

Aging and Neurodegeneration

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Aging causes a slow deterioration of the brain function leading to cognitive decline, memory loss, movement disorders and finally to functional decline and death. With a rapidly increasing aging population, neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's become an important economic burden on the society. Unfortunately, there are no effective current therapies. Therefore, it is quite urgent to find strategies that will lead to therapeutic benefits for the patients. Since aging is the major risk factor for the age-related neurodegenerative disorders, interfering with age-related molecular mechanisms or pathways might be an avenue to develop new therapeutics.

Aging is a regulated process with different molecular and genetic mechanisms involved. There are three known longevity intervention pathways: reduced insulin-like signaling, increased AMPK (AMP-dependent protein kinase)/reduced TOR (target of rapamycin) and sirtuins [1]. Sirtuins are NAD-dependent protein deacetylases that were shown to display neuroprotective effects against age-related brain disorders. There are seven mammalian sirtuin homologues named as SIRT1-7 [2]. The most conserved member of the family, SIRT1, has been widely studied in neurodegenerative diseases [2].

SIRT1 has been shown to be protective against Alzheimer's Disease (AD) by different research labs via affecting different targets and mechanisms [3]. SIRT1 prevents the formation of Aβ peptides by deacetylating RARβ (Retinoic Acid Receptor beta) and activating the "good" α-secretase, ADAM10 [4]. SIRT1 deacetylates tau leading to its degradation thereby preventing its accumulation [5]. SIRT1 might prevent AD by being involved in other mechanisms such as mitochondrial biogenesis and inflammation. SIRT1 deacetylates PGC1α and induces mitochondrial biogenesis [6]. By this way, SIRT1 might prevent mitochondrial dysfunction in AD. Inflammation is one of the main factors that triggers AD and preventing inflammation is known to be beneficial. SIRT1 prevents inflammation by deacetylating LXR and NFκB [7,8]. Therefore, preventing inflammation might be another area that SIRT1 presents its protective effects against AD.

Both SIRT1 and SIRT2 have been studied in Parkinson's Disease (PD). SIRT1 was shown to reduce α-synuclein aggregates by activating HSF1 (Heat Shock Factor 1) [9]. It might also reduce neurotoxicity by activating PGC1α [2]. As opposed to SIRT1, inhibition of SIRT2 was shown to be protective against neurodegeneration [10]. Inhibition of SIRT2 was shown to prevent α-synuclein aggregates in cell culture and Drosophila model [11]. Then, in an MPTP model of PD, deletion of SIRT2 was shown to decrease nigrostriatal damage in mouse brain by preventing apoptotic neuronal death [12].

In Huntington's Disease (HD), SIRT1 was demonstrated to induce neuronal survival by activating BDNF in a mouse model [13]. In another study, inhibition of SIRT2 was shown to be beneficial in HD by decreasing neuronal cholesterol [14].

Sirtuins are enzymes that can be activated or inhibited by small molecules. Having followed all these advancements in the recent years,

we hope that small molecule activators of SIRT1 and inhibitors of SIRT2 that could cross blood brain barrier can be developed and used for the neurodegenerative disorders.

Finally, it will also be interesting to learn the functions and roles of other sirtuin family members in the mammalian brain and to understand whether they have any effects in brain diseases in developing or adult animals.

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