Involvement of sorbitol-mediated signaling mechanisms in neuronal and retinal degeneration associated with metabolic syndrome

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Obesity is a multifactorial and highly complex medical condition involving excessive body-fat accumulation that can cause health impairment. Epidemiological studies suggest that obesity and metabolic syndrome are associated with various progressive age-related diseases, including neurological and retinal disorders. However, underlying molecular basis for increased risk of neurodegeneration in obesity is unknown. A suitable animal model would immensely help in understanding the obesity-linked neurological problems. In this study we describe neuronal and retinal degeneration as a consequence of obesity in spontaneously developed obese rat models: WNIN/Ob and WNIN/GR-Ob, the former with euglycemia and the latter with an additional impaired glucose tolerance (IGT) trait. By morphological evaluation, the onset of retinal degeneration in the WNIN-Ob rat appears to occur between 4-6 months age and by 9-15 months; there is a severe retinal degeneration in WNIN-Ob retinas. Immunohistochemical analysis with retinal markers further confirmed retinal degeneration, particularly rod cell loss in the obese rat retina. Gene expression by microarray analysis and qRT-PCR established activation of stress response, tissue remodeling, impaired phototransduction, and photoreceptor degeneration in obese rat retina. Electroretinogram evaluation indicates a significant impairment in retinal function in WNIN-Ob rats when compared to the corresponding lean rats from 3-month age onwards as measured by the a- and b-wave amplitude of the full field scotopic and the b-wave amplitude of the photopic ERG. Neurons in the cerebral cortex of obese rats showed swollen mitochondria, disrupted ER and degenerating axons, nucleus and finally neurons. Results showed altered UPS, existence of ER stress, up-regulation of apoptotic markers and apoptosis in the cerebral cortex of obese rats. It appears that UCHL-1 mediated apoptosis through stabilizing p53 might play a role in neuronal cell death in obese rat. The above mentioned retinal and neuronal changes were more prominent and severe in WNIN-GR/Ob rat compared to WNIN-Ob rat at corresponding ages suggesting synergistic effect of IGT and obesity on retinal degeneration. These rat models of metabolic syndrome may thus be valuable tools for investigating obesity-associated retinal and neuronal abnormalities and for developing intervention strategies based on these observations. Therefore, we further investigated the effect of food restriction on obesity associated retinal and neurodegeneration in these obese rat model. The data suggest that retinal and neurodegeneration in the obese rats appears to be ameliorated significantly by food restriction. Immunohistochemical analysis with retinal and neuronal markers further confirmed prevention of retinal degeneration in the obese rats by these dietary approaches. Food restriction modulated ER-stress and UPS components in the retina and brain. These studies suggest that dietary intervention could provide a viable approach to prevent obesity-associated retinal and neurodegeneration.