Clearing Neurofibrillary Tangles from the Brains of Alzheimer’s Disease Mice

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Why should we care about curing Alzheimer’s Disease?

The disease is costly and debilitating
5.4 million Americans are affected
6th leading cause of death in the USA
Of the top 10 causes of death, it is the only one that cannot be prevented, cured, or even slowed.

The ratio of cells with neurofibrillary tangles to total cells drops significantly with treatment.

Both inhibitors of CDK5 reduced the number of neurons with neurofibrillary tangles.

The compounds reach the brain and are not significantly toxic.

Neurofibrillary tangles, Tau, and CDK5 in Alzheimer’s Disease

Model Steps in pathology:
1. Kinase proteins such as CDK5 hyperphosphorylate Tau
2. Tau detaches from microtubules (skeleton of the neuron)
3. Tau aggregates to form neurofibrillary tangles
4. Cell mechanisms fail to clear tangles from the neuron
5. Cell Death

Summary
Autopsy of an Alzheimer’s Disease brain reveals aggregations of two specific proteins inside or outside of the cell. These proteins normally attach to the microtubules (skeleton of the neuron) or the outer cell membrane. Our aim was to take a mouse model that develops these two hallmarks of the disease and try to clear the brain of one of these protein aggregations. We focused upon the aggregation of Tau inside of the nerve cell. Tau is a protein that normally attaches to the microtubules to stabilize their structure. However, if kinase proteins, such as CDK5, add multiple phosphate chemical groups to the Tau protein, then Tau detaches from the microtubules and forms clumps in the cell that are called neurofibrillary tangles. Our experiments treated mice with inhibitors of the protein kinase CDK5 to monitor the clearance of Tau neurofibrillary tangles in the brain.

Verification of Histological Results

The density of the upper band of hyperphosphorylated Tau decreases upon treatment with Compound 1 or Compound 2.

The upper band of Tau is found in the hippocampus but not in the cortex of the brain.

The Sarkosyl assay isolates insoluble proteins
Our upper and lower bands of hyperphosphorylated tau are insoluble

Mass spectrometry reveals that CDK5 inhibition prohibited phosphorylation of Tau at two specific sites.

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