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Abnormalities of mitochondrial enzymes in Alzheimer disease

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Summary. Abundant evidence, including critical information gathered by Prof. Siegfried Hoyer and his colleagues, indicates that abnormalities of cerebral metabolism are common in neurodegenerative diseases, including Alzheimer's Disease (AD). Alterations in mitochondrial enzymes likely underlie these deficits. Replicable reductions in AD brain occur in the pyruvate dehydrogenase complex (the link of glycolysis to the Kreb's cycle), the α-ketoglutarate dehydrogenase complex (KGDHC; the link of Kreb's cycle to glutamate metabolism) and cytochrome oxidase (the link of the Kreb's cycle to oxygen utilization). Available evidence suggests that deficiencies in KGDHC may be genetic in some cases, whereas evidence that the other two enzyme systems have a genetic component is lacking. Additional results indicate that the reductions can also be secondary to other causes including oxidative stress. A variety of data suggest that the mitochondrial insufficiencies contribute significantly to the pathophysiology of AD.

Keywords: Alzheimer's disease, mitochondria, α-ketoglutarate dehydrogenase, cytochrome oxidase, pyruvate dehydrogenase, neurodegenerative disease.

Introduction

Extensive evidence gathered over the last 50 years and reviewed elsewhere (Blass, 1993a,b, 1997) indicates that the rate of cerebral metabolism is reduced in Alzheimer's Disease (AD). Decreased cerebral metabolism precedes the development of clinical (neuropsychological) or neuroanatomic (imaging) evidence of the disease. These data were gathered by PET scanning of subjects whose familial and/or APOE status put them at very high risk to develop AD (Reiman et al., 1996; Small et al., 1995). Hoyer and colleagues (Baur et al., 1997; Blum-Degen et al., 1995; Hoyer, 1996, 1997) have shown that alterations in the pattern of substrates metabolized by brain accompany the very earliest clinical signs of AD (Hoyer, 1996, 1997). These deficits in brain

metabolism are likely to be important to diminished brain function since treatment with glucose causes a statistically significant improvement in mentation, as measured by neuropsychological testing, in patients with AD but not in non-AD controls (Craft et al., 1992; Manning et al., 1993). Four lines of evidence suggest that alterations in mitochondrial enzymes underlie these deficits:

- Measurements of mitochondrial enzyme activities indicate inherent damage to mitochondria in AD brain (Perry et al., 1980; Sorbi et al., 1983; Yates et al., 1990; Butterworth and Besnard, 1990; Gibson et al., 1988; Mastrogiacomo et al., 1994; Chandrasekaran et al., 1996; Kish et al., 1992; Simonian and Hyman, 1994). The mitochondrial enzyme complexes for which this point has been studied in detail include the α-ketoglutarate dehydrogenase complex (KGDHC), the pyruvate dehydrogenase complex (PDHC), and cytochrome oxidase (COX).
- Two approaches indicate that genetic abnormalities in these enzymes may underlie their reduction in Alzheimer brain. Molecular genetic studies document an association between AD and a gene, DLST, which encodes a critical component of the KGDHC complex (Ali et al., 1994; Sheu et al., 1996, 1997, 1998a; Nakano et al., 1994, 1997). Changes in COX persist following transfer of mitochondrial DNA from Alzheimer patient platelets to neuroblastoma cells depleted of endogenous mtDNA (Swerdlow et al., 1997), although this is not necessarily evidence of changes in the mitochondrial CO1 and CO2 genes encoding components of COX.
- These enzymes can also change secondarily to other pathologic events in AD, including oxidative stress. Evidence suggests that this secondary reduction may be part of a critical cascade of events that lead to neurodegeneration.
- Interference with these enzymes can be readily related to the pathophysiology of AD.

1. Activities of specific mitochondrial enzyme complexes are reduced in AD

Deficient activities of three mitochondrial enzyme complexes have been reported in AD: cytochrome oxidase (COX), the pyruvate dehydrogenase complex (PDHC), and the α-ketoglutarate dehydrogenase complex (KGDHC). Normal activities have been found for several other mitochondrial enzymes, including fumarase [a component of the Krebs tricarboxylic acid cycle (Sorbi et al., 1983)], glutamate dehydrogenase [an enzyme coupling glutamate to KGDHC (Gibson et al., 1988)] and components of the electron transport chain such as COX (Kish et al., 1992; Simonian and Hyman, 1994).

