

1 α ,25(OH) $_2$ - Vitamin D $_3$ signaling in AD peripheral blood mononuclear cells (PBMC) and macrophages

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Vitamin D $_3$ deficiency contributes to Alzheimer's disease (AD) pathophysiology. 1 α , 25(OH) $_2$ -vitamin D $_3$ (1,25D $_3$) inhibits the deleterious effects of amyloid-beta 1-42 (A β_{1-42}) to neurons and innate immune cells. In AD PBMCs, the ability of 1,25D $_3$ to attenuate A β_{1-42} mediated stimulation of inflammation is at least in part dependent on the nongenomic effects of 1,25D $_3$. This conclusion is based on a) comparing the effects 1,25D $_3$ and the non-genomic selective analogue of 1,25D $_3$, 1 α ,25(OH) $_2$ -lumisterol D $_3$ (JN), have on A β_{1-42} induced mRNA expression of forty three inflammation and AD markers and b) 1,25D $_3$ stimulation of FAM-A β_{1-42} 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). 1,25D $_3$ stimulation of FAM-A β_{1-42} 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 A β_{1-42} 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 A α 1-42 in some, while 1,25D $_3$ 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 1,25D $_3$ nongenomic signaling is crucial in supporting macrophage processing of A β_{1-42} and PBMC modulation of inflammation in AD.

Biography

Mathew T. Mizwicki has completed his Ph.D. at age of 28 years from the University of California, Riverside and postdoctoral studies at UCR and UCLA. He is an Assistant Researcher in the Department of Surgery: Liver and Pancreas Transplantation at UCLA. He has published more than 25 papers in reputed journals, authored three book chapters and serves as an editorial board member of reputed.

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