Branched-chain amino acid supplementation promotes mitochondrial biogenesis and antioxidant defense in the hippocampus of middle-aged mice

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Evidence suggest that exercise enhances brain function by engaging adaptive responses including mitochondrial biogenesis, possibly contributing to forestall age-related cognitive decline and neurodegeneration (Mattson, 2012). We have recently showed that dietary supplementation with a branched-chain amino acid-enriched mixture (BCAAem) increases endothelial nitric oxide synthase (eNOS)-dependent mitochondrial biogenesis in cardiac and skeletal muscle of middle-aged mice (D'Antona et al., 2010). Supplemented mice displayed enhanced motor coordination and physical endurance and extended average life span. BCAAem-mediated effects were even more remarkable in long-term exercise-trained mice (D'Antona et al., 2010). The present study was undertaken to investigate the effects of BCAAem on neuronal mitochondrial biogenesis both in vitro and in vivo. We found that exposure of fully differentiated mouse primary cortical neurons to BCAAem for 72 h induced the expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α, a master regulator of mitochondrial biogenesis) as well as of the nuclear respiratory factor-1 (NRF-1) and mtDNA transcription factor A (Tfam). Further, BCAAem increased cytochrome C and cytochrome oxidase IV levels and augmented mtDNA content and citrate synthase activity. For the in vivo experiments, middle-aged (16 months old) mice were unsupplemented or supplemented with BCAAem (1.5 mg/g body weight/day in drinking water) for 3 months as described (D'Antona et al., 2010). A separate group of middle-aged mice was trained on a treadmill (5 days/week for 4 weeks). Likewise exercise training, dietary supplementation with BCAAem induced eNOS expression and increased mitochondrial biogenesis and mtDNA content in the hippocampus of middle-aged mice. Moreover, the genes of the ROS defense system, including copper/zinc superoxide dismutase, manganese superoxide dismutase, catalase and glutathione peroxidase, whose expression is increased by PGC-1α activation (St-Pierre et al., 2006), were upregulated by BCAAem supplementation and by exercise training in the hippocampus of middle-aged mice. Dietary supplementation with amino acid formulas containing BCAAs exerts a variety of beneficial effects in humans (Valerio et al., 2011). Our data suggest that BCAA-based nutraceutical interventions might be valuable approaches to mimic the beneficial effects of exercise on brain health in middle aged-sedentary subjects.

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