COX is complex IV of the mitochondrial electron transport chain, the component of the electron transport chain which interacts directly with molecular oxygen. Kish et al. (1992) that COX activity declined moderately in cerebral cortex of 29 AD patients compared to 29 control subjects. COX in cerebral cortex was reduced by 16–26% in the AD group. COX activity in AD has been reported to be modestly reduced in 9 independent studies ($p < 0.05$ in

5), since the original report (see Kish, 1997 for a detailed discussion). Deficiency of COX has been described in both severely and less severely histologically affected areas of brain (Chandrasekaran et al., 1996; Kish et al., 1992; Simonian and Hyman, 1994). The extent and region of the reductions vary among reports. For example, some (Wong-Riley et al., 1997), but not other (Simonian and Hyman, 1994) studies find differences in visual cortex. The pattern of down-regulation for both mitochondrial and nuclear gene expression coding for subunits of COX in the AD brain resembles those in normal brain caused by chronic sensory deprivation (Chandrasekaran et al., 1996). Thus, the results suggest a generalized suppression of oxidative metabolism throughout the cortex (Wong-Riley et al., 1997) and appear to reflect physiological down regulation of COX gene expression (Chandrasekaran et al., 1996). Physiological down-regulation of COX gene expression in AD is consistent with PET evidence that cognitive or psychophysical activation of mildly to moderately demented Alzheimer's patients can augment brain-blood flow and glucose metabolism to the same extent as in control subjects (Chandrasekaran et al., 1996). Evidence that oxidative metabolism can be rapidly activated is also provided by studies showing that glucose causes significant improvement in mentation in AD (Craft et al., 1992; Manning et al., 1993). Nevertheless, some reports suggest that COX structure may be modified in AD; COX purified from AD brain showed a loss of one of the two kinetically identifiable sites for reduced cytochrome c (Parker and Parks, 1995).

Persistence of AD-related deficits in non-neuronal tissues suggest that the abnormalities are not just secondary to neurodegeneration, and that they reflect constitutive properties of the cells. Deficiency of COX activity in platelets has been reported (Parker et al., 1990) and disputed (VanZuylen et al., 1992). Fibroblasts from AD patients display decreased COX activity ($P < 0.05$; Curti et al., 1997), whereas lymphocytes do not have altered activities (Molina et al., 1997).

PDHC catalyzes the reaction by which pyruvate (usually derived from glucose) is converted to acetyl-CoA which then enters the Krebs tricarboxylic acid cycle (Sorbi et al., 1983). This large multi-enzyme complex is composed of three major and two minor protein components (Sorbi et al., 1983). Deficiency of PDHC activity has been documented in AD brain, in at least four independent laboratories (Sorbi et al., 1983; Perry et al., 1980; Yates et al., 1990; Butterworth and Besnard, 1990) with no contravening reports. The enzyme is deficient in both histologically affected and histologically unaffected areas of brain (Sorbi et al., 1983). However, repeated studies under a number of different experimental conditions have not shown reliable deficiencies in PDHC in non-neural tissues, and specifically none in cultured AD skin fibroblasts (Blass, unpublished results). Nor have preliminary studies demonstrated any evidence for an association between AD and genes encoding components of the PDHC complex (Blass, unpublished results). Thus, available evidence does not argue for a primary genetic abnormality in PDHC in an appreciable proportion of patients with AD.

