufficient (Goldberg and Barres, 2000). Retrogradely transported signals like CREB (Silva et al., 1998) and signaling by the ras/raf/MAP pathway may play important roles in intra-neuronal signaling of plasticity (Perron and Bixby, 1999) (see Sections 3.2, 6).

The relationship between plasticity and the classical plaque pathology of AD is unclear. Granule cell dendritic regression is not modified by plaque association (Einstein et al., 1994). Transgenic mice expressing anti-NGF antibody develop amyloid plaques, NFT-like inclusions, neuron losses, and behavioral deficiencies with age (Capsoni et al., 2000) including impaired spatial learning (Van der Zee et al., 1995a,b; Chen KS et al., 1997). Ex-boxers with an increased plasticity burden (injury-induced) have AD-like neuropathological changes (Tokuda et al., 1991; Geddes et al., 1996). The increased risk of AD with head injury and stroke (Salib and Hillier, 1997; Snowdon et al., 1997) may require widespread or chronic injury combined

with factors or events that inhibit neuroplasticity responses (see Sections 3.5, 5.4).

8.2 Cell Cycle

If a neuron that is committed to permanent cessation of cell division is forced, through ectopic expression of cell cycle proteins, to reenter the cell cycle, it may die. In AD frontal cortex during the early Braak I/II stage, when there in no τ or amyloid pathology or related dementia, mitotic events are activated including increased MAP2 and ERK1/2, which may lead to cell death (Arendt, 2001b). Tau kinases like MAP kinases, Cdk5, and others, are all associated with the cell cycle (reviewed in Arendt, 2001a,b). MAP kinases are activated by cell surface receptors through p21ras (Stokoe et al., 1994), which also plays a role in dendritic proliferation and synaptogenesis (Phillips and Belardo, 1994) (see Section 8.3).

8.3 Nitric Oxide (NO)

NO participates in axonal remodeling at the growth cone and synaptogenesis during development and regeneration (Hess et al., 1993; Wu et al., 1994; Yu, 1994; Luth et al., 1995; Rossiter et al., 1996; Yan et al., 1996; Downen et al., 1999). NO may be the retrograde messenger in LTP and may serve to help maintain normal LTP; however, NO also mediates some excitotoxicity (glutaminergic) mechanisms and has anti-proliferative effects (Arendt, 2001b). The NO synthesizing enzyme nNOS is dynamically regulated in neuronal development, plasticity, and responses to injury (Dawson et al., 1994, 1998; Dawson and Snyder, 1994; Forstermann et al., 1995). Activation of NF-κB in astrocytes increases iNOS expression and NO production. Changes of NOS (nNOS, neuronal) and iNOS (glial) (Srivastava et al., 1997) in AD are inconsistent (Law et al., 2001). Endothelial eNOS mediates neuroprotective actions of NO in ischemia and multi-infarct dementia (Law et al., 2001).

NO and other oxidative stress intermediates activate p21ras, a potential endogenous NO-redox-sensitive effector molecule (Yun et al., 1998). p21ras is highly colocalized with nNOS expression in AD and in NFT-bearing neurons (Luth et al., 2000). P21ras is overexpressed in advanced AD (Gartner et al., 1995), and is upregulated in early AD in affected regions before neurofibrillary degeneration (Gartner et al., 1999) (see Sections 3.4, 10.4), paralleling nNOS (Luth and Arendt, 1998; Luth et al., 2000). This may set up an autocrine loop (Lander et al., 1997) and may exacerbate neurofibrillary degeneration and limit the ability to terminate the vicious cycle. This relationship may switch two potentially neuroprotective mechanisms of NO and p21ras into a chronic neurodegenerative process (Arendt, 2001b).

9.1 GENDER AND ESTROGEN

Estrogen plays a powerful, pleiotropic role in many neurodegenerative conditions including AD (reviewed in Brinton, 2001; Garcia-Segura et al., 2001; McEwen, 2001; Wise et al., 2001a,b). Women have been shown to have increased risk, earlier onset, and more rapid progression of AD than men, although gender-specific morbidity is an issue (Sanderson et al., 2002). Postmenopausal loss of estrogens leads to generally reversible decreases in memory that respond to ERT (Sherwin and Tulandi, 1996). Besides mechanisms of blocking neurotoxicity directly, estrogen acts at various levels of plasticity: axon sprouting, synaptogenesis, and promoting synaptic transmission (electrophysiologically and biochemically). These effects can be ascribed to either receptor-dependent mechanisms, primarily transcriptional, including direct effects of ER in transcription and indirect effects through other transcription factors like CREB and Akt, as well as their retrograde transport (McEwen, 2001) or receptor-independent (rapid) mechanisms involving activational effects of second messenger systems, coexisting neurotransmission, or coordinated activation of both (Kelly et al., 1977; Nabekura et al., 1986; Wong and Moss, 1992; Garcia-Segura et al., 2001) (see Section 8.1), as well as oxidative effects of the estrogen molecule (see Section 9.3). Other secondary effects could be mediated through effects on AB, τ, microtubules, apoE, GAP-43, BDNF, ERK, IGF-1, NF-κB, CREB, gliosis, neurogenesis (Blanco et al., 1990; Gould et al., 1999; Tanapat et al., 1999), differentiation, or many other modulators of plasticity.

