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Research on Alzheimer's Disease: Time as a Factor in Anti-Herpes Drug Treating HSV1 Virus and A-ßeta Related Oligomer Plaques

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Abstract: *Researches in the past had utilize anti-herpes medication on mice to determine its effect on treating Alzheimer's Disease by eliminating possible plaque formations. While the medication was proved to be effective on mice, however, its usage on human patients in clinical trials indicated to have no results. Yet, patients in clinical trials are in terminal stages of the pathology, thus the effectiveness of any medication may be doubted. Based on this problem, this work designs a new experiment to assess the amplitude of the mice's recovery from Alzheimer's when they are injected with the Anti-herpes virus drug at different times. From comparing the extent of oligomer deposits to the experimental mice and the control group, we could obtain the best timing for the medication to be properly working. Then it can apply those on human Alzheimer's patients at appropriate stage of the pathology for efficacious treatment.*

Keywords: *Alzheimer's Disease, HSV1 virus, Amyloid-ßeta, Oligomers, Antiviral treatment*

1. Introduction

Alzheimer's Disease had long been a chronic neurodegenerative disease that many scientists and doctors researched extensively upon, with its symptoms of losing recent memories. The cause of Alzheimer's was barely known for centuries and researchers had proposed various possible theories for this cause. Eimer's paper, published in 2018, used accurate experimental results to point out that Amyloid ßeta oligomers' aggressive fight responses against Herpesviridae virus infection has led to acceleration in ßeta-Amyloid deposition, in which its over-accumulation would drive neuroinflammation which will lead to the progression of Alzheimer's development[1][2]. Another study, conducted by Pandey and his team, by detecting immunity of HSV1 in Alzheimer's patients, further proves this association between Amyloid ßeta and HSV1.[3]

Then, based on this theory, scientists in another experiment developed an Anti-herpes virus drug in attempt to alleviate the pathology of Alzheimer's, by slowing down ßeta-Amyloid oligomer plaques formation as a result of the elimination of Herpes virus. 5×106 PFU/μl of HSV1 are injected into the hippocampus of numerous transgenic AD mice (5XFAD) and Anti-herpes virus drugs are adopted on those mice[4]. While those mice exhibit recoveries in memory and cognitive abilities, similar experiments in clinical trials on Alzheimer's patients do not display the same results[2][4]. Then I noticed that most Alzheimer's patients in clinical trials are in the late stage of pathology. Injection of the Anti-herpes virus drug may not be meaningful since the Amyloid ßeta already attacked the Herpes virus and formed extensive ßeta-Amyloid oligomers for a long period of time. Hence, I hypothesize that the timing of the development of Alzheimer's is the key factor determining the difference in the effectiveness of the Anti-herpes drug apart from the different brain structure of mice and humans.

2. Results

The experiment involves a total of 150 5XFAD mice around the age of 8 to 10 months that are put into 12 separate groups. All conditions remained the same for every group, including the food they eat, the amount of light they receive, the temperature and moisture in the area. The identical condition serves to ensure the variable is the only difference among the 5XFAD mice. The independent variable in this experiment is the time in which 5XFAD mice received the Anti-herpes virus drug after herpes virus injection. The 5XFAD mice possess Amyloid Precursor Protein gene that would produce APP and be cut by secretase into a segment called Amyloid ßeta.

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As we inject 5×106 PFU/μl of HSV1 into the hippocampal region of each 5XFAD mice, the Amyloid ßeta will instantaneously fight against Herpes infection and speed up oligomer deposits, which will drive Alzheimer's pathology into a severe state. The injection of Anti-herpes virus drugs into the 5XFAD mice are believed to be effective in treating Alzheimer's; yet, the extent of the effectiveness may depend greatly on the development of the pathology. Thus, by feeding the 5XFAD mice Anti-herpes virus drugs at several different times as they are injected with the virus, in other words different stages of development of Alzheimer's, we can measure the dependent variable: progression of the Alzheimer's development on the various times drugs are adopted. We can use the data to find the period of time when the drug is most useful in treating the disease and the period of time that the drug will still be effective on the patient.

The control group will have 40 5XFAD mice, which after injection of the HSV1 virus, are not injected with the antiviral drug, while each 11 experimental groups of 10 mice will receive the Anti-herpes virus drug after a certain period of time after injection of Herpes virus, ranging from 3 hours to 1 year (3 hours, 12 hours, 24 hours, 3 days, 1 week, 2 weeks, 1 months, 3 months, 6 months, 10 months, 1 year). The sample size of 10 mice per group ensures any outliers in the experiment and will collect a more averaged data to be accurate. The behaviors of the mice after medicine taking will be recorded. Then, after about 5 days after the Anti-herpes virus ingestion, the hippocampal region of the mice in each group will be dissected and examined to measure the amount of oligomer deposits remaining in the area. The amount of oligomer deposits in each experimental group will be compared with the amount in the control group to determine the effectiveness of the drug according to the different time the mice take the drug.