KGDHC catalyzes a critical reaction within the Krebs tricarboxylic acid cycle, namely the oxidation of α-ketoglutarate to succinyl-CoA (Blass,

1993a,b, 1997; Gibson et al., 1988). KGDHC is also an important enzyme in glutamate metabolism, since α-ketoglutarate is readily interconverted with glutamic acid by transamination and is the product of glutamate oxidation by the glutamate dehydrogenase catalyzed reaction (Blass, 1997). KGDHC, like PDHC, is a large multi-enzyme complex with three major protein components. In KGDHC, these are E1k, E2k, and E3. E1k is α-ketoglutarate dehydrogenase, which is encoded on the OGDH gene on chromosome 7p13–p11 (Szabo et al., 1994). E2k is dihydrolipoyl succinyltransferase, and is encoded on the DLST gene on chromosome 14q24.3 (Ali et al., 1994; Nakano et al., 1994). E3 is dihydrolipoamide dehydrogenase and is a common component of the PDHC and KGDHC dehydrogenase complexes. It is encoded by the DLD gene on chromosome 7q31–q32 (Scherer et al., 1991).

KGDHC activity is reduced in AD brain, in both histopathologically affected and histopathologically unaffected areas of brain (Gibson et al., 1988; Mastrogiacomo et al., 1994; Butterworth and Besnard, 1990). This finding, originally reported by our group at Burke (Gibson et al., 1988), is robust. It has been replicated independently in at least two other laboratories (Mastrogiacomo et al., 1994; Butterworth and Besnard, 1990) as well as in several independent studies in this laboratory; there are no contravening reports. To determine whether the reduction in brain KGDHC activity in AD is associated with an abnormality in one of its three constituent enzyme subunits, Kish and coworkers measured the protein levels of E1k, E2k and E3 in postmortem brains of 29 patients with AD (mean age, 73 years; age range of onset, 50–78 years) and 29 control subjects (Mastrogiacomo et al., 1996). In the AD group protein levels of all three subunits were significantly reduced by 23 to 41% in the temporal cortex, whereas in the parietal cortex (E1: −28%; E3: −32%) and hippocampus (E3: −33%) significant changes were limited to E1k and E3. KGDHC activities were more markedly reduced (by 46–68%) and did not correlate with protein levels, suggesting that decreased enzyme activity cannot be directly explained by loss of KGDHC protein.

Activity of KGDHC has also been found to be reduced in cultured skin fibroblasts from "sporadic" patients with AD (Blass et al., 1997a,b) and in some (Sheu et al., 1994) but not all (Blass et al., 1997a) patients with presenilin-1 mutations. Two groups have found reduced oxidation of [U^{14}C]glutamine to $^{14}CO_2$ in AD compared to non-AD control cultured skin fibroblasts (Sims et al., 1987; Peterson and Goldman, 1986). The reduced oxidation of glutamine in AD cells is also consistent with a functional block in KGDHC, since glutamine rapidly converts to glutamate which is readily converted to α-ketoglutarate by either transamination or the glutamate dehydrogenase catalyzed reaction (Blass, 1993a,b, 1997). However, the oxidation of [^{14}C]-ketoglutarate does not vary between control and AD cells, nor does amino acid metabolism as measured by the incorporation of $^{13}NH_3$ into relevant amino acids, in cultured AD fibroblasts (Cooper et al., 1996).

Thus, the data that reductions in the activities of these key enzymes occur in AD brain occur and that such decreases could underlie the reduced metabolism in vivo are strong and replicable. Superficially, studies of biopsy brain from living patients are difficult to reconcile with this data. For instance,

pyruvate/malate-dependent oxygen consumption, measured directly with an O_2 electrode in homogenates of freshly biopsied frontal neocortex in AD and non-AD human brain under carefully standardized conditions, is not decreased either with or without ADP or in the presence of CCCP, which uncouples oxidation from phosphorylation (ATP production) (Sims et al., 1987b). These results indicate that rates of PDHC and oxygen utilization by COX can be normal in AD brain, at least under the saturating conditions used in these experiments. In earlier studies, the rate of conversion of [U-^{14}C]glucose by slices of biopsied AD brain was 39% higher compared to controls (Sims et al., 1981, 1983). This result is consistent with a lack of functional control on pyruvate oxidation, as suggested by the studies of the human brain homogenates (Sims et al., 1987a,b). Thus, the biopsy studies suggest that neither PDHC nor COX are limiting in AD brain.

