Abstract
Alzheimer’s disease is an incurable and terminal neurodegenerative disorder and is the most common form of dementia. There are 5.2 million people in the United States living with Alzheimer’s and it is projected that 10 million baby boomers will eventually develop the disease. One of the three major competing hypotheses explaining Alzheimer’s involves hyperphosphorylation, the addition of more than one phosphate group, to tau, an intracellular microtubule protein. Thrombin is a serine protease involved in the final step of blood coagulation and is normally present in the brain’s neurons, where it cleaves tau. It is necessary for thrombin to cleave tau in order to prevent clumping of the microtubules for normal neuron function. In Alzheimer’s patients, extracellular thrombin binds and cleaves PAR-1, a protease activated receptor embedded in the cell membrane. The interaction between thrombin and PAR-1 exposes a peptide sequence that activates kinase enzymes adding phosphate groups to tau. This leads to tau hyperphosphorylation and tangled microtubules because intracellular thrombin is unable to cleave the phosphorylated tau. Scientists are interested in studying the binding of thrombin to PAR-1 because this interaction is a possible therapeutic target for developing treatments for Alzheimer’s and other neurodegenerative disorders.

I. Introduction
Alzheimer’s disease affects the elderly, causing memory loss and dementia. Thrombin, a serine protease, is found in high levels in the brains of Alzheimer’s disease patients. There it binds PAR-1, a membrane embedded receptor, and triggers a multistep process that leads to the tangling of a microtubule protein, tau. The resulting tau tangling is one hypothesis that explains the destruction of neurons and progression of Alzheimer’s disease.

II. Normal vs. Alzheimer’s Disease Thrombin-Tau Interactions

Normal

Alzheimer’s Disease

Thrombin is unable to cleave phosphorylated tau because the phosphorylated residues mask the sites normally recognized by thrombin.

III. Laboratory Evidence: Effect of Thrombin on Tau

Hypothesis: Excess thrombin results in tau aggregation.

Data:

<table>
<thead>
<tr>
<th>Total Tau</th>
<th>Phosphorylated Tau</th>
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Conclusion:

- Without thrombin, tau is not phosphorylated, as shown by the absence of fluorescent spots in the top row.
- In the presence of thrombin, tau is phosphorylated, leading to tangling, as shown in the bottom row.

IV. Summary
Thrombin, a protein normally found in the brain’s neurons, is present outside the brain cells in Alzheimer’s disease. Thrombin cleaves the PAR-1 receptor and initiates a signaling process that eventually results in hyperphosphorylation of tau. Intracellular thrombin, normally responsible for cleaving tau, is unable to do so. The resulting tau tangling progressively destroys the brain’s neurons and leads to death.

References:
- www.noelderabuse.com (Section 1 Photograph)
- www.afar.com (Section 2 Photograph)

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