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NEUROBIOLOGICAL SYSTEMS DISRUPTED BY ALZHEIMER'S DISEASE AND MOLECULAR BIOLOGICAL THEORIES OF VULNERABILITY

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INTRODUCTION

Alzheimer's disease (AD) is a neuropathological process which progressively and relentlessly devastates the brains of its victims. The AD pathology produces progressively more severe deficits in cognition, behavior, and activities of daily living over a time course of deterioration averaging 8 years (Ashford et al., 1995). Most of the studies of AD pathology have examined the composition and distribution of the neurofibrillary tangles and senile plaques first described by Alois Alzheimer in 1907 (see Greenson and Jarvik, 1989). However, Alzheimer's first comments on this disease referred to the psychosocial disruptions which he found in his patient. To solve this disease, the psychosocial clinical problems and the neurobiological system dysfunctions must be defined to the point that they indicate what neuromolecular mechanisms are attacked by the AD process.

The AD process has no direct effects on most functions of the body and is restricted in its attack on the brain. Investigations into the biology of AD have yet to reveal the basis of this process. Clearly the most important factor associated with the development of AD is age (Friedlich & Butcher, 1994), with AD changes appearing in many individuals at a young age and developing in a majority of individuals as age progresses past 60 years (Ohm et al., 1995). Studies of family constellations, DNA polymorphisms, and genetic mechanisms have revealed that genetic factors play a significant role in predisposing some individuals to developing AD (Roses, 1994; the genetic aspects of AD are discussed in the chapter by Matsuyama in this volume). Certain environmental factors, including a possible contribution by aluminum (Bertholf, 1987; Lovell et al., 1993; Harrington et al., 1994; Forbes et al., 1994), may also influence the onset of the disease. However, a major concern is understanding which neuronal systems in the brain are affected by the AD process, and how their unique physiological processes may predispose them to allow the progressive development of this disease process. The affected neurobiological systems seem to be those which underlie learning, and the AD process appears to attack mechanisms for storing new information from molecular biological machinery, to specific neurotransmitter systems to macroscopic anatomical structures of the cerebrum (Ashford & Jarvik, 1985; see Table 1). Through more complete understanding of the attack of the AD process, it is hoped that approaches can be developed to prevent or slow the development of AD.

TABLE 1 - BIOPSYCHOSOCIAL SYSTEMS AFFECTED BY AD
(MNEMONIC FUNCTION AT EACH LEVEL IS ATTACKED BY AD)

SOCIAL SYSTEMS
- DYSFUNCTION IN INSTRUMENTAL BEHAVIORS (EARLY AD)
  (REMEMBERING A GROCERY LIST OR PHONE NUMBER)
- DYSFUNCTION IN PERSONAL CARE (LATE AD)
  (REMEMBERING HOW TO DRESS OR BATHE)

PSYCHOLOGICAL SYSTEMS
- PRIMARY LOSS OF ABILITY TO LEARN NEW INFORMATION
  INCLUDING INABILITY TO KNOW OF THIS DEFICIT
- SECONDARY LOSS OF PREVIOUSLY LEARNED INFORMATION
  LATER LOSS OF LEARNED PERCEPTUAL AND MOTOR SKILLS
  (APHASIA, AGNOSIA, APRAXIA)

CORTICAL SYSTEMS
- ENTORHINAL CORTEX (MEMORY NETWORK) (EARLY AD)
- HIPPOCAMPUS (ARCHICORTEX) - LOCATIONAL MEMORY
- AMYGDALA (PALEOCORTEX) - EMOTIONAL MEMORY
- TEMPORO-PARIETAL CORTEX (NEOCORTEX) (MIDDLE AD)
  SENSORY ANALYSIS AND PERCEPTION STORAGE
- FRONTAL CORTEX - EXECUTIVE FUNCTION (MID-LATE AD)
- PRIMARY CORTEX - PRIMARY SENSORY/MOTOR ANALYSIS (LATE)

CORTICAL NEUROTRANSMITTER SYSTEMS
- GLUTAMATE (INFORMATION STORAGE MEDIATION)
- GABA-SOMATOSTATIN (UNKNOWN MNEMONIC FUNCTION)

SUBCORTICAL NEUROCHEMICAL SYSTEMS PROJECTING TO CORTEX
- NUCLEUS BASALIS OF MEYNERT - ACETYLCHOLINE
  (MEMORY; CLASSICAL CONDITIONING)
- ROSTRAL RAPHE NUCLEI - SEROTONIN
  (SENSITIZATION CONDITIONING)
- LOCUS COERULEUS - NOREPINEPHRINE
  (REWARD-RELATED CONDITIONING)

NEURONAL SYSTEMS (PRIMARILY CORTICAL)
- MICROTUBULE ASSOCIATED PROTEIN - TAU
  (PROCESS GROWTH FOR ESTABLISHING NEW SYNAPSES)
  NEUROFIBRILLARY TANGLES, NEURITIC PLAQUES
- AMYLOID PRE-PROTEIN (APP)
  (POSSIBLE INVOLVEMENT IN FORMATION OF NEW SYNAPSES)
  â-AMYLOID IN SENILE PLAQUES, AMYLOID ANGIOPATHY

PSYCHOSOCIAL SYSTEMS AFFECTED BY AD

In the study of AD, the first principle is that investigations of pathology must be linked to clinical dysfunctions. In AD, there is a progressive development of complex psychological and social symptoms. However, it is important to decipher these complex changes into simple psychological precepts which can be meaningfully related to the underlying organic disease. Though the psychological and social difficulties of the AD patients seem diverse, there may be a common thread in the signs and symptoms which is the failure of memory (Ashford et al., 1989; Carlesino & Oscar-Berman, 1992), and more specifically, the disruption of the fundamental mechanism for storing new information.

In most cases, the first reported symptoms of AD patients are failures of memory for recent events (Oppenheim, 1994). Tests of the most mildly affected patients indicate that the earliest difficulties involve the storage of new information into memory, that is, learning (Ashford et al., 1989a; 1995; Welsh et al., 1991; Fillenbaum et al., 1994; Masur et al., 1994). Even various psychiatric symptoms found in AD patients (Oppenheim, 1994; Cohen et al., 1993) can be linked to the failure of learning mechanisms. For example, claims of "stolen keys" usually turn out to be keys which were placed consciously, but the placement not retained. "Unfaithful spouses" are in fact spouses whose whereabouts the night before is not available for recall, though they were within the patient's view the entire time. Thus, the primary symptoms of AD seem to relate to difficulties with the neural mechanism for storing new information.

As AD progresses into more moderate phases, patients begin to lose the ability to recall information which had been learned prior to the onset of the disease. Neurological signs and symptoms such as aphasia, agnosia, and apraxia, which develop insidiously during the middle course of the disease, bear no resemblance to the failures seen after such critical brain injuries as stroke, but rather relate to the associative failure to recall a word, the purpose of an object, or how to perform a specific task. Consequently, the middle phase psychosocial symptoms of AD point to a disruption of neural connections related to the long-term storage memory mechanisms.