The apparent contradiction between reduced activities of PDHC and COX in AD brain at autopsy but normal or increased oxidation of pyruvate or glucose in the ex vivo experiments suggests that different phenomena are being measured in the two types of studies. The measurements in autopsy brain were of total enzymatic activity under conditions where mitochondria had been disrupted and mitochondrial control mechanisms were therefore lost. In those studies, the deficiency in PDHC activity in AD brain appeared to be associated with a reduced amount of immunochemically normal enzyme complex (Sheu et al., 1985). The majority of the data on the deficiency of COX suggests that it is associated with down-regulation of this complex (see above). The measurements of enzyme activity are therefore compatible with a reduction (i) in the number of mitochondria, (ii) in the amount of PDHC and/or COX per mitochondrion, or (iii) with a reduction in PDHC and COX activity in a subgroup of damaged mitochondria (e.g., from damaged cells). The normal values for maximal (CCCP-stimulated) O_2 uptake in AD brain in the ex vivo studies argue against a dramatic reduction in the number of mitochondria in these patient samples, although other explanations are possible. Possibly, oxygen uptake measured under the conditions of these experiments was carried out by mitochondria which were largely intact in AD brain. The mitochondria in the human brain microslices derive essentially from synaptosomes (Sims et al., 1981), and different populations of brain mitochondria can have strikingly different compositions (Westergaard et al., 1995), creating an experimental difference between the autopsy and biopsy studies. Another possibility is that in the intact AD mitochondria in the homogenates studied in the ex vivo experiments, the rate of oxidation was limited not by the PDHC or COX activities but by as yet unspecified control mechanisms or perhaps by later steps in the Krebs cycle, such as that catalyzed by KGDHC (Blass, 1993a,b). Further experiments to explore these issues have been hindered by a lack of biopsy material from AD and control patients.

The quantitative relationships among these enzymes in normal human frontal cortex and in AD are shown in Fig. 1. Choline acetyltransferase, the synthetic enzyme for acetylcholine which is known to be diminished in AD brain, is shown as a reference. Figure 1A shows that the activities of the dehydrogenase complexes are an order of magnitude or more lower than

