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Article

Using the COmplex PAthway SImulator, stage analysis, and chemical kinetics to develop a novel solution to lower Tau concentrations in Alzheimer's disease

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SUMMARY

Alzheimer's is a disease which afflicts 5.5 million Americans. In this study, we asked whether a Tau immunotherapy treatment, Hsp70 protein treatment, or dual treatment approach of both the Tau imunotherapy treatment and Hsp70 protein treatment leads to a greater reduction in Tau protein concentration. As a high concentration of Tau protein is directly related to Dementia and Alzheimer's, the proposed treatment which reduces the Tau protein concentration the most is the best Alzheimer's/Dementia treatment. We determined through our experimentation that the Tau immunotherapy treatment results in the least Tau protein concentration in early and advanced cases, less than the joint treatment and single Hsp70 protein treatment. However, the joint treatment was more effective at reducing Tau levels when initial Tau levels were consistent with those found in medium stage Alzheimer's. The dual treatment had similar effects as the immunotherapy treatment, but with less impacts to Tau concentration. The Hsp70 treatment slowed the increase in Tau concentration, delaying the simulated progression of the disease but not stopping the disease. However, the Hsp70 treatment had the lowest standard deviation, demonstrating it is the most consistent treatment. Overall, we were able to display that the effectiveness of the treatment ultimately relies on the stage of Alzheimer's.

INTRODUCTION

Alzheimer's disease is a disease that causes loss of neural function such as loss of memory and logical thinking to the extent where daily functions are difficult to carry out (1). Dementia is known as the general sphere of diseases which cause memory loss, while Alzheimer's disease is the most common type of Dementia, accounting for 60% to 80% of all cases of Dementia (1). Other forms of Dementia are Lewy body dementia, frontotemporal disorders, and vascular dementia (2). Alzheimer's disease affects mostly elderly individuals over the age of 65 but is not a natural part of aging (1). Alzheimer's disease is a progressive disease, as it does not manifest itself in its full form initially (1). One usually has minor memory loss initially, which then progresses into more major memory loss (1). Alzheimer's disease has no cure, but medications can make the disease more tolerable (1).

Currently, more than 5.5 million Americans live with Alzheimer's disease (2). These individuals suffer tremendously due to their lack of mental capability (2). Alzheimer's disease is also deadly, as it is the sixth leading killer in the United States for all ages and the third leading killer for those 65 years old or older (2).

Scientists have narrowed down the cause of Alzheimer's disease to two factors: plaques and Neurofibrillary tangles (3). These plaques are formed from beta-amyloid, which is residue from the protein, amyloid precursor protein (3-4). Currently, the function of the amyloid precursor protein is unknown (4). The amyloid precursor protein extends as a long rod, extending from inside the cell through the cell membrane to outside the cell (4). Scientists have determined the amyloid precursor protein splits into several pieces which reside both inside and outside the cell (4). One of the cut pieces called is beta-amyloid (4). These beta-amyloids join to form large plaques, which harms neurons and consequently brain function (3). The beta-amyloids first form very small groups, called oligomers, then chains of these oligomers form fibrils, then collections of these fibrils to build beta-sheets. The beta-amyloids are particularly sticky, resulting in a greater tendency to form large blocks (4). The brain naturally builds microtubules with Tau proteins to transfer nutrients and signals between neurons (3). Tau protein is malleable, as they are used to build microtubules between neurons in a variety of angles and shapes (3). When a patient has Alzheimer's disease, the patient's Tau protein forms abnormal Neurofibrillary tangles, which block the connections between the neurons (3).

One potential solution to decreasing the amount of Tau protein is through using Tau immunotherapy (5). Tau immunotherapy involves usage of antibodies to attach themselves to the Tau protein and remove them from the brain (6). The Tau immunotherapy approach offers insight into removing the Tau residing in the brain. This treatment has been successful in treating mice and will move to human trials in the future. Although this treatment has promise, it is built in removing the Tau once it is created not on slowing or stopping the creation of the Tau.

