Novel multi target neuroprotective and neurorestorative drugs for Alzheimer's Disease

Moussa B.H. Youdim
Faculty of Medicine, Technion – Israel Institute of Technology, Israel

We have developed several novel neuroprotective and neurorestorative multi-target , brain permeable drugs, possessing cholinesterase- monoamine oxidase inhibitor activities and iron chelating-radical scavenging properties. We have studied M30, on the neuropathology and deficits of spatial learning and memory in amyloid precursor protein (APP) and presenilin 1 (PS1) double-transgenic (Tg) Alzheimer's disease (AD) mice. Systemic treatment of APP/PS1 Tg mice with M30 significantly attenuated cognitive impairments in a variety of tasks of spatial learning and memory retention, working memory, learning abilities, anxiety levels, and memory for novel food and nesting behavior. M30 reduced cerebral iron accumulation accompanied by a marked decrease in several AD-like phenotypes, including cerebral APP levels, amyloid β (Aβ) levels and plaques, phospho-APP and phospho-tau. Signaling studies revealed that M30 markedly down regulated the levels of phosphorylated cyclin-dependent kinase 5 and increased protein kinase B and glycogen synthase kinase 3β phosphorylation. Accumulation and deposition of brain iron is central to neuropathological processes in AD, including oxidative stress, amyloid deposition, and tau phosphorylation. Thus, the concept of iron chelation holds considerable promise as a therapeutic strategy for AD pathogenesis. When systemically administered to APP/PS1 Tg mice, M30, effectively reduced Aβ accumulation and tau phosphorylation, and attenuated memory deficits. 30 and its derivative activate HIF (hypoxia inducing factor) that regulates cell cycle, causing cell cycle arrest and induces release of several neurotrophins including BDNF, VEGF and erythropoeitin These findings suggest that M30 is a potential therapeutic agent for the prevention and treatment of Alzheimer's disease for which it is being developed.

Biography

Prof. Youdim trained as biochemist and is now Professor Emeritus at Technion and Distinguished Professor of Yonsei World Central University in Seoul. He has published more than 800 papers and has been on the editorial board of 45 international journals. He has received numerous national and international prizes, honorary and Doctor of Philosophy . Recently he was awarded The ECNP Lifetime Achievement Award, CINP Pioneer Award and Catecholamine Pioneer Award and the Arid Carlson Medal. He is the elected member of Leopoldina German Academy of Sciences, the oldest academy in the world.

youdim@tx.technion.ac.il