Vitamin D3 deficiency contributes to Alzheimer's disease (AD) pathophysiology. 1α, 25(OH)2-vitamin D3 (1,25D3) inhibits the deleterious effects of amyloid-beta 1-42 (Aβ1-42) to neurons and innate immune cells. In AD PBMCs, the ability of 1,25D3 to attenuate Aβ1-42 mediated stimulation of inflammation is at least in part dependent on the nongenomic effects of 1,25D3. This conclusion is based on a) comparing the effects 1,25D3 and the non-genomic selective analogue of 1,25D3, 1α,25(OH)2-lumisterol D3 (JN), have on Aβ1-42 induced mRNA expression of forty three inflammation and AD markers and b) 1,25D3 stimulation of FAM-Aβ1-42 by AD macrophages requires its ability to modulate intracellular calcium and the activity of phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase kinase (MEK1/2), protein kinase A (PKA) and the voltage-sensitive chloride channel (CLC3). 1,25D3 stimulation of FAM-Aβ1-42 by AD macrophages also required both the nuclear vitamin D receptor (VDR) and the protein disulfide isomerase-3 (PDIA3). Thus these two receptors and vitamin D sterols function at multiple layers to correct the imbalance that exists in AD macrophages between Aβ1-42 initiated inflammation and phagocytosis, both natural biochemical pathways. Curcuminoids have also attracted interest as AD preventatives/therapeutics and bind specifically to the VDR at low micromolar concentrations. However, curcuminoids only attenuate the effects of Aα1-42 in some, while 1,25D3 is effective in all AD macrophages. Results perhaps explained by the evidence that AD patients differ in their levels of systemic inflammation at baseline. Thus 1,25D3 nongenomic signaling is crucial in supporting macrophage processing of Aβ1-42 and PBMC modulation of inflammation in AD.

Biography
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