Since we are not able to perform the experiment in actual offline laboratories, we predict several possible results and their further value in clinical usage. The time of medicine intake effective for 5XFAD mice may not be consistent with the time for humans due to stark physiological differences. Yet, the proportion of the time to lifespans and the stage of Alzheimer's plaque development can shed light into the approximate time effective for human Alzheimer's patients.

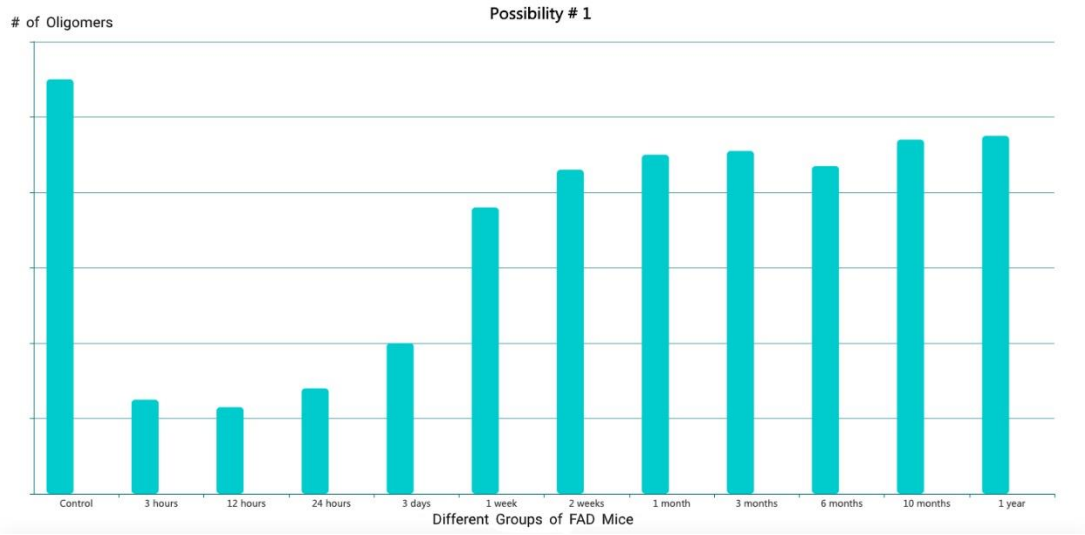

Figure 1 Only mice injected with Anti-viral drug within short time exhibit decline in oligomers

First and foremost possibility, as Figure 1 demonstrates, only the hippocampal region of the experimental mice in groups of 3 hours, 12 hours, 24 hours, and 3 days exhibit explicit decreases in the oligomer plaques, and the other 8 groups display no obvious decline. In this case, the Anti-herpes virus drug may be only effective when the mice intake it in a short period of time after the HSV1 virus invasion. In real life cases on humans, they might not be able to realize their Alzheimer's symptoms in such a short period of time. Therefore, the usefulness will be relatively low and further research into new medicine to treat the pathology will be needed.

The second possibility, shown in Figure 2, will be the experimental mice in groups with time to six months all exhibit declines in the Amyloid plaques in their hippocampus of the brain. Then, the medicine will be promising for patients in their early and middle stages of Alzheimer's while further new types of drugs will be needed to develop in order to treat the patients with long term pathology of Alzheimer's.

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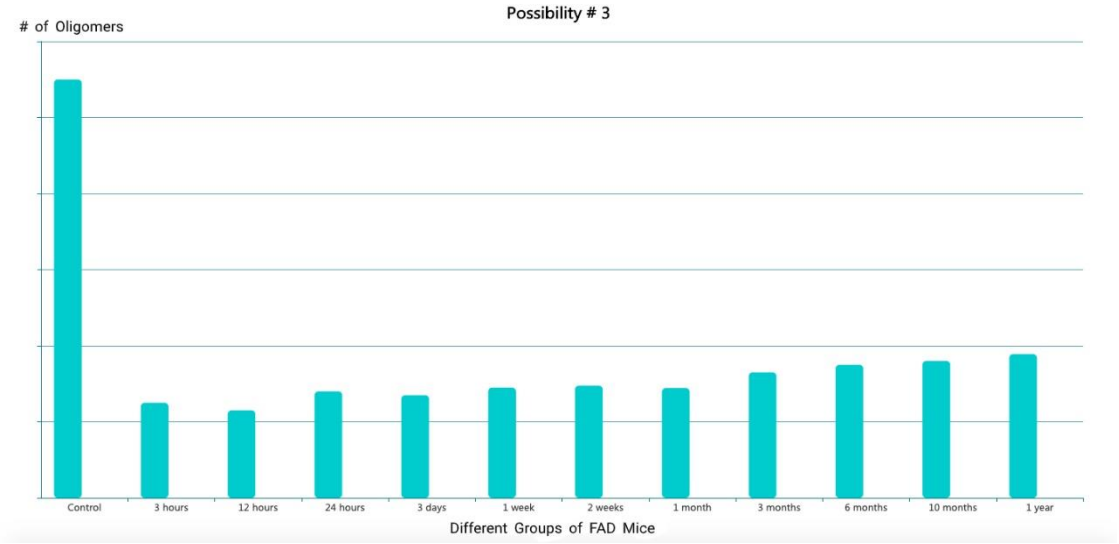