Another solution to decreasing the amount of Tau proteins

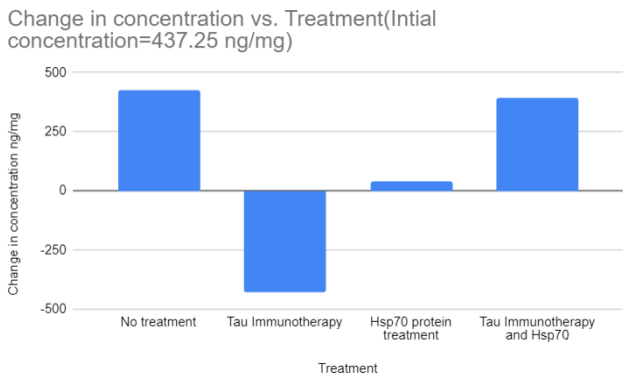

Figure 1. The resulting Tau concentrations and the change in Tau concentration for initial concentrations of 473.25 ng/mL. No treatment, Tau immunotherapy treatment, Hsp70 protein, or dual treatment of Tau immunotherapy and Hsp70.

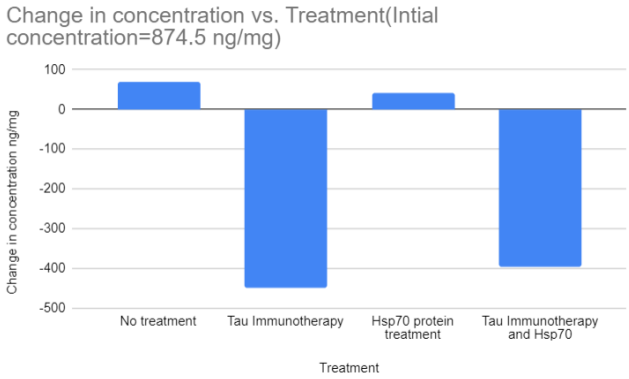

Figure 2. Resulting Tau concentrations and the change in Tau concentration for initial concentrations of 874.5 ng/mL. No treatment, Tau immunotherapy treatment, Hsp70 protein, or dual treatment of Tau immunotherapy and Hsp70.

is through using the Hsp70 protein (7). Hsp70 is a protein that has been shown to decrease the Tau protein production in the brain (8). Hsp70 does this through decreasing mutations in the MAPT gene that encodes Tau, thus limiting the production of Tau protein (8). The weakness with this approach is the production of Tau is decreased, but the current amount of Tau in the patient's brain remains the same (8). The Hsp70 treatment cannot reduce the amount of Tau in the brain, only the production of that Tau (8).

We utilized a simulation to determine whether a Tau immunotherapy treatment, Hsp70 treatment, or joint treatment of Tau immunotherapy and Hsp70 treatment resulted in the greatest decrease in Tau protein concentrations. We determined this through running simulations with a COmplex PAthway SImulator (COPASI). We modeled the brain through COPASI, a chemical simulator.

The brain contains 86 billing brain cells and 7000 connections. As we did not have enough computing power to simulate such a complex organ, so we simplified the brain to 86,000 neurons. We ran the simulations for different initial concentrations of a variety of different chemicals involved in Tau production and removal and measured the results for the Tau concentration over time. We hypothesized the dual treatment would be the most effective, as we reasoned when the amount of antibodies are increased, the rate of Tau removal should increase. This coupled with the decrease in the Tau production with Hsp70 would make the dual treatment most effective. In the simulations, we determined the Tau immunotherapy treatment approach was the most effective Tau treatment as it caused the greatest decrease in Tau concentration.

RESULTS

We simulated the effects of Tau immunotherapy treatment, Hsp70 protein treatment, and a dual treatment approach. We used the COPASI simulator to collect data on each of these treatments and compared the Tau concentrations over time to determine the most effective treatments. The Tau protein concentration in the brain for an Alzheimer's patient is 874.5 ± 51.34 ng/mL (8). We set the Tau concentration to 437.25 ng/mL, 874.5 ng/mL, and 1749 ng/mL. We conducted four different trials for each treatment, with a total of twelve trials. Each trial consisted of an initial concentration of half the Tau concentration (437.25), the Tau concentration (874.5), and double the Tau concentration (1749).

