

Abstract

In addition to the well-known effects of vitamin D (VitD) in maintaining bone health, there is increasing appreciation that this vitamin may serve important roles in other organs and tissues, including the brain. Given that VitD deficiency is especially widespread among the elderly, it is important to understand how the range of serum VitD levels that mimic those found in humans (from low to high) affects the brain during aging from middle age to old age. To address this issue, 27 male F344 rats were split into three groups and fed isocaloric diets containing low (100 IU/kg food), control (1000 IU/kg food), or high (10,000 IU/kg food) VitD beginning at middle age (12 months) and continued for a period of 4–5 months. We compared the effects of these dietary VitD manipulations on oxidative and nitrosative stress measures in posterior brain cortices. The low-VitD group showed global elevation of 3-nitrotyrosine compared to control and high-VitD-treated groups. Further investigation showed that this elevation may involve dysregulation of the nuclear factor κ -light-chain enhancer of activated B cells (NF- κ B) pathway and NF- κ B-mediated transcription of inducible nitric oxide synthase (iNOS) as indicated by translocation of NF- κ B to the nucleus and elevation of iNOS levels. Proteomics techniques were used to provide insight into potential mechanisms underlying these effects. Several brain proteins were found at significantly elevated levels in the low-VitD group compared to the control and high-VitD groups. Three of these proteins, 6-phosphofructokinase, triose phosphate isomerase, and pyruvate kinase, are involved directly in glycolysis. Two others, peroxiredoxin-3 and DJ-1/PARK7, have peroxidase activity and are found in mitochondria. Peptidyl–prolyl *cis–trans* isomerase A (cyclophilin A) has been shown to have multiple roles, including protein folding, regulation of protein kinases and phosphatases, immunoregulation, cell signaling, and redox status. Together, these results suggest that dietary VitD deficiency contributes to significant nitrosative stress in brain and may promote cognitive decline in middle-aged and elderly adults.