Long term caloric restriction induces hippocampal volume loss in mice

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Increased free radical production and accumulation of unrepaired nuclear (n) DNA damage play a major role in the aging process of the brain. We have recently shown that hippocampal pyramidal and granule cells as well as cerebellar granule cells in the mouse brain accumulated unrepaired nDNA damage (single strand breaks) during aging whereas they were not reduced in number. In contrast, cerebellar Purkinje cells were reduced in number but did not accumulate unrepaired nDNA damage during aging. Based on these findings we propose that age-related loss of damaged neurons might be a beneficial mechanism, only present in distinct types of neurons. Here we aimed to improve the aging process of the mouse brain by two means: 1) attenuating damage by oxygen radicals by transgenically overexpressing normal human Superoxide Dismutase (SOD) and 2) feeding mice with a diet enriched in exogeneous antioxidants but restricted in calories. A total cohort of 240 male mice was housed under specified pathogen free conditions and was subdivided into four groups of 60 mice, based on diet and transgenic background. At 12 months of age, 6 mice per group were analyzed for hippocampal volumes and neuron numbers. The volumes of the entire hippocampus and hippocampal cell layers were significantly ($p < 0.05$) decreased (respectively 15%, 19% and 9%) in mice fed with the caloric restricted diet. Hippocampal volumes of the transgenic mice did not differ from those of the wild type mice. Our studies will soon establish whether caloric restriction indeed induced neuron loss. In addition, effects of caloric restriction and SOD overexpression on nDNA damage accumulation in the remaining hippocampal neurons will be investigated. It is tempting to speculate that a main beneficial effect of caloric restriction is the induction of apoptosis of damaged neurons.
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