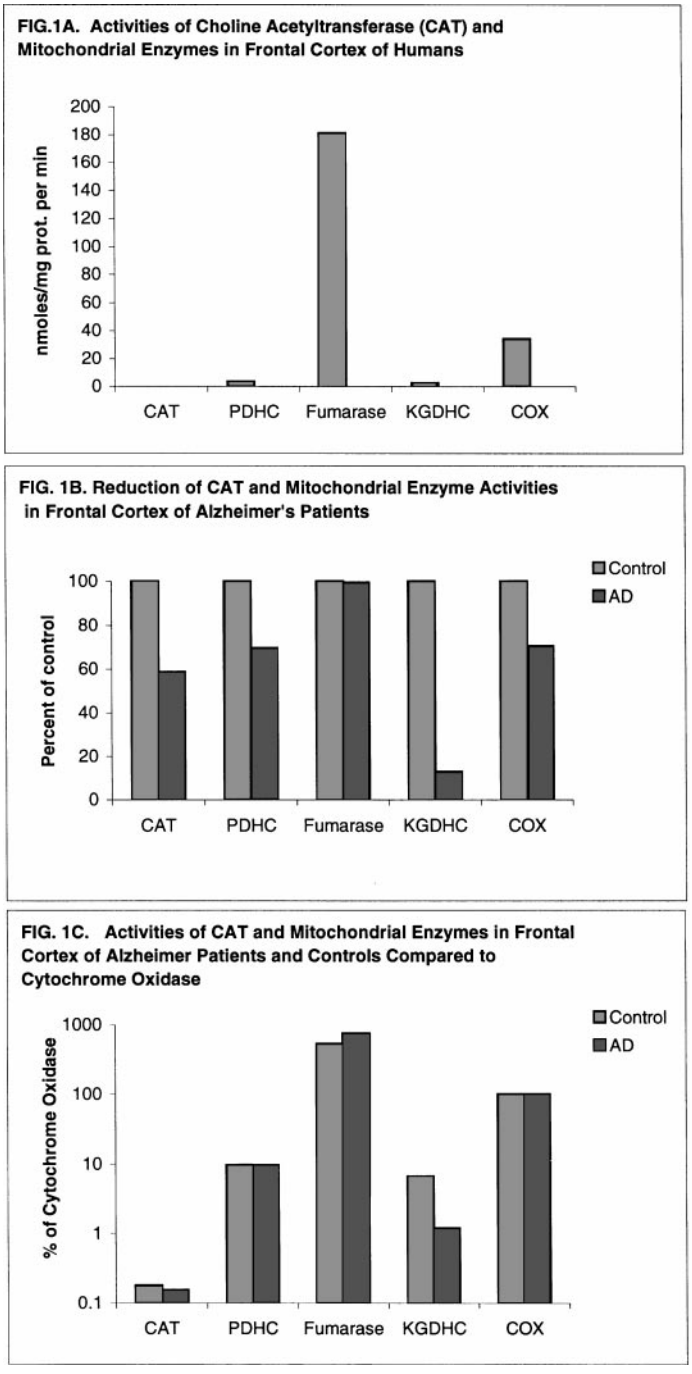

Fig. 1. Enzyme activities in Alzheimer's Disease brain. In **A**, the relative enzyme values (nmoles/mg proteins per minute) are shown for CAT (0.063; Kish et al., 1992), PDHC (3.3; Sorbi et al., 1982), fumarase (Kish et al., 1992), KGDHC (2.25; Gibson et al., 1988), COX (34; Kish et al., 1992). The calculated values for the derived values in **B** and **C** are from these same references

those of COX or fumarase, with KGDHC being slightly lower than PDHC (Fig. 1A). The decline in activities with AD in KGDHC is more severe than for the other mitochondrial enzymes or choline acetyltransferase (Fig. 1B). As shown in Fig. 1C, KGDHC but not PDHC or fumarase showed reduced activities compared to the COX activity (remaining) in AD brain. There are risks in trying to extrapolate enzyme activities measured under forcing conditions to enzyme activities within biopsies to the control mechanisms operating in living cells. Nevertheless, the data shown in the figure are consistent with KGDHC being a potentially rate-limiting enzyme (i.e., having a relatively high control coefficient) in cerebral oxidative metabolism.

2. Genetic abnormalities may underlie enzymatic abnormalities in mitochondrial enzymes in AD brain

COX

Studies of cybrids have been interpreted to implicate genetic abnormalities of mtDNA COX genes in AD (Swerdlow et al., 1997). Cybrids are cells which have been depleted of their own mtDNA, which are then repopulated with mitochondria from AD or control subjects. AD cybrids have reduced COX, changes in calcium regulation and elevated free radical production (Sheehan et al., 1997). These studies are relatively new and independent replication of the experiments with cybrids has not been reported. A recent report proposed the existence in AD of discrete mutations in mitochondrial DNA (mtDNA) of the CO1 and CO2 genes encoding the corresponding components of COX (Davis et al., 1997), but subsequent studies (Wallace et al., 1997; Hirano et al., 1997) indicated that the apparent "mutations" were attributable to PCR coamplification of pseudogenes for CO1 and CO2 on nuclear DNA (nDNA). While the reported alteration in nDNA pseudogene/mtDNA gene amplification suggests that there is, indeed, some difference between mtDNA in AD and control tissues, the current evidence argues against the existence of discrete AD-associated mutations in the CO1 or CO2 genes of mtDNA (Wallace et al., 1997; Hirano et al., 1997). In AD brain, a significant decrease was found in the ratio of PCR amplification of the mtDNA CO1 gene when compared to the nuclear DNA (nDNA) CO1 pseudogene when compared to age and sex matched non-AD controls (Brown et al., 1998). However, the study provided no evidence for a mutation of CO1 gene in AD. Nor is there any evidence of abnormalities in nDNA genes encoding components of COX. Several reports have suggested that point mutations of the mitochondrial DNA (mtDNA) might contribute to the pathogenesis of AD. A recent study screened brain tissue from 65 AD patients for each of the previously reported mtDNA mutations. The results failed to demonstrate an increased incidence of any of the mutations in the AD cases (Hutchin et al., 1997). Thus, the role of mtDNA mutations in the pathogenesis of AD remains unclear.

