Small molecule pro-neurotrophic therapeutic activity in murine models of Alzheimer's disease

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Age-related neurodegenerative diseases, such as Alzheimer's disease, will represent one of the largest future burdens on worldwide healthcare systems due to the increasing proportion of elderly in our society. As deficiencies in neurotrophins are implicated in the pathogenesis of many age-related neurodegenerative disorders, it is reasonable to consider that global neurotrophin resistance may also become a major healthcare threat. Central nervous system networks are effectively maintained through aging by neuroprotective and neuroplasticity signaling mechanisms which are predominantly controlled by neurotrophin receptor signaling. Neurotrophin receptors are single pass receptor tyrosine kinases that form dimeric structures upon ligand binding to initiate cellular signaling events that control many protective and plasticity-related pathways. Declining functionality of the neurotrophin ligand–receptor system is considered one of the hallmarks of neuropathological aging. Therefore, it is imperative to develop effective therapeutic strategies to contend with this significant issue. The development of nonpeptidergic, small-molecule ligands can overcome these limitations, and productively regulate this important receptor system with beneficial effects. We have found that in multiple models of Alzheimer's disease the previously employed anti-depressant Elavil can exert potent pro-neurotrophic activity through a series of complementary mechanisms. This small molecular agent possesses the capacity to significantly enhance cognitive performance in mouse models possessing considerable levels of dementia and amyloid pathology. In this respect agents such as Elavil may represent an important addition to a new wave of therapeutic strategies against dementia.

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