NUCLEAR AND MITOCHONDRIAL BASE EXCISION REPAIR ACTIVITIES IN BRAINS FROM ALZHEIMER'S DISEASE PATIENTS

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Alzheimer's disease (AD) is characterized by a progressive cognitive decline, which affects the individual's social and occupational roles. Several lines of evidence suggest that the accumulation of DNA lesions and changes in the pathways that remove these may have a role in the progression of AD. Base Excision Repair (BER) is the main repair pathway for small base modifications, abasic sites and single strand breaks, which are quantitatively the most relevant types of DNA lesions in AD patients. We investigated whether alterations in BER activities in the brain play a causative role during the development of AD. Nuclear and mitochondrial fractions were prepared from autopsy brain samples from cognitively normal, AD subjects and individuals who show neuropathological features of AD, but remained cognitively normal (asymptomatic AD - asAD). BER activities were measured using a fluorescence-based in vitro assay. Mitochondrial and nuclear UDG activity were significantly reduced in both AD and asAD, when compared with disease-free controls. These activities were inversely correlated with CERAD and Braak stages. On the other hand, APE1 activity was decreased only in nuclear extracts from the AD group, when compared with either controls or asAD, while conversely, asAD cases displayed higher mitochondrial APE1 activity in the cerebellum. As BER activities contribute to maintaining mtDNA integrity, we measured mtDNA copy number and deletions, but no changes between the groups were observed in the samples analyzed thus far. We are employing the Random Mutation Capture assay to determine the mutation rate and spectrum in the mtDNA of our samples. This observation of reduced BER activities in AD brains - even in the cerebellum, the last brain region to show AD-associated pathological features - suggests that BER capacity may be an underlying variable that modulates the cellular responses to the insults that result in the AD neuropathology.

Keywords: DNA repair; Alzheimer's disease; DNA damage.

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