9.2 Estrogen Replacement Therapy (ERT)

Estrogen replacement decreases the risk of AD in postmenopausal women (Paganini-Hill, 1996; Kawas et al., 1997), delays the age of onset (Tang et al., 1996), and perhaps slows the decline; however, it remains controversial whether ERT can treat the disease once it has reached the clinical stage (Henderson et al., 2000; Marder and Sano, 2000; Mulnard et al., 2000; Wang et al., 2000). This latter effect is consistent with experimental results indicating that neuroprotective effects of estrogen occur only when administered before or during the neurodegenerative stimulus, but not after (Garcia-Segura et al., 2001). The therapeutic efficacy of ERT depends on its administration protocol: time course, treatment window, endogenous vs. exogenous hormone, and neuron population-specific effects on promoting survival vs. death. The mechanism of ERT efficacy is unlikely to include antioxidant effects as they require very high hormone concentrations to reduce lipid peroxidation (Vedder et al., 1999) (see Sections 4.4, 10.2); however, whether hormone concentrations are modulated by local aromatase expression are not known (Garcia-Segura et al., 2001). This is critical for considerations of testosterone therapy for men, in terms of its estrogenic actions (Cyr et al., 2000; Goodenough et al., 2000; Twist et al., 2000; Bowen, 2001). Testosterone also has estrogen-independent, potentially beneficial actions on amyloid toxicity (Pike, 2001).

9.3 Estrogen/Plasticity

(Reviewed in Toran-Allerand et al., 1999; Brinton, 2001; McEwen, 2001; Kelly and Levin, 2001).

Estrogen stimulates axon and dendrite plasticity in the limbic neurons of both male and female brain (Ferreira and Caceres, 1991; Lorenzo et al., 1992; Woolley and

McEwen, 1992; Woolley et al., 1996; McEwen et al., 1997; Teter et al., 1999a). Estrogens may support neuronal functions and confer resistance to neural damage by their ability to maintain synaptic connections (McEwen, 2001). Many studies demonstrate neuroprotective effects of estrogen in a variety of systems, and these are often associated with changes in gene expression, including genes that effect axonal elongation and synaptogenesis (GAP-43, τ, microtubules) (Ferreira and Caceres, 1991; Shughrue and Dorsa, 1993). Estrogen modulates plasticity during development and in adult CNS (Matsumoto, 1991; Garcia-Segura et al., 1994; McEwen, 1996; Woolley, 1998). Estrogen enhances neurite outgrowth by repressing GFAP and reorganizing laminin (Rozovsky et al., 2002). Estrogen can activate neurite mRNA translation (Pierce et al., 2000; Tiedge et al., 2001; Steward and Schuman, 2001).

Granule cell sprouting is stimulated by physiological levels of estrogen (which is blocked by progesterone and tamoxifen) in both wild-type OHSC (Teter et al., 1999a) (see Sections 4.6, 4.11) and in purified neuron cultures (Chawen et al., 1992; Woolley and McEwen, 1993). This effect is hippocampal region-specific, occurring only in the dorsal dentate region, both in OHSC (in the same region that is also dependent on apoE expression) and in vivo in adult, female rats, where short-term estrogen replacement in long-term estrogen-deprived females increases dentate granule cell spine density primarily by the dorsal region (Miranda et al., 1999). Sprouting of hippocampal neurons in response to ECL (see Section 3.6) was reduced by ovariectomy in rats and mice (Stone et al., 1998, 2000), and estrogen replacement rescues sprouting (Morse et al., 1986, 1992; Stone et al., 1998) (see Section 4.11).

Estrogen stimulates cyclic induction of synapses and dendritic spines in the hypothalamus and hippocampus of female rats (reviewed in Woolley and McEwen, 1992; McEwen, 2001). Synapse formation induced by estrogen may differ from that occurring during development, however (see Section 2.2): estrogen increases the number of synapses on multiple synaptic boutons between neurons not connected previously (Yankova et al., 2001). Estrogen induces both pre- and postsynaptic markers where new spines are formed (Brake et al., 2001).