KGDHC

AD is associated with polymorphisms of the DLST gene, which encodes a component of KGDHC. Molecular genetic studies in our unit have indicated

that polymorphisms of DLST, which encode the core protein of KGDHC, are associated with AD (Sheu et al., 1994, 1996, 1997, 1998a,b). Association of AD with polymorphisms of DLST have now been found in over 1,400 subjects, studied in three different laboratories on three different continents (Sheu et al., 1996, 1998; Nakano et al., 1997). Associations have been observed in both familial (APP- and PS1-negative) AD and apparently sporadic AD (Sheu et al., 1998a,b; Lilius et al., in preparation), and in patients who carry the ∈-4 allele of the APOE gene (APOE4 positive) and in subjects who are APOE4 negative (Sheu et al., 1998). Thus, a genetic association with AD at this locus is a confirmed finding.

The polymorphisms of DLST which have been associated with AD are A19117G in intron 13 and T19183C in exon 14. Homozygosity for the G,C allele has been shown to enhance the association of APOE4 with AD in our Caucasian Jewish series of 429 subjects, and homozygosity for A,C/A,C with AD in the Japanese series of 251 patients and 452 controls (Nakano et al., 1997). The T19183C mutation does not alter the amino acid composition of the DLST protein; both bases encode a glycine (codon 366). It is hard to postulate how this silent polymorphism would lead to a pathophysiologically important change. The intron 13 polymorphism is a base change at a potential branch site, and therefore might conceivably affect mRNA processing. However, it is hard to visualize a mechanism by which A at position 19,117 would be pathogenetic in Japanese and G in Caucasians.

The hypothesis we currently favor is that the polymorphisms of DLST so far discovered to be associated with AD are markers for other, not yet elucidated pathogenetic alterations linked to these markers. The molecular genetic data by themselves are compatible with a defect in either DLST or in a nearby gene on chromosome 14q24.3. However, the combination of biochemical and genetic data make it likely that the genetic abnormality is in the DLST gene itself.

3. Mitochondrial enzymes can also be affected secondarily by other mechanisms in AD, including oxidative stress

In one of the few AD families in which the causative gene defect is known (i.e., the APP670/671 mutation that leads to overproduction of amyloid-β-peptide), KGDHC is also down in brain. In patients bearing the APP670/671 mutation, KGDHC activities were reduced 55–57% compared to control values. The immunochemical levels of KGDHC subunits E1k (−51%), E2k (−76%) declined, while E3 concentrations were unchanged. The results with the APP670/671 mutation bearing patients suggest that mitochondrial dysfunction is a part of the pathophysiological process in AD even when the primary pathogenic event is non-mitochondrial (Gibson et al., 1997).

The evidence that oxidative stress is involved in the pathophysiology of AD is very strong (Markesbery, 1997). However, the mechanisms leading to this manifestation of the disease are as yet undetermined. The toxic effects of Alzheimer β-amyloid appear to be mediated by oxidative stress (Markesbery, 1997), and the "toxic fragment" of the Aβ peptide appears to form spontane-

ously free radicals which are not formed by the scrambled or reverse peptides (Yatin et al., 1997). Furthermore, the toxic effects of Aβ are ameliorated by the addition of a variety of free radical scavengers (Bruce et al., 1996; Tomiyama et al., 1996; Richardson et al., 1996; Kumar et al., 1994; Goodman et al., 1994; Goodman and Mattson, 1994). Both inflammation and apoptosis are associated with free radical mechanisms, and both these processes occur in AD (Markesbery, 1997; Blass, 1996).

Oxidative stress can damage COX, KGDHC and PDHC, although these interactions have not been studied in detail in brain. Depletion of glutathione levels in cultured cardiac myocytes significantly reduced pyruvate dehydrogenase activity (Tirmenstein et al., 1997). A study on the relative susceptibility of (membrane-associated, contractile and mitochondrial) proteins in normal human muscle to oxidative damage by ROS revealed that succinate dehydrogenase (complex II) and cytochrome oxidase (complex IV) were particularly susceptible. At the ultrastructural level, mitochondria were identified as being particularly susceptible to ROS induced oxidative damage. Thus, oxidative damage to mitochondria and/or mitochondrial proteins may represent the principal initial route of free radical-induced damage within skeletal muscle tissue (Haycock et al., 1996), and a similar process may occur in neurodegenerative diseases.