Figure 2 Only mice injected with Anti-viral drug within short and mid-range time exhibit decline in oligomers

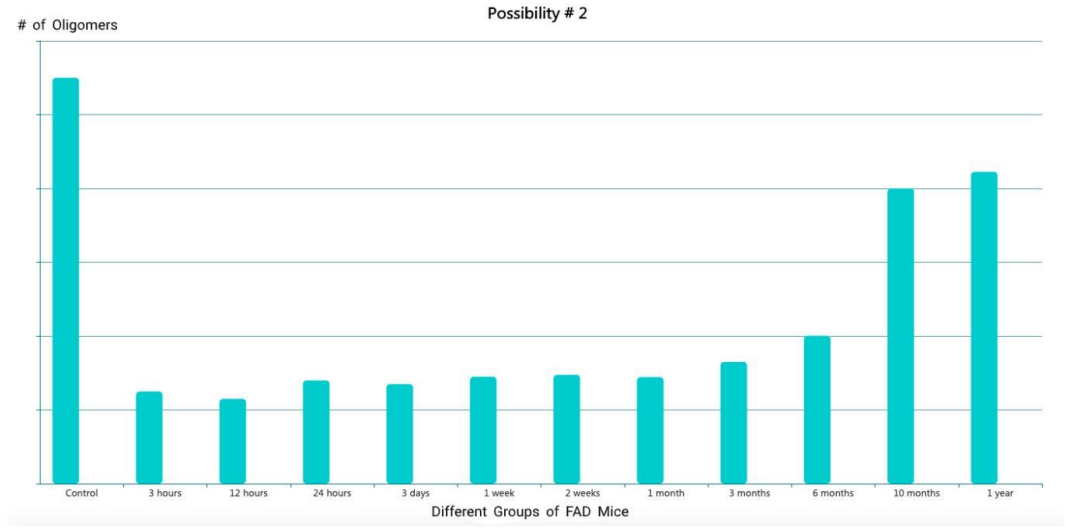

Figure 3 Mice injected with Anti-viral drug within all time periods exhibit decline in oligomers

The last possibility, illustrated in Figure 3, would be that the anti-herpes virus shed promising results on all 5XFAD mice with all ranges of time, but may still not be effective in treating human Alzheimer's patients as a result of the obvious differences in the brain structure of mice and humans. Further clinical trials will be needed; yet, patients who are only in early stages of Alzheimer's pathology would not likely be tested with the drug due to moral issues and thus the practicality remains relatively low. New types of medicine effective for terminal Alzheimer's patients need to be developed and put into clinical trials for its usage by normal patients.

3. Summary & Conclusion

The primary purpose of our experiment was to test the effectiveness of Anti-herpes virus drugs in treating the conditions of human Alzheimer's patients. If the mice in all experimental groups with various times all achieve similar results on the decline of oligomers, then, with the former experiment of this medicine non-effective on terminal Alzheimer's patients, we will come to understand that time is not the factor of the effectiveness of the medicine. Hence, the medicine's practical usages on human patients are challenged in this condition. On the other hand, if the only the mice in experimental groups of late stages (6 months, 1 year) do not display significant recoveries in the Alzheimer's pathology while all other groups of mice experience sharp decline in oligomer plaques, then the Anti-herpes virus medicine retain the possibility to treat human Alzheimer's patients who are not in their last stages of the pathology. Nevertheless, scientists will need to perform further scientific research to determine the exact effective

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time for the human patients, adopting the time of effectiveness of the 5XFAD mice as references. One Conceivable method is comparing the state of oligomer plaques in the hippocampal region of the mice brain and human Alzheimer's brain to attain knowledge of the time. For example, if the 5XFAD mice in experimental group of time until six months all exhibit effective medicine treatment, scientists can compare the amount of oligomers in the hippocampus of control group of 5XFAD mice to human patients with similar oligomer development and deduce the time of after Alzheimer's infection for human. Further clinical trials will also need to be conducted to ensure its safety and effectiveness to be able to adopt it for all Alzheimer's patients. Research can often be obstructed by moral issues, economical conditions, and unexpected events such as the current COVID-19 pandemic. Yet, research would always go on as scientists continue to grasp on their motivation and enthusiasm to solve for unknown quests and to help to dissolve the pains of humans pathologically. Biology is a magic that can bring hope to individuals and I want to contribute to this process of human salvation.

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