In **Figure 1**, we simulated early stage Alzheimer's, with Tau concentrations at 437.25 ng/mL. We observed the best treatment here was Tau immunotherapy, as it reduced the Tau concentration more than other approaches. In the early stage, Tau immunotherapy was the only treatment which decreased the Tau concentration. Additionally, both the joint treatment and Hsp70 slowed the growth of Tau compared to the control simulations but did not lower tau concentrations. In **Figure 2**, Tau immunotherapy was also the most successful treatment, as it caused the greatest decrease in tau. In the middle stage simulations, the joint treatment also caused a decrease in tau concentration, but not as much as Tau immunotherapy alone. Hsp70 reduced Tau production in comparison to the control simulations but did not lower tau concentrations. However, in **Figure 3**, the joint treatment of Hsp70 and Tau immunotherapy alone was most effective.

In summary, every treatment in every simulation produced better results than the control simulations. In early and middle stage Alzheimer's the Tau immunotherapy was most effective. In late stage Alzheimer's, the dual treatment was more effective.

DISCUSSION

In this study, we simulated the effects of Tau immunotherapy treatment, Hsp70 treatment, and a joint treatment of both Tau immunotherapy and Hsp70 treatment to determine the most effective Tau treatment as a possible cure to Alzheimer's disease.

Figure 1 lists the changes in concentrations of Tau protein in simulations without treatment, with Tau immunotherapy treatment, Hsp70 treatment, and a dual approach of both

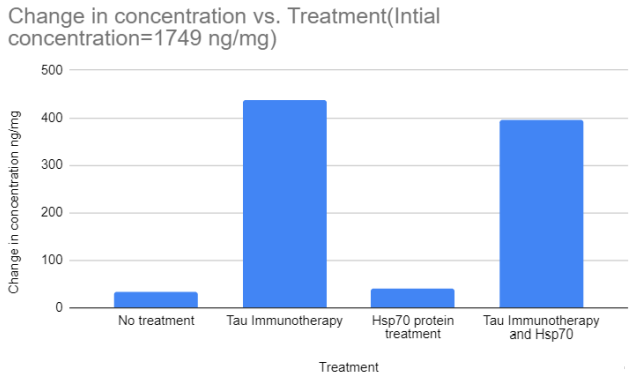

Figure 3. The resulting Tau concentrations and the change in Tau concentration for initial concentrations of 1749 ng/mL. No treatment, Tau immunotherapy treatment, Hsp70 protein, or dual treatment of Tau immunotherapy and Hsp70.

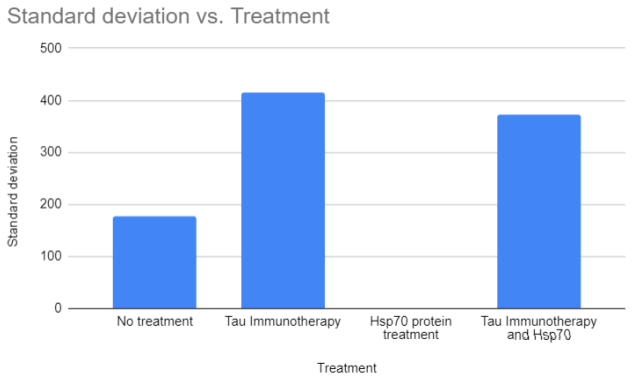

Figure 4. Standard deviation calculations for all four treatments.

Tau immunotherapy treatment and Hsp70 treatment. The Tau concentration in these simulations were 437.25 ng/mL, best modeling a patient in the early stages of Alzheimer's. In this case, the Tau concentration increased 427.474 ng/mL in the non-treatment simulation. Therefore, any treatment which resulted in a lower increase in Tau concentration would be more effective than no treatment at all. The Tau immunotherapy treatment was the most effective of all the treatments in **Figure 1**, resulting in Tau concentration decreasing by 427.473 ng/mL. The next most effective Tau treatment was the dual approach, which resulted in a decrease of 393.6473 ng/mL. The least effective approach was the Hsp70 treatment, which resulted in a 41.61 ng/mL increase in Tau concentration. Although the Hsp70 treatment was the only treatment which resulted in an increase in Tau concentration, it must be noted the increase in Tau in the Hsp70 treatment was less than that in the no treatment group, indicating Hsp70 is a valid way to slow the progression of Alzheimer's but not cure it. From the data we gathered from the 427.474 ng/mL Tau concentration group, we can conclude that the Tau immunotherapy is likely to be effective for patients with early stages of Alzheimer's.