As AD progresses into late phases, a host of diverse symptoms develop, including disruption of activities of daily living. Yet, with careful consideration, each of the symptoms can be traced to failures of cortical information retention.

The logical leap in making the connection between memory mechanisms and such diverse symptoms as inability to shop, bathe, or toilette, lies in understanding that information is stored in the brain in a distributed fashion (Ashford & Fuster, 1985; McLelland & Rummelhart, 1989; Fuster, 1995). As new information is stored, it is placed (as a vector convolution; B.B. Murdock, 1982; Lewandowsky & Murdock, 1989) on top of the information which is already in place (Fuster, 1995; Ungerleider, 1995). If the mechanism for storing the new information

disrupts neuronal structure, then slowly, old information and habits will be lost as well. Consequently, the psychosocial symptoms and their progression point to a neuropathological process which attacks the mechanism for learning or storing information. This brain mechanism which is so vulnerable to the AD process is presumed to be neuroplasticity (Ashford & Jarvik, 1985; Horwitz, 1988; Repressa et al., 1988; Butcher & Woolf, 1989; Woolf & Butcher, 1990; Di Patre, 1991; Geddes & Cotman, 1991; Larner, 1995).

NEUROBIOLOGIC SYSTEMS AFFECTED BY ALZHEIMER PATHOLOGY

AD is known as a neurodegenerative disorder. The major signs of the disorder are dystrophic neurites, neurofibrillary tangles (NFT's) and neuritic amyloid plaques (NAP's). The dystrophic neurites and the NFT's are composed of paired helical filaments (PHF's) which are primarily abnormally phosphorylated microtubule associate protein-tau (Trojanowski & Lee, 1995). The PHF's clog the dendrites of the neurons and coalesce to form the NFT's in the neuronal cell bodies. They appear to reside indefinitely in situ after the neuron has died. NAP's are complex structures which contain a core of beta-amyloid (Aâ) and activated microglia (Itagaki et al., 1989; Streit & Kincaid-Colton, 1995), with reactive astrocytes (Sadowski et al., 1995) and invading neurites (Geddes et al., 1986), which contain PHF's. The distribution of these changes is not random, preferentially occurring in particular regions of the cortex (Brun & Englund, 1981) and subcortical nucleii projecting to those cortical regions (German et al., 1987). The process disrupts memory presumably by causing loss of synapses and the death of neurons.

1) Telencephalic Systems Affected by AD

Alzheimer pathology is most concentrated in the structures of the temporal lobe, particularly the amygdala, the hippocampus, the entorhinal cortex, and the amygdala (Hirano et al., 1962; Hyman et al., 1984). In the development of AD, the AD process makes its initial appearance in the transitional entorhinal cortex, then spreads to entorhinal cortex, then selective regions of the hippocampus (Braak & Braak, 1991). At a later stage, about the time that there is a transition from mild memory deficits to significant functional impairment, pathology begins to develop in the convexity of the temporal lobe (Bancher et al., 1993). In some cases, dementia develops without significant pathology in the medial temporal lobe structures, but still in association with the lateral distribution. Development of pathology in the neocortex also follows a progression, with successive appearance of disease occurring in the parietal cortex, frontal cortex, and late in the primary cortical regions. Even the occipital cortex, containing the primary and secondary visual cortical regions, shows a gradient of pathological involvement, increasing from the primary visual area 17 to areas 18 and then 19 (Lewis et al., 1987). However, considerable variation occurs between individual cases. Alzheimer pathology can

disproportionately affect one side of the brain or one lobe more in one case than another.

The degree of clinically relevant AD pathology in specific regions of the cortex is indicated most clearly by the concentration of neurofibrillary tangles (Arriagada et al., 1992; Hyman, 1994; Nagy et al., 1995), while plaques, diffuse or neuritic types, are less clearly associated with the severity of the pathology (Braak & Braak, 1991). However, the cortical change most closely associated with cognitive dysfunction is the loss of synapses (Davies et al., 1987), occurring in the temporal (Scheff & Price, 1993), frontal (DeKosky and Scheff, 1990; Scheff et al., 1990; DeKosky et al., 1992), and parietal regions (Terry et al., 1991). Yet, it is not clear whether this association is based on the critical role of these cortical regions in functions which are most clearly measured by cognitive testing in the middle phases of the disease, rather than directly reflecting the global advance of the disease process. In another analysis, atrophy of the hippocampal formation subdivisions corresponds closely to stage (Bobinski et al., 1995) and duration (Jobst et al., 1994) of AD. Since dementia symptoms are highly dependent on premorbid factors such as education and occupational attainment (Stern et al., 1994), and probably numerous other factors, including variation in pathology between cases and in presentation, variability can be expected in the relationship between pathology and function. In the clarification of these relationships, it is important to analyze the time-course of development of the pathological factors (Ashford et al., 1995).

The sequence of appearance of Alzheimer pathology in macroscopic structures is generally consistent with the concept that the principle target of the underlying process of Alzheimer pathology is a neuroplastic mechanism. The hippocampus has been long associated with memory formation (O'Keefe & Nadel, 1978; Squire & Zola-Morgan, 1991; Grady et al., 1995), and the amygdala also plays an important role in learning (Mishkin, 1982). However, the reason why the entorhinal cortex would be the primary site of attack of the Alzheimer process is unclear. Part of the explanation could be that this region is the critical pathway connecting the neocortex to the hippocampus (VanHoesen et al., 1975; Rosene & VanHoesen, 1987) for consolidation of information into long term memory. An important concept in this regard is that information is processed in the neocortex while connections with the medial temporal lobe (in particular, the hippocampus and amygdala) serve to coordinate the encoding of that information in the neocortex (Coburn et al., 1990; Ungerleider, 1995). Thus, processed information is not actually transferred form associative cortical regions to the medial temporal lobe, but reciprocal connections with the medial temporal lobe through the entorhinal cortex serve to initiate and foster the consolidation of information bearing connections in those regions of the convexity of the brain. Accordingly, the transitional region of the entorhinal cortex serves as the critical bridge between the medial and lateral structures during memory consolidation. The major burden of this role potentially explains why the AD process makes its initial appearance in this site. The evolutionary association of the olfactory system with the cortex, especially

