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OC.13- BRAIN-DERIVED NEUROTROPHIC FACTOR MODULATES CHOLESTEROL HOMEOSTASIS AND APOLIPOPROTEIN E SYNTHESIS IN HUMAN MODELS OF ASTROCYTES AND NEURONS

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In the central nervous system (CNS), cholesterol is critical to maintain membrane plasticity, cellular function, and synaptic integrity. A breakdown of brain cholesterol metabolism has been associated with different CNS diseases, including Alzheimer disease. Brain-derived neurotrophic factor (BDNF) was previously reported to elicit cholesterol biosynthesis and promote the accumulation of presynaptic proteins in cholesterol-rich lipid rafts, but no data are available on its ability to modulate physiological mechanisms involved in cholesterol homeostasis. Major aim of our research was to study whether BDNF influences critical events in cholesterol homeostasis, namely: a) the synthesis of Apolipoprotein E (ApoE), which is the strongest genetic risk factor for Alzheimer disease, b) the cholesterol efflux from astrocytes and c) the cholesterol incorporation into neurons. Our results show that BDNF significantly stimulates cholesterol efflux by primary astrocytes, as well as ATP binding cassette A1 (ABCA1) transporter and ApoE expression. Conversely, cholesterol uptake in neurons was downregulated by BDNF. This effect was associated with the increase of Liver X Receptor (LXR)-beta expression in neurons exposed to BDNF. Interestingly, the level of apoptosis markers was found increased in neurons treated with high cholesterol, but significantly lower when the cells were exposed to cholesterol in the presence of BDNF, thus suggesting a critical neuroprotective role of the neurotrophin, likely through its reducing effect of neuronal cholesterol uptake. Also, cholesterol treatment actually induces BDNF production by neurons. Overall, our findings evidenced a novel critical role of BDNF in the modulation of ApoE and cholesterol homeostasis in glial and neuronal cells.