How gamma-tocotrienol, a vitamin E isomer mimics BH3-only proteins to kill neuroblastoma cells

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The dysregulation of apoptosis process is the hallmark of cancer, with B-cell lymphoma 2 (Bcl-2) family proteins playing a crucial role in the initiation of the intrinsic apoptosis pathway. BH3-only proteins trigger apoptosis by binding to prosurvival proteins such as Bcl-2 to release the proapoptotic proteins such as Bax, Bak from sequestration of Bcl-2 protein. Therefore, small molecules (BH3 mimetics) mimicking BH3-only proteins could be potential anticancer agents. In this study, we examined the potential action of gamma-tocotrienol, $\gamma$T3 (a vitamin E isomer) as an antagonist of Bcl-2 protein in human neuroblastoma SH-SY5Y cells. Previous studies have showed that $\gamma$T3 was able to induce cancer cell death via several cellular pathways. However, our data present the first report of $\gamma$T3 with BH3 mimetic-like properties as the possible mechanism of action. Our results showed that $\gamma$T3 reduced cell viability of neuroblastoma in a concentration dependent manner. $\gamma$T3 induced apoptosis by depolarizing mitochondrial membrane potential and releasing cytochrome c from mitochondria to cytosol. $\gamma$T3 also induced caspase-9 and caspase-3 activities while caspase-8 activity was not affected. These result indicated that $\gamma$T3 induced apoptosis by intrinsic pathway. \textit{In silico} docking analysis suggested $\gamma$T3 binds to BH3 domain of Bcl-2 protein. \textit{In vitro} binding assay demonstrated $\gamma$T3 was bound to Bcl-2 protein. In conclusion, our data suggested $\gamma$T3 induced apoptosis by inhibiting Bcl-2 protein function by binding to the BH3 domain to initiate the apoptosis process.