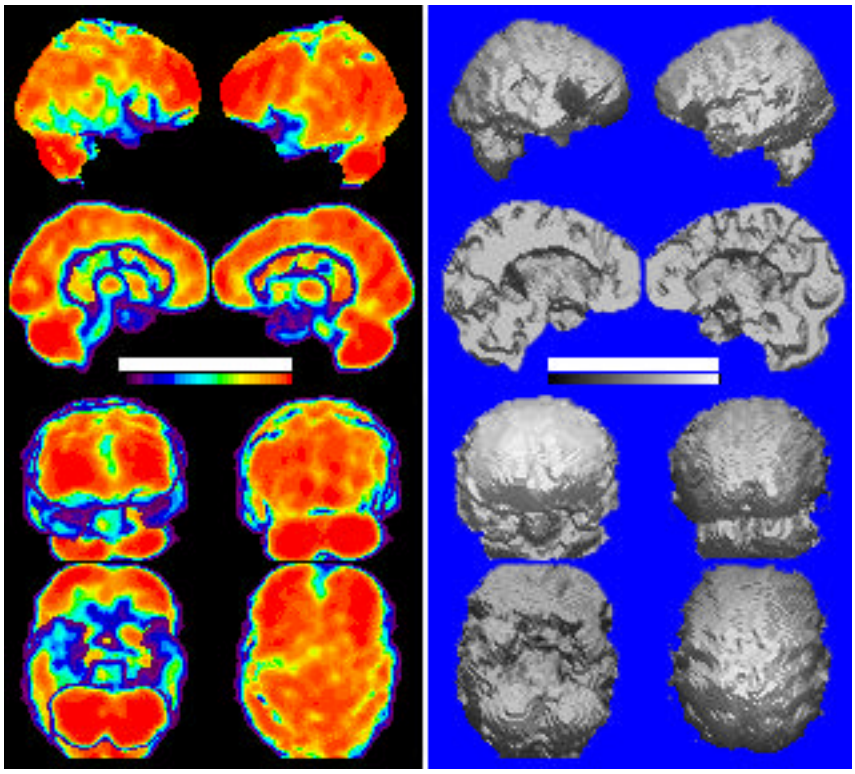
the medial temporal regions involved in memory, may further explain this vulnerability (see below). As AD progresses and information storage continues to be attempted in broadly distributed cortical regions, those regions which are burdened with relatively more storage requirements can be supposed to be affected earlier in the disease course than areas which have lower storage demands.

An important recent development is the field of brain imaging. New techniques are being used to define and track the macroscopic development of AD pathology in the brains of living patients. As noted above, atrophy of the hippocampus (Bobinski et al., 1995; Jobst et al., 1994) accompanies the progression of AD. Loss of metabolism in the temporo-parietal cortex also develops with respect to disease severity (Kuhl et al., 1985). Further, metabolic losses can be traced over time from the temporal to parietal to frontal regions (Jagust et al., 1988; Jagust, 1994). Metabolic loss could be related to a variety of different factors including local loss of neurons to loss of activation by projecting fibers. However, the most parsimonious explanation of loss of local metabolic activity is loss of synapses. Synapse quantity is an indicator of the volume of the neuropil of a cortical region, and maintenance of membrane polarization of axonal and dendritic fibers in the neuropil is the major metabolic demand in the cortex. Loss of neuropil substance will result in a loss of metabolic activity and a resulting loss of blood flow. While not directly reflecting metabolism, the pattern of loss of cerebral blood flow in AD patients resembles the loss of glucose metabolism (Jagust et al., 1990) and does appear similar to the reported distribution of AD pathology in the brain (Figure 1). Both metabolism and blood flow changes can be quantified over time in the living patient. It is now important to link the temporal relationships of the development of pathology in the living patients with the concentration or rate of development of particular components of the cellular pathology, such as neurofibrillary tangles or senile plaques. The development of special ligands applicable for use in living patients for these primary pathologic microscopic structures would help to trace the time-course of their appearance.

FIGURE 1: Cerebral Blood Flow in a Severe AD Patient's Brain

These images of cerebral blood flow were produced from SPECT (Single Photon Emission Computed Tomography) of a 75 year old male with severe Alzheimer's disease (Mini-Mental State Score = 0) who was still able to walk and state his name (testing performed by Cathy Cool, R.N., M.S.N., VA Medical Center, Lexington). The SPECT images were obtained with Neurolite (ECD - ethylene cysteine dimer) which was injected intravenously. The patient was scanned after 30 minutes of resting in a dimly lit room. Scanning was performed with a 3-headed Picker Prism camera for 20 minutes (horizontal detectors every 2mm, 120 angles of acquisition; full-width, half-maximum resolution of 6.7 mm at 10 cm for the technetium tracer). Image data was back projected into a three-dimensional array with voxels 2 mm on a side. (The data array was provided by Dr. Wei-Jen Shih, VA Medical Center, Lexington.) The external surface images were constructed by directing lateral rays toward the brain, thresholding out non-brain structures and seeking local maxima across 3 voxels. The anterior and posterior aspects of the left and right side views were justified with the anterior and posterior images so that these two images (only) did not show tangential diminution of cerebral blood flow activity. (Three-dimensional analysis and imaging program by J.W. Ashford.) The color images on the left show blood flow with red being normal relative to the cerebellum and purple representing severe diminishment of flow. The black and white images on the right are three-dimensionally shaded reconstructions indicating the locations of the cerebral blood flow pixels. The top images represent the left and right lateral views. The bottom row shows the inferior and superior views.

Note that the medial and inferior aspects of the anterior temporal lobe shows the most diminution of blood flow with less decline spreading out over the lateral temporal and parietal lobes. A unique finding in this demonstration is the severe involvement of the entire limbic lobe, including the cingulate and basal frontal cortex. By contrast, aged matched normals show only slight decrease of flow in the limbic structures. Three-dimensional display characterizes the distribution of blood flow more clearly than cross-sectional images using SPECT or PET (Burdette et al., 1995). Further, the distribution of the blood flow decline demonstrated here clearly corresponds to the distribution of pathology seen at autopsy (Brun & Englund, 1981; Braak & Braak, 1991; 1995). This approach provides a means to stage Alzheimer pathology in the living patient.



2) Neurotransmitter systems affected by AD

In recent years, researchers have found that several neurotransmitter systems are selectively disrupted in the brain of Alzheimer patients (Figure 2). The initial discovery of a deficit of choline acetyltransferase (ChAT), an indicator of acetylcholine (ACh) activity, was followed by reports that several other neurotransmitters were also deficient in the Alzheimer brain. However, the only systems that have been found to be consistently disrupted are ACh, serotonin, norepinephrine, glutamate, somatostatin (which colocalizes with GABA and represents a subpopulation of the GABA inhibitory neurons), neuropeptide-Y and vasopressin. No other neurotransmitter systems are consistently reported as significantly diminished in AD, including dopamine, GABA (as a whole), aspartate, and substance-P. In fact, the disruption is so selective that a particular neurotransmitter can be affected when it belongs to one neural system, but not when its neuronal cell bodies belong to a different system or even different cortical projection. The general pattern of disruption of the neurotransmitter systems also provides support for the notion that memory mechanisms are selectively attacked by the AD process. Neurotransmitter disruption may also be reflected to some extent by changes found in the cerebro-spinal fluid. See (Table 2), for a brief synopsis of measures of neurotransmitter losses in AD.

Neurotransmitter receptors are affected by the disease, but not necessarily in direct relation to the disruption of the neurotransmitters. A loss of a particular receptor may reflect loss of the presynaptic activity, while there may be postsynaptic supersensitivity to compensate for the presynaptic loss. Loss in the post-synaptic neuron could reflect additional pathology in the local system. Certain neurotransmitter receptors seem to function as calcium channel gates, such as certain glutamate and nicotinic cholinergic receptors. Pathologic activation of these receptors could allow entry of calcium into the cell and initiate pathological cascades leading to AD pathology. Thus, which neurotransmitter receptors a neuron carries on its dendrites may be more relevant to AD pathological process than which neurotransmitter it releases at its axonal terminals.