The effects of oxidative stress on KGDHC have been studied more comprehensively. The sulfhydryl groups of the FAD containing E3 may make KGDHC particularly vulnerable to free radicals. Cellular intoxication by elevated concentrations of O_2 results in excessive free radical production by normal metabolic pathways. Exposure of cultures of either HeLa cells or Chinese hamster ovary (CHO) cells to 80% O_2 for 2 days causes progressive growth inhibition and loss of reproductive capacity. This impairment is correlated with inhibition of cellular O_2 consumption and partial inactivation of NADH and succinate dehydrogenase, and total inactivation of KGDHC (Schoonen et al, 1990a). In an oxygen-resistant substrain of CHO cells, succinate dehydrogenase and KGDHC are relatively resistant to inactivation by hyperoxia (Shoonen et al., 1991, 1990b). This finding supports the suggestion that damage to these enzymes is a critical part of a cascade in the pathological response to free radicals in non-mutant CHO cells.

Mitochondrial damage may also be predicted to lead to oxidative stress by at least two mechanisms. One is increased production of ROS due to damage to the electron transport chain; for instance, loss of activity of COX might back up electrons at center P of the Q cycle portion of the Complex III site with the possible formation of ROS (Kristal et al., 1997). The other mechanism is impaired ROS sequestration due to impaired chemical flux. Removal of ROS eventually requires their chemical reduction, and a functional deficiency in the Krebs tricarboxylic acid cycle can be predicted to lead to reduced production of the electrons (i.e., NADH equivalents) which are needed for the chemical reduction of ROS. A functional deficiency of KGDHC could be predicted to favor increased ROS production (Blass 1993a, 1996, 1997). Free radical/ROS mechanisms in relation to AD are now under study in many laboratories (Markesbery, 1997).

Nitric Oxide (NO) production in the brain can also lead to oxidative stress (Bolanos et al., 1997). Under certain circumstances NO synthesis may be excessive and NO may become neurotoxic. This is particularly true in the presence of superoxide, since the combination of superoxide and NO forms peroxynitrite. Peroxynitrite can interfere with key enzymes of the tricarboxylic acid cycle, the mitochondrial respiratory chain, or mitochondrial calcium metabolism, and/or cause DNA damage with subsequent activation of the energy-consuming pathway involving poly(ADP-ribose) synthetase (Bolanos et al., 1997). Recent results indicate that oxidative stress in the presence of NO leads to peroxynitrite formation, which leads to the nitration and inactivation of KGDHC (Park et al., 1998).

4. Impaired mitochondrial metabolism can be readily linked to the pathophysiology of Alzheimer's disease

KGDHC, PDHC and COX may be critical steps in the cascade of events that lead to AD, regardless of whether they are primary genetic defects or secondary events due to oxidative stress. PDHC activity has been linked to key aspects of major neuropathologic correlates of AD (i.e., the plaques, tangles and cholinergic deficit). PDHC can be phosphorylated and inactivated in vivo by tau protein kinase (TPKI), a kinase that is critical to the formation of tangles in AD brain (Imahori and Uchida, 1997), reduces PDHC activity (Imahori and Uchida, 1997). In primary culture of rat hippocampal cells, amyloid-β-peptide, the main component of plaques, inactivated PDH in inverse relation to its effects on the activation of TPKI. The amyloid-β-peptide-induced inhibition of PDHC lead to accumulation of pyruvate or lactate, energy failure, and a shortage of acetylcholine, all of which are characteristic of AD brain. Neither choline acetyltransferase activity nor choline metabolism is affected by the kinase. Therefore, the major cause of reduced acetylcholine synthesis is likely to be an inadequate supply of acetyl-CoA due to reduced PDHC activity.

