.The resulting cybrids then enable one to determine whether any observed defects in oxidative phospho– rylation are attributable to alterations in the patient's mtDNA, since the patient's mitochondria now func– tion in the presence of a di?erent nuclear back– ground.Neurocbrillary tangle bearing neurons showed increased immunostaining with anti– bodies to advanced glycation end products, hemeox– ygenase–1, malondialdehyde, 4–hydroxynonenal, pro– tein carbonyl groups, carbonylated neuroclaments, and 3–nitrotyrosine [13,32^38].Previous studies showed that impairment of cytochrome oxidase in vitro leads to an increase in C–terminal fragments of the amyloid precursor pro– tein, which contain the L–amyloid peptide [39], and a decrease in non–amyloidogenic processing of the amyloid precursor protein [40].Phosphorus magnetic resonance spectroscopy has demonstrated abnormalities in either phospho–creatine (PCr) or inorganic phosphate (Pi) in Alz– heimer's disease patients as compared with elderly controls [11,12].Familial autosomal dominant Alzheimer's disease is associ– ated with point mutations in the amyloid precursor protein as well as in novel proteins entitled preseni– lin–1 and presenilin–2.Studies utilizing posi– tron emission tomography consistently show reduced glucose metabolism in temporoparietal regions of Alzheimer's disease patients, and this appears to oc– cur quite early in the disease course [4].Recent stud– ies have demonstrated that this occurs in patients at risk for Alzheimer's disease [5], and there appeared to be reduced glucose utilization in asymptomatic patients who are homozygous for the Apo O4 allele, a known risk factor for sporadic Alzheimer's disease [6].An increase in intra– cellular L–amyloid 1^42 was found after exposure of cultured guinea pig neurons to hydrogen peroxide, and oxidative stress increased L–amyloid in mamma– lian lens tissue [41,42].Reduced ATP generation also leads to activation of ERK1 M.F. Beal / Biochimica et Biophysica Acta 1366 (1998) 211^223 213 and ERK2 kinases which phosphorylate tau proteins into a paired helical clament–like state similar to that in ADAlthough prior biochemical studies suggested that there were decreases in cytochrome oxidase activity in Alzheimer's disease platelets and cerebral tissue, it was unclear whether this was a primary or secondary e?ect of the disease process.The cytochrome oxidase activity shows a reduction in catalytic activity yet normal amounts of cytochrome aa3 , suggesting that reduced complex IV activity is a consequence of abnormal catalytic activity rather than decreased enzyme levels [16].Ethidium bromide is con– centrated within mitochondria and preferentially in– M.F. Beal / Biochimica et Biophysica Acta 1366 (1998) 211^223212 hibits mtDNA replication in comparison to nuclear DNA replication.The Alzheimer's disease cybrids show elevated basal cytosolic calcium con– centrations as well as enhanced sensitivity to inosi– tol–1,4,5–triphosphate mediated calcium release.A sporadic inheritance pattern with familial as– sociation and evidence for maternal transmission are characteristic features of known mitochondrial genet– ic diseases.Recent studies using the cybrid technique to dem–onstrated that the cytochrome oxidase defects in Alz– heimer's disease appear to be encoded on mtDNA [20,21].Point mutations were found in the cyto– chrome oxidase–1 and cytochrome oxidase–2 mtDNA encoded subunits of cytochrome oxidase, however further work needs to be done to exclude the possi–bility that these mutations are not present in nuclear pseudogenes.The study of Smith and colleagues demonstrated a reduction in PCr/Pi ratio in the fron– tal cortex of Alzheimer's disease patients [13].Studies of post– mortem cerebral tissue of Alzheimer's disease patients concrmed reduced cytochrome oxidase ac– tivity [17,18].Cell lines from a variety of sources can be depleted of

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mitochondrial DNA (mtDNA) by exposing them to low concentra- tions of ethidium bromide.Nuclear pseudogenes are mitochondrial DNA sequences which are randomly incorporated into the nuclear genome by unclear mechanisms, but which exist for much of the mitochondrial ge- nome.Consistent with this possibility we found a 3-fold increase in 8-hy- droxy-2-deoxyguanosine content of mtDNA in AD postmortem tissue as compared to age-matched con- trols [28].Positron emission tomography studies also show increased oxygen utilization in comparison with glu- cose utilization in Alzheimer's disease patients [7].Familial Alzheimer's disease accounts for approximately 5% of all cases.

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