FIGURE 2

Neurotransmitter Systems Projecting from Subcortical Regions to the Cortex

These systems project from subcortical regions throughout the cortex. They are: scattered neurons of the nucleus basalis of Meynert in the lateral hypothalamus; the serotonergic system of the midbrain raphe; and the noradrenergic neurons in the rostral locus coeruleus of the pons. These systems are all affected by AD. The dopamine system which extends medial to the substantia nigra projects to the frontal cortex but is generally unaffected by AD.

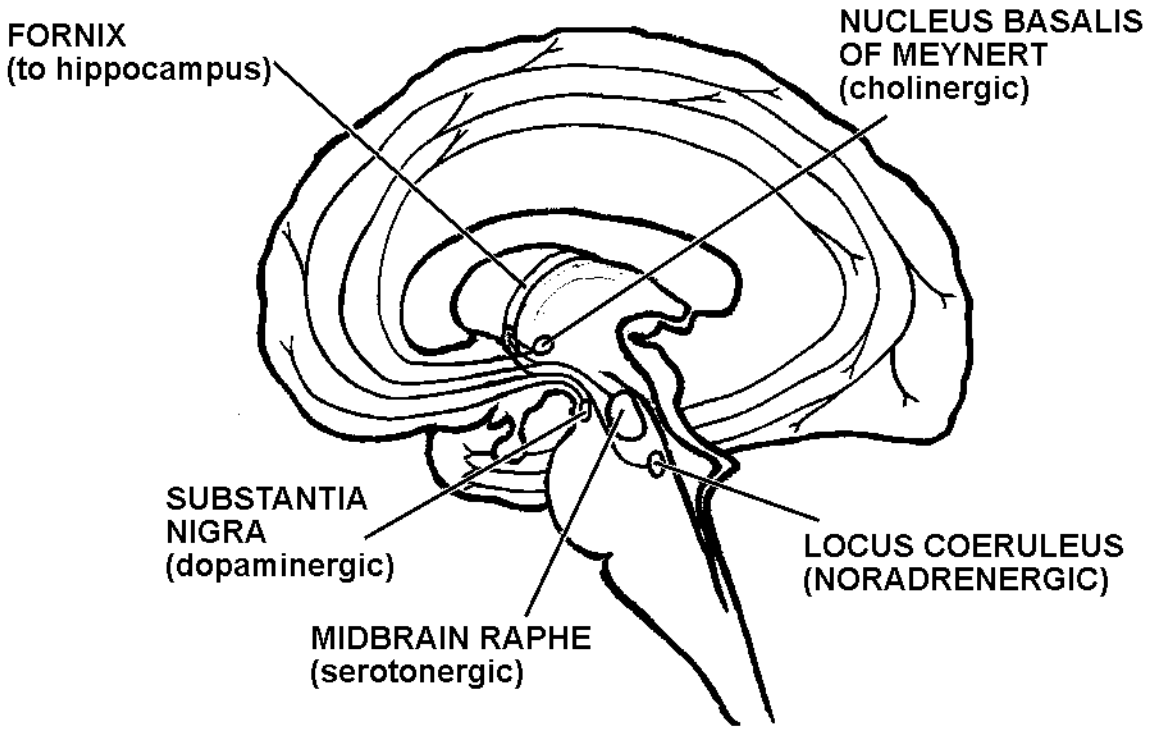


TABLE 2

NEUROTRANSMITTER LOSSES IN AD:
CONCENTRATIONS FROM AD BRAIN AS PERCENT OF CONTROL

	TEMPORAL	FRONTAL	HIPPOCAMPUS	r
ChAT	40	50	50	.6(a);.4(p)
Serotonin	30 (51)	10 (65)	20	.5(a)
Norepinephrine	50 (48)	60 (67)	60	.2(a)
Glutamate	(72)	(ns)	20	
Somatostatin	30 (61)	50 (ns)	40	.3(a);.5(p)
Neuropeptide-Y	30	50	40	
Vasopressin	(ns)	(ns)	70	

Values for temporal and frontal cortex and hippocampus are from autopsy studies.

Only significant changes are listed. ns=not significant.

r=correlation with dementia severity; a=antemortem; p=postmortem.

Values in parentheses () and r-values: from (Francis et al., 1993).

Other values from (Adolfsson et al., 1979; Arai et al., 1992; Beal et al., 1986a; b; Gottfries et al., 1983; Mazurek et al., 1986; Palmer et al., 1986; 1987; Rossor, 1982).

2a) The Cholinergic System

Findings of neurotransmitter changes in the brains of AD patients began in 1976, when three separate laboratories in the United Kingdom (Davies & Malloney, 1976; Bowen et al., 1976; Perry et al., 1977) independently discovered that ChAT is decreased in brains affected by AD, confirming long standing suspicions about a cholinergic deficit in this disease (Bigl et al., 1990). Numerous additional studies have supported the relevance of this finding including:

a) widespread confirmation of the finding (Bartus, et al., 1982);

b) demonstration of a significant relation between a decline of metabolism of ACh in the cortex and dementia (Francis et al., 1985);

c) a selective loss of ACh neurons in the nucleus basalis of Meynert in the basal forebrain (Whitehouse et al., 1982);

d) anatomical demonstration of a relationship between ChAT loss in small cortical regions and loss of projecting acetylcholine nerve groups in the nucleus basalis (Mesulam et al., 1984),

However, there are additional findings which have modified the implications of the ChAT loss (Harrison, 1986):

a) ACh neuron loss is relatively restricted to the nucleus basalis, and little loss of ACh neurons is found among numerous other groups of ACh neurons (Woolf & Butcher; 1990);

b) there is a major loss of brain nicotinic receptors, which are in part likely to be post-synaptic (Sugaya et al., 1990);

c) muscarinic receptors in the cortex are variably affected (Whitehouse & Kellar, 1987);

d) numerous neurotransmitter systems other than ACh are also selectively affected in AD;

e) treatment of AD patients with cholinergic agents has met limited success (Ashford et al., 1989b).

The resulting picture indicates that the group of cholinergic neurons in the basal forebrain which project to the neocortical and medial temporal regions affected by AD are selectively damaged. Pharmacologic disruption of ACh function produces a severe impairment of learning (Drachman, 1977). Selective poisoning of these neurons in animals, including primates, also disrupts learning (Aigner et al., 1987). Therefore the role that the basal forebrain ACh neurons play in memory storage offers an explanation for their vulnerability to the AD process. The affected neurons project long axons to the cortex which ramify extensively within a small region. Numerous substances are transmitted anterogradely in the axon (Steward & Banker, 1992) and other substances, including nerve growth factor (NGF), are transmitted retrogradely. Any of these substances, or aberrant by-products of these substances could put these long, fine fibers at particular risk for clogging, particularly at branch-points and at the terminal ramifications. Disruption of axons in AD prevents retrograde transport of NGF, which is critical for sustaining the cholinergic neuron cell bodies (Scott et al., 1995). However, the mRNA for NGF is

not decreased in the cortex of AD patients (Jette et al., 1994), supporting the premise that it is not lack of NGF which initiates Alzheimer pathology (Woolf & Butcher, 1990).