Relatively extensive studies of the biochemical pathophysiology of AD have documented a variety of mechanisms other than oxidative stress which can relate a deficiency in mitochondrial substrate oxidation (i.e. in energy/oxidative metabolism) to specific clinical and pathological characteristics of AD. These have been reviewed elsewhere (Blass, 1993a,b, 1996, 1997). They include cognitive impairments, neurotransmitter and specifically cholinergic impairments, abnormalities in signal transduction similar to those seen in AD, cytoskeletal lesions, and abnormal processing of amyloid precursor protein (Blass, 1993a,b, 1996, 1997). Thus there is a body of work supporting the pathophysiological significance of mitochondrial abnormalities in AD.

5. Implications

A body of pathophysiological, biochemical, and molecular genetic studies all support the importance of studying the mitochondrial lesion in AD. Mitochondrial abnormalities appear to be a common mechanism in AD from a variety of genetic causes. Accumulating evidence indicates that a mutation of

a gene encoding a mitochondrial constituent may predispose to the development of the disease in a proportion of AD patients. In other patients, genetic abnormalities in other genes including APP and the presenilins appear to lead to mitochondrial abnormality (Cruts et al., 1998; Rubinsztein, 1997; Farrer et al., 1997), perhaps via free radical formation (Markesbery, 1997).

The existence of primary genetic and secondary abnormalities in a mitochondrial component in AD are, of course, not mutually exclusive. For instance, there is no contradiction between evidence that deficiency of KGDHC in AD can sometimes be associated with polymorphisms in a gene encoding the core component of KGDHC and at other times with inactivation of KGDHC by peroxynitrites or other reactive oxygen species (ROS). Conceivably, the effect of the genetic abnormality may be to make the encoded protein more sensitive to damage by ROS. Diseases with multiple genetic causes may be more common than single gene diseases, and the common forms of AD are being increasingly accepted to be polygenetic disorders. Possibly, a gene encoding a specific component of the mitochondrion may interact with the effects of other genes encoding other components (non-mitochondrial or mitochondrial) in leading to the impairments which are the pathophysiological mechanisms of AD. Current evidence for this possibility is strongest for KGDHC and for the DLST gene which encodes its core protein component. These potential interactions are diagrammed in Fig. 2.

Mitochondrial insufficiency can be related to the pathophysiology of AD by plausible and well-established mechanisms for which there is abundant evidence. Further studies of the mitochondrial deficit in AD are warranted.

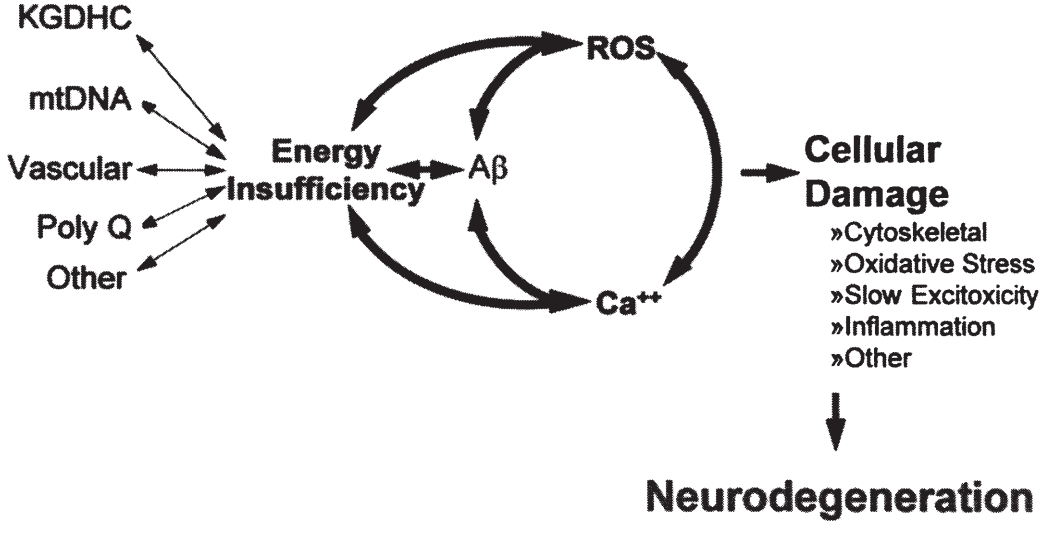

Fig. 2. Pathophysiological mechanisms in Alzheimer's disease (from Blass et al., 1997b)

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