10.1 TREATMENTS FOR PLASTICITY (see Sections 3.7, 4.12, 5, 9.2)

The public health impact of AD is predicted to rise at least three-fold in the next 50 years (Sloane et al., 2002). Clearly, all rational therapeutic avenues should be tested, but therapeutic stimulation, stabilization, or recovery of plasticity mechanisms could impact all neurodegenerative diseases. Current AD therapy targets cholinergic dysfunction, which may be linked to effects on plasticity through modulation of APP metabolism (and τ phosphorylation) by affecting the coupling of M1 muscarinic ACh receptors to G proteins (Fisher et al., 2000) (see Section 5.3). Other therapies under development focus specifically on AB, τ, inflammation, and oxidation (Galasko, 2001); if these pathologic phenotypes contribute to AD indirectly through interaction with an underlying process of plasticity, the effectiveness of interventions targeting these hallmarks may be enhanced if age-related plasticity failure is also treated. New drug strategies that target mediators of either neurodegenerative processes or neuroplastic processes must be considered for their pleiotropic and potentially confounding roles in both, as exemplified by apoE, NF-κB, etc. Of critical importance for the efficacy of plasticity-stimulating therapies is whether they create neural networks that are competent to replace lost function (see Section 10.5).

There are several avenues for stimulating plasticity in the damaged CNS, with targets at all levels of plasticity failure (Horner and Gage, 2000). Enhancing regrowth has been targeted as a therapeutic strategy. Putative neurotrophic agents such as Cerebrolysin have been reported to have positive effects in clinical trials, with sustained improvement after short treatment of AD (Bae et al., 2000; Ruther et al., 2000; Xiao et al., 2000); Cerebrolysin also ameliorates behavioral deficits and neurodegeneration in apoE-ko mice (Masliah et al., 1999). Propentofylline shows neurotrophic effects on glia function (Wilkinson, 2001), and cholesterol inhibitors like statins may reduce the incidence of AD (see Section 3.7). Memory rehabilitation, which targets mechanisms of cognitive reserve and compensatory reorganization to activate alternative, intact brain structures (facilitation of residual explicit memory, or, the 'use it or lose it' phenomenon), can be clinically effective (Grady, 1996), and alternative and innovative techniques are still under refinement (De Vreese et al., 2001).

10.2 Oxidation

As a lipid rich organ, the CNS is particularly susceptible to effects of lipid peroxidation in modulating cellular signaling pathways, cell dysfunction, and cell death in the nervous system (Keller and Mattson, 1998). In AD, emerging evidence provides strong support for a role for oxidative stress in neurodegeneration, as multiple indices of oxidative stress have been observed, including protein oxidation, decreased polyunsaturated fatty acids, mitochondrial and nuclear DNA damage, as well lipid peroxidation markers 4HNE (Sayre et al., 1997; Markesbery and Carney, 1999), and F2 and F4 isoprostanes (Nourooz-Zadeh et al., 1999), variously detected in brain and CSF. Vitamin E slows cognitive decline in AD (Sano et al., 1997a) and in rat models (Yamada et al., 1999) (see Section 4.4). Although it is not clear what causal relation oxidation has to AD etiology, e.g., whether it is a secondary effect of the stress caused by synaptic or neuronal loss, antioxidant therapies have shown limited but promising efficacy in treating AD (Pitchumoni and Doraiswamy, 1999).

Lipid peroxidation toxicity could inhibit sprouting by the inability to efflux such toxins; an efflux defect is shown by oxidized HDL (Therond et al., 1999). This oxidation-induced lipoprotein aggregation is neurotoxic to primary neurons and is accompanied by cytoskeletal microtubule disruption and inhibition of neuritogenesis

(Kivatinitz et al., 1997). Importantly, 4HNE disruption of microtubule organization inhibits neuronal sprouting (Neely et al., 1999). Effects of lipid peroxidation toxicity on inhibiting neuritogenesis could also involve apoE (see Sections 4.4, 8, 8.3).

10.3 Inflammation/NF-κB

NF-κB is directly required for synaptic plasticity, as shown in in vitro hippocampal slices (Albensi and Mattson, 2000). NF-κB is activated in association with LTP (Worley et al., 1993; Meberg et al., 1996). NF-κB is located in synapses at considerable distance from its canonical nuclear site of action, suggesting that it modulates synaptic function locally (O'Neill and Kaltschmidt, 1997).

NF-κB activation (reviewed in Mattson and Camandola, 2001) is implicated in AD (Perez-Otano et al., 1996; Lukiw and Bazan, 1998). NF-κB activity is increased in AD brain, including cholinergic neurons in the basal forebrain (Boissiere et al., 1997; O'Neill and Kaltschmidt, 1997). This could represent a neuroprotective and a cytoprotective response to plaques, because Aβ and secreted APP can activate NF-κB (Barger et al., 1995), and is associated with neuroprotective response to metabolic/excitotoxic events (Barger and Mattson, 1996) and mutant PS-1 (Guo et al., 1998). NSAIDs that target NF-κB have been shown to reduce the incidence of AD (Akiyama et al., 2000), even at low NSAID doses (Broe et al., 2000). Some NSAIDs reduce Aβ production, however, by modulating γ-secretase (Weggen et al., 2001) and could thereby influence the mechanism of plasticity involving the processing balance of APP (see Sections 4.1, 5.3, 8.3, 9, 10).