2b) Other Cortically Projecting Neurotransmitter Systems:

Two other cortically projecting neurotransmitter systems are selectively disrupted by the AD process in a manner similar to the ACh system, the norepinephrine neurons of the locus coeruleus and the raphe neurons of the dorsal and central raphe nuclei. While the specific functions of these neurons are not known, there are substantial conjectures that norepinephrine neurons mediate reward related conditioning which pertains to cortical learning (Gratton & Wise, 1988), and that the serotonin neurons of these nuclei direct sensitization conditioning involving cortical function (Jacobs & Azmitia, 1992; Bailey & Kandel, 1995). Accordingly, there are three cortically projecting neurotransmitter systems which are affected in AD, each of these systems plays a significant role in the learning of new information, and that role may explain the vulnerability of each system to the AD process.

2c) Cortical Neurotransmitter Systems

In the cortex, the preponderance of neurons use the neurotransmitters glutamate and GABA. The glutamate neurons, which are the pyramidal cells, are devastated in regions of the brain affected by AD (Francis et al., 1993). Glutamate is now known as a transmitter which can initiate and regulate process growth in post-synaptic neurons (Mattson et al., 1988; Brewer & Cotman, 1989), and consequently seems to be a critical factor in learning and memory. Glutamate can open NMDA receptor channels which allow Ca++ into the neuron, and Ca++ can initiate several learning related changes in the neuron, but can also cause toxic changes. Some forms of mammalian associative conditioning may depend on interactions between ACh and glutamate in neocortical neurons, including classical conditioning (Woody & Gruen, 1993). The role of glutamate in memory offers an explanation for why this group of neurons is affected by the AD process.

The role of GABA is inhibitory, and it is the GABA neurons which co-localize with the neuropeptide somatostatin which is affected in regions of the brain attacked by the AD process (Bissette & Myers, 1992). However, the role of somatostatin in brain function is unclear as is the reason that this group of neurons is affected in AD.

3) Olfactory vs Connectivity vs Plasticity Theories of AD

The selective distribution of AD pathology in the brain, and particularly, its apparent systematic spread from the entorhinal transitional area (Braak & Braak, 1991), suggests that some mechanism exists whereby the AD pathology can be

transmitted from one group of neurons to another. An early observation in this regard suggested that memory dysfunction was due to the loss of connections between the entorhinal cortex and the hippocampus (Hyman et al., 1984), but this change does not account for the development of similar pathology in numerous other regions of the brain. Another theory suggests that the AD process is transmitted directly from one neuron to another (German et al., 1987; Saper et al., 1987; DeLaCoste & White, 1993), but this theory does not explain why some of the most widely connected systems, including the thalamus, the cerebellum, and the primary cortical regions, are relatively spared by the AD process.

An important line of speculation has invoked the relation between the preferential distribution of AD pathology and the olfactory system (Pearson et al., 1985; Ellison, 1995), noting that many of the regions affected by Alzheimer pathology relate to ancient projections of the olfactory bulb to "rhinencephalic cortex" (Brodal, 1969). One speculation suggested that the nasal epithelium may be infected by a substance which is transmitted to specific regions of the brain, then by certain connections to other regions (Roberts, 1986). This latter theory is not supported by the pathology (Davies et al., 1993) or the symptomatology which indicates that there is more impairment in olfactory recognition than detection (Serby et al., 1991). However, failure of olfactory function, including recollection of odors, occurs early in the disease with inability to detect most scents occurring in the middle phase (Serby et al., 1991). Further, the olfactory bulb is actually quite profoundly affected in AD (Struble & Clark, 1992). Also, specific AD-related pathological changes occur in olfactory neurons (Talamo et al., 1989; Wolozin et al., 1993). Further, the deficits in olfactory function in AD patients, particularly olfactory memory, correlate highly with loss of volume (Kesslak et al., 1991) and metabolism (Buchsbaum et al., 1991) in the medial temporal lobe olfactory regions.

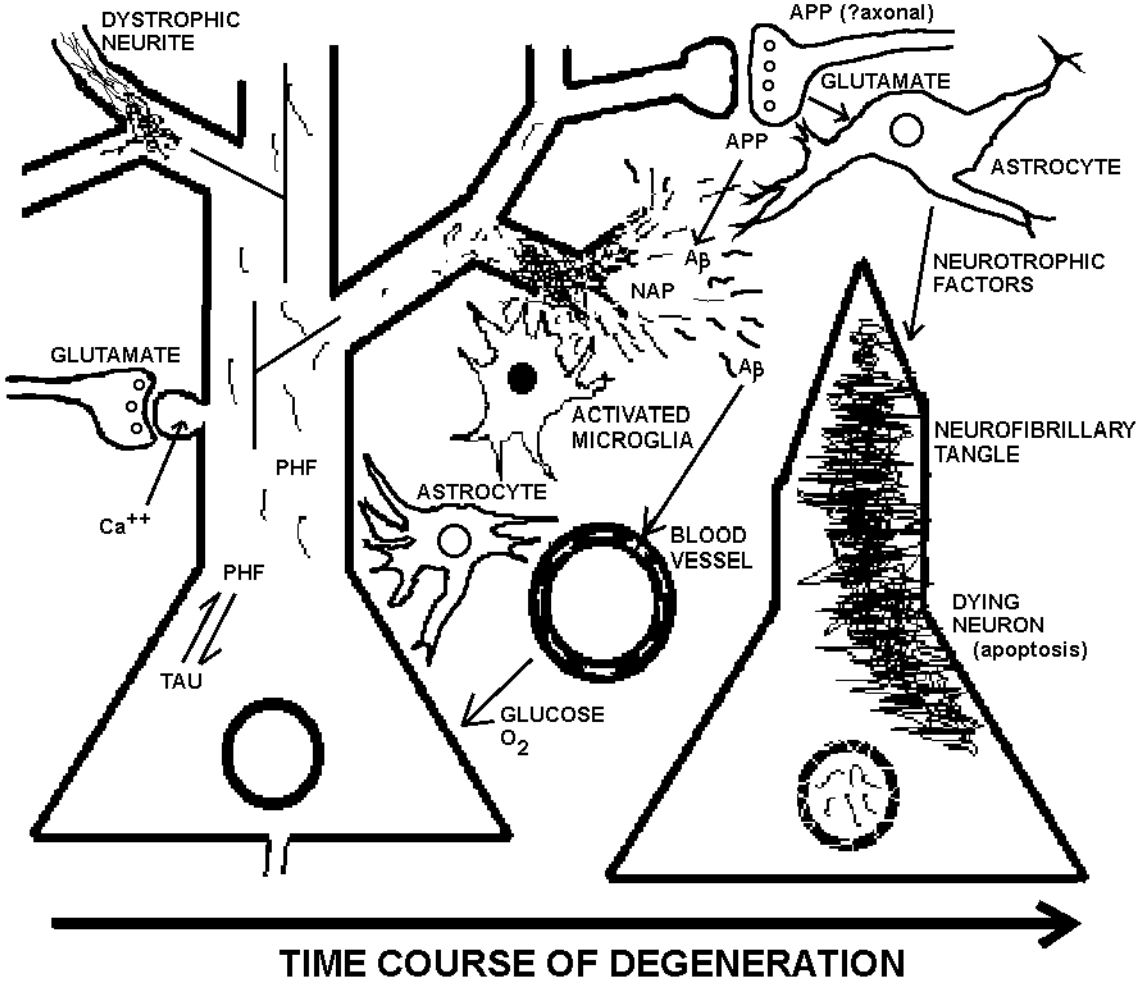
Evolutionarily, the olfactory system played a major role in the development of the cortex (Nauta & Karten, 1970), particularly those regions now associated with learning and memory (Haberly, 1990; Staubli et al., 1995). Olfactory sensation involves a tremendous number of receptors in the olfactory epithelium (Axel, 1995). The olfactory neurons transmit information to the olfactory bulb for a type of analysis, parallel distributed processing, which is similar to the analysis conducted on information by the cortex (Kauer, 1991). Several neurotransmitters are used for this processing including glutamate (Trombley & Shepherd, 1993; Kaba et al., 1994). The mechanism of olfactory memory, requiring a distributed representation of information, is actually the most similar to the mechanism thought to be at play in the storage of information in neocortical association cortex. Therefore, some important mechanism in the olfactory system associated with learning, may explain the vulnerability of the brain to AD. The entorhinal transition cortex, which is first attacked by the AD process, sits in an evolutionary cross-roads from the olfactory system to the archi-cortex (hippocampus), paleocortex (amygdala), and neocortex (Haberly, 1990). This position, with an abundance of plastic connections to numerous regions of the brain (VanHoesen et al., 1975; Rosene & VanHoesen, 1987), may explain its vulnerability to the AD process. Thus, the relationship