Hsp70 treatment was more effective than no treatment, despite the increase in Tau concentration. Overall, Hsp70 was the least effective treatment, although it still slowed the progress of the disease, while the Tau immunotherapy treatment was the most effective treatment for the 874.5 ng/mL Tau concentration simulation.

Then, we reviewed the effectiveness of the treatments when the Tau concentration is 1749 ng/mL (**Figure 3**). This Tau concentration was used to simulate patients who are in the advanced stages of Alzheimer's disease. The most effective treatment was the Tau immunotherapy treatment, which results in a decrease of 437.25 ng/mL in the Tau concentrations.

With **Figures 1-3**, we were able to determine which treatment was most effective in particular stages of Alzheimer's. However, another important factor is standard deviation, given we do not know the Tau concentration. We determined the Hsp70 protein treatment had the lowest standard deviation, and therefore was the most consistent. Secondly was the no treatment approach. However, although the standard deviation was second lowest, standard deviation is how much the data points deviate. Because of this, the no treatment was consistent, but consistently ineffective. The highest standard deviation for the treatments was Tau immunotherapy.

Overall, the Tau immunotherapy treatment resulted in the greatest decrease in Tau concentration in the patients who were in early and advanced stages of Alzheimer's. The joint treatment was more effective for medium stage Alzheimer's. Due to the standard deviation calculations, the Tau immunotherapy treatment is not the most consistent given we do not know the Tau concentrations. If we do not know the Tau concentrations, the Hsp70 protein treatment is most consistent. We are not entirely sure why the Tau immunotherapy treatment is more effective in the early stages and finals stages, but it does validate our model. In a poorly made model, the joint treatment would be more effective in all stages, as it would be simply the addition of two treatments. However, here we can see the joint treatment was effective only one of three times.

Future experiments would include testing other treatments to Alzheimer's and other combinations of treatments to find an even more effective treatment and testing these treatments in animal models, such as mice.

METHODS

We used the COPASI simulator to determine the Tau concentrations over time with Tau immunotherapy treatment, Hsp70 treatment, and dual treatment approach. We used the Tau protein concentration to determine the most effective treatment.

We used COPASI version 4.27, Windows 64 bit. We imported a neuron environment to simulate where the reactions will occur. We also manually created 7 species: Tau, Hsp70, Hsp1, Binding immunoglobulin protein, MAPT, TauN

Table 1. Kinematics equations used in COPASI.

Parameter	Reaction	Rate Law
Hsp70_creation	HSP1 + "Binding immunoglobulin protein" -> Hsp70	Mass action(irreversible)
Tau_Creation	MAPT -> Tau; Hsp70	Mass action(irreversible)
Tau_destrction	Tau + Tau immunotherapy_Drug -> TauN	Mass action(irreversible)

and Tauimmunotherapy_Drug. We created three reactions: Hsp70_creation, Tau_Creation and Tau_destrction. We then ran the simulations with varying amounts of initial concentration.

We defined a function which gave the end points of the brain, then randomly generated neuron locations between those endpoints. We ensured neurons were not closer than 20 nanometers. We then connected close neurons to each other. At each of these neurons, we inserted tau proteins with 874.5 ng/mL, 437.25 ng/mL, and 1749 ng/mL. We then defined known reactions, as can be seen in **Table 1**. We then ran this simulation on our 86,000 neurons. We summed the remaining tau and recorded the results.

COPASI offered data in graphs in data tables. The graphs provided valuable visual analysis of the data but did not allow us to quantitatively measure which approach was more effective. Therefore, we used the data points from COPASI to measure quantitatively the most effective treatment.

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