10.4 Growth Factors

NGF can induce sprouting and outgrowth, particularly after injury (Ramer et al., 2000; reviewed in Sofroniew et al., 2001), consistent with retrograde transport of trkA signaling complexes that alters gene expression in NGF-responsive neurons, including cholinergic neurons (Knipper et al., 1994; Holtzman et al., 1995a), which account for most of the NGF-responsive neurons in the adult CNS. The extent to which NGF is necessary for cholinergic survival of adult cholinergic neurons is controversial (reviewed in Rattray, 2001) (see Section 8). Indeed, AD brain shows increased NGF in the cortex and hippocampus (Jette et al., 1994; Scott et al., 1995; Fahnestock et al., 1996; Hock et al., 1998), which may reflect an increased demand for cholinergic input with a decreased ability of cholinergic neurons for retrograde transport of NGF. Although NGF may not have a classical neurotrophic role in cholinergic survival, i.e., through actions that are independent of retrograde signaling and gene expression, it is an important regulator of neuron morphology and function that would be predicted to maintain or improve cholinergic function in AD by promoting survival of degenerating neurons, promoting sprouting and enhancing neurotransmitter synthesis, and enhancing neuronal firing (reviewed in Rattray, 2001). Abnormal neurite growth might be associated with elevated NGF receptors (Ernfors et al., 1990; Mufson and Kordower, 1992) that precedes neurofibrillary degeneration (Arendt, 1993) (see Sections 3.4, 8.3).

NGF has been considered as a therapeutic target; however, problems with CNS delivery and side effects (pain) limit its clinical application (Eriksdotter Jonhagen et al., 1998). NGF application to the uninjured CNS causes cholinergic neurons to grow, sprout, increase ChAT, and increase choline uptake (Mobley et al., 1985; Higgins et al., 1989; Lapchak et al., 1992; Heisenberg et al., 1994). Experimental methods of delivery include gene transfer, cell grafts, or direct administration of NGF by intracerebroventricular infusion (reviewed in Rattray, 2001). These approaches have been successful in enhancing cholinergic neuron function and restoring some behavioral function in response to deafferenting lesions or impaired cognitive function. Drugs that increase NGF synthesis in astrocytes include propentofylline, a phosphodiesterase inhibitor (Rother et al., 1998), and various quinone derivatives (Takeuchi et al., 1990; Yamaguchi et al., 1993; Yamada et al., 1999). Nicotinic treatment that targets NGF production is also a possibility (Rattray, 2001). NGF mimetic drugs, like Neotrofin and AIT-082, are being tested in clinical trials (Emilien et al., 2000).

Neurotrophins are pivotal regulators of neurite outgrowth (Crutcher, 1986; Kang and Schuman, 1995). For example, BDNF acts at the synaptic level and is altered in AD (Murer et al., 2001). Further, GDNF clinical trials are underway (Maimone et al., 2001) and other neurotrophic strategies are being considered (Siegel and Chauhan, 2000).

10.5 Neurogenesis

Adult hippocampal neurons retain their proliferative capacity (Brewer, 1999, 2000; Seaberg and van der Kooy, 2002), where they provide a continuous replacement of neurons in the dentate gyrus (Seaberg and van der Kooy, 2002), particularly in conditions of enhanced learning (Kempermann et al., 1997, 1998a,b; Huang et al., 1998; Gould et al., 1999). Neurogenesis in the hippocampus declines with age (Cameron and McKay, 1999). An unanswered question is whether neurogenic capacity declines more in AD. Regardless, replacing lost neurons and reversing the age-related decrease in neurogenesis could be a therapeutic target using neural stem cell technology or other neuronal sources. This approach is attractive because neurogenesis occurs naturally and replacement does not suffer from caveats invoked for stimulation of aberrant sprouting, although it is not clear whether neural networks created by these new neurons are competent to replace lost function (see Section 2). Of critical importance is the orchestration of topographically accurate migration, targeted differentiation, and synaptic functionality of transplanted cells (Gage et al., 1995; Flax et al., 1998; Zhou et al., 1998; reviewed in Horner and Gage, 2000). Multipotent cells from the blood lineage, injected peripherally, migrate through the blood brain barrier; these may also provide a source and therapeutic avenue for CNS neuron

replacement (Bartlett, 1982; Bjornson et al., 1999; Brustle et al., 1999; Ono et al., 1999) (see Sections 5.2, 9.1).

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