between olfaction and AD is consistent with the hypothesis that a plastic mechanism is associated with the vulnerability to AD pathology (Ashford & Jarvik, 1985; Di Patre, 1991), and offers an evolutionary line of investigation to understand that mechanism.

NEUROMOLECULAR MECHANISMS AFFECTED BY AD

There is a clear genetic basis for some forms of AD with mutations in specific genes causing the disease (see Mullan and Crawford, 1993 for review; see also, Matsuyama this volume). Several familial forms of AD arise from mutations in the â-amyloid precursor protein (âAPP) gene, which is located on chromosome 21. The fact that essentially all persons with Down's syndrome (trisomy 21) develop AD pathology emphasizes the importance of chromosome 21 and the âAPP gene in the pathogenesis of AD. Other inherited forms of AD have been linked to mutations on chromosomes 14 and 19. In addition, a "predisposition factor" was recently identified, namely dosage of the apolipoprotein E4 allele (Saunders et al., 1993). Although some forms of AD have a genetic basis the majority of cases of AD are sporadic (i.e., not linked to specific mutations), and the cause(s) of most cases of AD are therefore unknown. The selective vulnerability of particular brain regions and neuronal populations in AD and the pattern of progression of the neurodegenerative process provide both an explanation for the symptoms of the disease and clues to the cellular and molecular basis of the neurodegenerative process. Specific groups of neurons in the entorhinal cortex (layer 2 cells) and hippocampus (CA1 pyramidal neurons) are among the first to degenerate (Braak & Braak, 1991). Other brain regions heavily involved in AD pathology include superior and middle temporal gyri, inferior parietal cortex and multiple association cortices, while relatively non-vulnerable regions include the cerebellum and primary sensory and motor cortices. Several hypotheses have been forwarded to account for the neurodegenerative process in AD. Several of the most prominent hypotheses concerning vulnerability at the cellular level are probably correct and collectively provide an integrated view of the molecular and cellular bases of the neurodegenerative process in AD (Figure 3).

FIGURE 3 Model of Neuromolecular Progression of AD
In this model, glutamate activation of dendritic spines of highly plastic neurons causes entry of Ca++, which plays a role in the induction of excess phosphorylation of tau and allows transformation of tau into PHF's. The PHF's accumulate in dendritic segments at some distance from the soma to form dystrophic neurites. These PHF deposits clog the dendrites, especially at branch points. With disruption of dendritic flow, portions of the dendrite distal to the soma lose their integrity, releasing their contents, including normal tau and PHF's, into extracellular space. APP may be axonally transported to terminal fields. If APP is abnormally released, it may be aberrantly transformed into Aß, which can accumulate in the neuritic plaque (NAP). In the region of the dendrite break, extracellular PHF and Aß forms amyloid cores which are surrounded by activated microglia. Under normal circumstances, astrocytes can keep Ca++ concentrations at non-toxic levels, absorb glutamate, and provide neurotrophic factors to axons and dendrites. When the Alzheimer state develops, excess neurotrophic activity amy stimulate excess APP production, which may be transformed into Aß, which can cause additional toxicity before being transported to blood vessel walls. As PHF production increases due to the stress on the neuron and accumulates, a neurofibrillary tangle is formed in the cell soma. As a late event, the cell becomes apoptotic and dies.



1) The 'Amyloid' Hypothesis:

Investigations of the molecular and cellular biology of âAPP have yielded information vital to our current understanding of the pathogenesis of AD (see Selkoe, 1993; Mattson et al., 1993a for review). A hallmark histopathological feature of AD brain is the accumulation of amyloid plaques which are often associated with degenerating neurons. The plaques are comprised of amyloid â-peptide (Aâ), a 40-42 amino acid fragment of the âAPP-amyloid precursor protein (âAPP). âAPP is widely expressed in the brain with both neurons and astrocytes being major cellular sources. âAPP can be enzymatically processed in two major ways, one of which involves a cleavage within the Aâ sequence liberating secreted forms of âAPP (sAPP) from the cell surface and precluding release of amyloidogenic Aâ. The other cleavage results in release of Aâ; Aâ is normally produced in low amounts and circulates at nanomolar concentrations in CSF and blood. A striking property of Aâ is its ability to rapidly aggregate and form fibrils with â-sheet structure. Mutations in âAPP that cause some forms of AD may alter processing of âAPP such that increased amounts of Aâ are produced, or these mutations may cause Aâ to aggregate more readily. A causal role for Aâ in the neurodegenerative process in AD is suggested from experimental studies showing that Aâ can be neurotoxic and can increase neuronal vulnerability to excitotoxicity and energy deprivation (see Mattson et al., 1993a for review). Specific mechanisms whereby Aâ damages neurons have been elucidated. Aâ itself can generate free radicals by a mechanism involving interaction of specific amino acids with molecular oxygen (Hensley et al., 1994); these peptide-derived radicals may play a central role in the covalent cross-linking of the peptide. Aâ accumulates at the plasma membrane where it induces free radical production and lipid peroxidation (Mattson et al., 1993a; Goodman and Mattson, 1994). Lipid peroxidation results in dysfunction of membrane ion-motive ATPases (sodium and calcium pumps) resulting in disruption of ion homeostasis membrane depolarization and elevation of intracellular calcium levels (Mark et al., 1995). Both calcium and free radicals contribute to damage to proteins, lipids and DNA and eventual cell death. Lower subtoxic levels of Aâ can severely disrupt signal transduction mechanisms and render neurons exquisitely vulnerable to metabolic perturbations.

