Apolipoprotein E production by astrocytes is regulated by 24(S)-hydroxycholesterol

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Apolipoprotein E (apoE) is well known for its key role in the transport of cholesterol. It is a component of several classes of lipoproteins and mediates their interaction with cellular receptors. A strong association between inheritance of e4 allele and an individual's relative risk to develop Alzheimer's disease (AD) as well as the age of onset has been established. Here we focus on the relationship between apoE, AD and cerebral cholesterol metabolism. In the brain, apoE is synthesized predominantly by astrocytes and secreted by these cells in association with cholesterol and phospholipids in the form of high-density lipoprotein-like particles. These particles are thought to provide neurons with lipids required for the formation of new membranes, for example during outgrowth of synapses. The human brain continuously synthesizes cholesterol and the excess free cholesterol is eliminated in the form of an oxidized metabolite, 24(S)-hydroxycholesterol. 24(S)-Hydroxylase (CYP46), the enzyme responsible for this reaction, seems to be almost exclusively localized to neuronal structures in the brain. We hypothesized that 24(S)-hydroxycholesterol synthesized by neurons is not only responsible for cholesterol efflux from the brain, but also is an important signaling molecule through activation of the nuclear receptor LXR (Liver X-receptor).
Our results show that the synthetic LXR agonist GW683965A upregulates apoE synthesis in CCF-STTG1 human astrocytoma cells, but not in SH-SY-5Y human neuroblastoma cells. The natural oxysterol LXR ligand, 24(S)-hydroxycholesterol, upregulates apoE synthesis in CCF-STTG1 cells in a concentration-dependent manner, but not in SH-SY-5Y cells. 24(S)-hydroxycholesterol is a stronger regulator of apoE synthesis than 22(R)-hydroxycholesterol, retinoic acid (ligand for RXR, the obligate heterodimeric patern of LXR) or free cholesterol. These results suggest that regulation of ApoE in the brain is cell-type specific and that 24(S)-hydroxycholesterol plays a signaling role as LXR agonist. Transcriptional upregulation of cholesterol transport genes via LXR/RXR by 24(S)-hydroxycholesterol, including apoE may controling the lipid supply in the form of apoE-containing HDL-like lipoproteins from astrocytes to neurons.

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