The role of Aâ in AD has been questioned since this substance is a frequent concomitant of aging, but its concentration has not been related to the severity of Alzheimer dementia or pathology (Arriagada et al., 1992), and in rare cases, AD has been diagnosed histopathologically in the absence of Aâ. Consequently, Aâ may be considered a major factor in the initiation of AD, but not a sufficient factor for pathogenesis (Selkoe, 1994). The stress of Aâ may be manifest most significantly on those cells that have the greatest memory-related metabolic demands. The toxicity of this normally present substance may exert its deleterious effect over long periods of time and serve as a factor which induces neurofibrillary change, and the consequent loss of cell processes and synapses. Curiously, Aâ levels are decreased in the CSF of AD patients (Motter et al., 1995; vanGool et al., 1995).

2) The Tau Hypothesis:

The microtubule associated protein tau seems to play a central role in AD (Trojanowski & Lee, 1995). This protein becomes aberrantly phosphorylated early in the pathologic process in dystrophic neurites, which then serves to form the backbone for the PHF's which turn into NFT's in the neuronal cell bodies. Why this aberrant phosphorylation occurs is unknown, but the critical problem could be a failure of dephosphorylation. Formation of the PHF's in neuronal processes could obstruct normal flow through axons and dendrites, serving to eliminate all parts of the process distal to the cell body from the obstruction. The most vulnerable location for an obstruction to occur would be at a dendritic or axonal branch point. Those parts of the cell process distal to the obstruction would become extravasated material, which could induce the formation of amyloid and plaques, with local attempts to regrow from the neuritic stump serving to produce the abnormal neurites in these structures (Geddes et al., 1985; 1986; Geddes & Cotman, 1991). In support of the concept of neuronal process breakage with extravasation of intracellular contents, several recent studies have found an elevation of tau in the CSF of AD patients (Arai et al., 1995; Hock et al., 1995; Mori et al., 1995; Tato et al., 1995; Vigo-Pelfrey et al., 1995; Jensen et al., 1995).

3) The Apo-lipoprotein-E Hypothesis:

Apo-lipoprotein-E alleles have been shown to have a relationship with AD (Roses, 1994). The mechanism of interaction between this protein and AD pathology is not yet clear, but at least three mechanisms are possible. This protein could support peripheral vascular pathology which instigates AD. Alternatively, the Apo-E could work as a chaperon protein for amyloid or tau, with inadequate removal from normal turnover leading the development of the AD pathology.

4) The Immune Hypothesis:

The immune system also appears to be intimately involved in pathological processes occurring in the brain in AD. Several studies have found an elevation of immunoglobins in serum (Cohen & Eisdorfer, 1980; Kumar et al., 1988) and CSF (McRae-Degueurce et al., 1987) of AD patients. Infiltration of microglia in the vicinity of amyloid plaques (Sadowski et al., 1995), and the recent reports of reduced incidence of AD in patients receiving chronic treatment with anti-inflammatory drugs further supports a central role for an immune response in AD (Breitner et al., 1995). It is unclear if this response could initiate or exacerbate the pathology.

5) The Metabolic Hypothesis:

A well-documented alteration in the brain of patients with AD is reduced glucose metabolism (Kuhl et al., 1987; Hoyer et al., 1988; Small et al., 1995; Burdette et al., 1996). Five possible causes of the reduced glucose uptake into brain cells are; 1) vascular alterations resulting in hypoperfusion; 2) decreased glucose uptake across the blood-brain barrier; 3) impaired glucose transport within neurons themselves; 4) a defect in energy metabolism (Beal, 1992; 1995); and 5) decreased demand for glucose due to diminished neuron surface membrane associated with loss of cell processes. Reduced energy availability (possible causes 1-4) would place neurons at risk because ATP is required to maintain ion homeostasis. Accordingly, reduced glucose availability to neurons would increase their vulnerability to glutamate excitotoxicity and Aâ toxicity (see below). This hypothesis predicts that neurons expressing high levels of glutamate receptors and/or exposed to high levels of Aâ would be expected to be particularly vulnerable in AD and, that larger neurons with a higher metabolic demand would also be more vulnerable. In this regard the metabolic hypothesis is supported by the fact that vulnerable neurons tend to be large and express high levels of glutamate receptors. Since neurons with high levels of glutamate receptors are likely to be more involved with information storage, and the production of new processes places a major metabolic load on neurons, the metabolic hypothesis also supports the central role of neuroplasticity in the vulnerability to the AD process.

6) The Free 'Radical' Hypothesis:

Considerable data indicate that free radical injury plays a major role in the damage to neurons in AD (Friedlich & Butcher, 1994). Levels of protein oxidation, DNA damage, and lipid peroxidation are increased in vulnerable regions of AD brain such as the hippocampus. The causes of radical accumulation in AD are likely multifold and may include: reduced energy availability due to circulatory alterations (see below); Aâ deposition; and formation of advanced glycation end products (Yan et al., 1994; see Benzi & Moretti, 1995 for review). Aâ has been shown to induce lipid peroxidation and accumulation of cellular peroxides in cultured neurons, as well as in synaptosomes (Butterfield et al., 1994; Goodman & Mattson, 1994; Hensley et al., 1994). Generation of free radicals in response to Aâ appears to be an early event in the neurodegenerative process that occurs prior to disruption of ion homeostasis. As described above, disruption of ion homeostasis by Aâ results from free radical damage to ion-motive ATPases (Mark et al., 1995). Trace elements are also implicated as inducers of free radical production in AD. Levels of both aluminum and iron are increased in neurofibrillary tangles. Iron damages neurons by inducing hydroxyl radical production via the Fenton reaction. Although most iron in the brain is normally in a bound (innocuous) form, it is conceivable that increased levels of free iron occur in AD and contribute to the neurodegenerative process.

7) The 'Calcium' Hypothesis:

Prolonged elevation of $[Ca^{2+}]_i$ can damage and kill neurons (Mattson, 1992). Studies of both acute neurodegenerative conditions (e.g., stroke and traumatic brain injury), and chronic neurodegenerative disorders including AD suggest that elevation of $[Ca^{2+}]_i$ is a final common pathway in the neurodegenerative process. Conditions believed to occur in AD brain result in elevation of neuronal $[Ca^{2+}]_i$ in experimental paradigms. For example, reduced energy availability (glucose deprivation and hypoxia) results in elevation of $[Ca^{2+}]_i$ which precedes cell degeneration in cultured neurons, and Aâ induces an elevation of rest $[Ca^{2+}]_i$ and potentiates $[Ca^{2+}]_i$ responses to glutamate (Mattson et al., 1993a). Studies of postmortem tissue from AD patients and age-matched controls suggest altered calcium homeostasis in AD. For example, Ca^{2+}-ATPase activity was reduced in synaptosomes from vulnerable regions of AD brain and Aâ impaired Na^+/K^+-ATPase and Ca^{2+}-ATPase activities in hippocampal synaptosomes from neurological normal individuals (see Mark et al., 1995). Differential expression of components of the $[Ca^{2+}]_i$-regulating systems in neurons may contribute to the pattern of selective neuronal vulnerability in AD. For example, neurons expressing the calcium binding protein calbindin may be resistant to Ca^{2+}-mediated injury, whereas neurons expressing high levels of NMDA glutamate receptors (a voltage- and ligand-regulated calcium channel) may be particularly vulnerable. Prolonged elevation of $[Ca^{2+}]_i$ results in damage to proteins, lipids and DNA. This damage is mediated largely by proteases and free radicals.

8) The 'Excitotoxicity' Hypothesis:

Many studies have shown that glutamate, the major excitatory neurotransmitter in the brain, is capable of damaging and killing neurons when energy levels are reduced or when neurons are exposed to Aâ. Exposure of cultured brain cells or adult rat brain to excitatory amino acids results in alterations in the neuronal cytoskeleton similar to those seen in AD (Mattson, 1990; Stein-Behrens et al., 1994). Epidemiological data also support the excitotoxic hypothesis. For example, domoic acid intoxication in a group of Canadians that ingested shellfish containing high concentrations of this excitotoxin resulted in memory loss and massive accumulation of neurofibrillary tangles (Zattore, 1990). A compelling aspect of the excitotoxicity hypothesis is its links with other hypotheses of AD. For example, glutamate induces accumulation of calcium and free radicals in neurons, metabolic impairment increases the vulnerability of neurons to excitotoxicity (Beal, 1992), and neurons vulnerable in AD bear high levels of glutamate receptors.

9) The Neurotrophic Factor Hypothesis:

Many studies have shown that neurotrophic factors, endogenous proteins in the brain that promote neuron survival, can protect neurons against many insults relevant to AD including glutamate, Aâ, and metabolic insults (see Mattson et al., 1993b for review). Included among such neurotrophic factors are basic fibroblast growth factor, brain-derived neurotrophic factor, and transforming growth factor-â. As noted above, NGF production is not diminished in the cortex of AD patients, but its lack of transport to the nucleus basalis of Meynert may be largely responsible for the death of cholinergic neurons in that structure.

10) The Steroid Hypotheses:

Steroid hormones also might play a role in the pathogenesis of AD. The evidence is strongest for glucocorticoids and estrogens. Glucocorticoids, the "stress steroids", have been shown to increase neuronal vulnerability to a variety of insults including excitotoxins and ischemic conditions (Stein-Behrens et al., 1994; Smith-Swintosky et al., 1995). Alterations in function of the neuroendocrine system controlling glucocorticoid production has been documented in AD patients. Postmenopausal women receiving estrogen replacement therapy have a reduced risk of developing AD (Henderson et al., 1994). In addition, estrogens have been shown to have antioxidant activity and may protect neurons against free radical damage (Goodman et al., 1996).

11) The Vascular Hypothesis:

Alterations in the vasculature may also contribute to AD. Aâ is deposited in blood vessels and numerous studies have documented alterations in the cerebral microvasculature in AD. The recent link between apolipoprotein E4 allele dosage and age of onset of AD bolsters a role for vascular alterations in AD because the E4 allele also increases risk of atherosclerosis. Small emboli may cause transient episodes of ischemia which could initiate a local onset AD pathology, particularly in regions of vascular vulnerability such as the medial temporal lobe.

12) The Peripheral Medical Factor Hypotheses:

There has been a broad search for peripheral diseases and medical conditions which might be associated with AD. For the most part, AD patients are generally no less healthy than age matched controls (Wolf-Klein et al., 1988; McCormick et al., 1994), though poor health may accelerate cognitive decline (Teri et al., 1990). However, there are certain conditions which have weak associations with AD, such as head trauma, cardiovascular disease, thyroid disease, and menopause. These conditions each put stresses on the neurons of the brain.

In neural trauma, connections between neurons are sheared and neuroplastic mechanism must be taxed to reestablish functional connectivity.

Hypoxic injury to the brain which allows the survival of a significant portion of the neurons, will still severely tax the capacity of the surviving neurons to reestablish a functioning neural network.

Thyroid hormone itself plays a role in the normal development of neuronal processes, which are associated with neuroplastic mechanisms. Low thyroid levels may stress dendritic arbors. Excess thyroid hormone may stimulate aberrant sprouting (Woolf & Butcher, 1990).

Other conditions such as peripheral amyloid deposits (Joachim et al., 1989) or calcium metabolism irregularities (Landfield et al., 1991), are medically benign, but may indicate that the affected individual may have a central vulnerability. Serum from elderly individuals and AD patients has been shown to stimulate Alzheimer-like changes in hippocampal neurons in culture (Brewer & Ashford, 1992). This finding supports a role for peripheral factors to play a causative role in AD pathology in the brain, including Apo-E dysfunction, through induction of vascular changes, and immunologic factors which could be initiated through temporary breaks in the blood-brain barrier.

13) Multivalent Cation Toxicity Theories:

There has been considerable speculation that aluminum or some other element may contribute to the development of AD. At this time, the evidence for a primary etiologic role for aluminum remains inconclusive (Lovell et al., 1993; Harrington et al., 1994; Forbes et al., 1994). However, the affinity of the AD pathological changes for the divalent silver cations leaves open the possibility that similar ions such as aluminum could interfere with the metabolism of those proteins whose disconformation leads to the AD pathology (Bertholf, 1987; Shin et al., 1994; Trojanowski & Lee, 1995). Similarly, there is weak evidence for roles for divalent cations such as mercury, zinc, and iron. Iron and aluminum are free-radical catalysts which may facilitate aggregration of Aâ into amyloid (Friedlich & Butcher, 1994). The calcium hypothesis, the role of zinc in the hippocampus, and the affinity of the AD pathologic structures for silver continues to sustain interest in a possible role for multivalent cations in AD.

SUMMATION

It can be appreciated, even from this brief discussion of the cellular and molecular underpinnings of AD, that the different hypotheses of AD are integrative in nature (Beal, 1995). For example, the fact that energy deprivation destabilizes neuronal calcium homeostasis and renders neurons vulnerable to excitotoxic insults and Aâ links the calcium and metabolic hypotheses. The interactive, and often synergistic, effects of calcium and free radical-generating systems make calcium a key component of the free radical hypothesis. The ability of neurotrophic factors to stabilize $[Ca^{2+}]_i$ and protect neurons against excitotoxicity, metabolic insults, and Aâ toxicity emphasizes the importance of $[Ca^{2+}]_i$-regulating systems in the mechanism of neurotrophic factor action. The vascular and hormonal hypotheses are also closely tied with the other hypotheses described above. Free radicals and calcium appear to be convergence points for the different hypotheses. There is an important need to ascertain changes in these neuromolecular systems, particularly those associated with neuroplasticity, with respect to the clinical progression of AD, in order to focus on the most relevant factors associated with the development of the disease. Clearly, fundamental knowledge of cellular and molecular mechanisms of neuronal degeneration in AD are providing a large number of preventative and therapeutic strategies for this devastating neurodegenerative disorder.

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