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The Impact of Herpes Virus on APP Intracellular Domain (AICD) may Worsen Alzheimer's Disease

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Abstract

The researches of Alzheimer's disease mainly focus on amyloid beta, a part of APP, because the accumulation of amyloid beta forms the plagues that lead to the development of Alzheimer's disease. However, whether AICD, another part of APP, will worsen the Alzheimer's disease is still unclear. To fill the blank in this field of research, our research mainly focuses on the influence of AICD on Alzheimer's disease when the host is infected by the herpes virus, and we hypothesize that the impact of herpes virus on AICD may worsen Alzheimer's disease. We designed to perform a series of experiments on 30 alives mice by infecting the mice with herpes virus and taking the samples of the brain tissues to do Western blot and RNA-sequencing to see the results. The three related experiments can explain whether the amount of AICD changes when the host is infected by the herpes virus, and if it does so, what specific changes in the gene expressions are responsible for worsening Alzheimer's disease. At last, we may treat the human cells the same way we treat the mice to illustrate the conclusion reached from the experiments on mice can also be applied to explain the role AICD plays on the aggravation of Alzheimer's disease of human.

Keywords

Alzheimer's disease; Herpes Virus; APP intracellular domain(AICD).

1. Introduction

There are almost sixty million people suffering from Alzheimer's disease all over the world. Alzheimer's disease, also referred to simply as Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and gradually worsens over time. The most apparent symptom is memory decline, which is caused by the accumulation of amyloid beta, a part of APP. Although APP is composed of three parts-sAPPβ, Aβ, and AICD-the majority of the researches of Alzheimer's mainly focus on the Aβ plaques, one of the factors contributing to the form of Aβ plaques is herpes virus [1]. However, the research of the role AICD plays on the development of Alzheimer's is still unclear. Moreover, noticing that HSV1 could account for 50% or more of Alzheimer's disease cases, we intended to search the impact of HSV on the spliting of APP, which will indirectly lead to Alzheimer's disease [2]. Therefore, the goal of this paper is to explore whether AICD has an influence on Alzheimer's disease when the host is infected by the herpes virus.

In the work, we designed a series of experiments in order to find out whether herpes virus has impact on AICD and whether the impact of herpes virus on AICD will worsen Alzheimer's. The following paragraphs are organized by four main sections. The first section is about the hypothesis, in which the hypothesis and the logic of it will be presented. Next, the designs of three related experiments will be displayed. Then, the possible results of the series of experiments and the conclusions drew

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from them will be discussed. Finally, the last section will be focused on the meaning of the paper to future study in this field.

2. Hypothesis

Several important facts are the premise of our hypothesis. First, since Aβ protects brain from virus infection, it is reasonable to predict that when the host is infected by herpes virus, more Aβ will be produced when brain is infected by herpes to protect the brain [3]. In order to produce more Aβ, the cutting of APP must increase since Aβ is a part of APP, but at the same time, the amount of other part of the APP, AICD, may increase also. As some researches indicate, AICD regulates certain gene expressions, such as neprilysin (nep) and glycogen synthase kinase 3β (gsk3β), whose products play a role in Aβ clearance and tau phosphorylation, respectively [4]. Because nep and gsk3β both control the amount of Aβ, we predicted the change of the amount of AICD will indirectly affect the amount of Aβ by changing the regulation of related gene expressions, which will have an impact on the Alzheimer's. Thus, we reached our hypothesis-- when the brain is infected by herpes virus, the AICD's regulation of gene expressions will change, which will worsen Alzheimer's.

3. Experiment

3.1 Preparation

Noticing that the logical chain behind our hypothesis is extensive, we separated the experiment into three sections for different purposes. In the first experiment, we intend to test whether the amount of AICD will increase after the brain is infected by the herpes virus. Secondly, we want to determine which genes' expressions are changed. Finally, in order to make a logical connection with experiment 1 and experiment 2, we designed experiment 3. In this experiment, we want to show the change of gene expressions is due to AICD. The details of each experiment design are described below.

Before the first experiment, we select 30 alive mice with similar conditions, such as almost the same amount of AICD expression. Then we randomly assign them to three groups with ten mice per group. One group is the control group, in which none of the mice is infected with viruses. Noticing that There are two types of herpes simplex viruses, HSV-1 (herpes type 1, or oral herpes) and HSV-2 (herpes type 2, or genital herpes), we infect one group with HSV-1 while infecting another group with HSV-2. Also, we prepare related buffers and gel to do experiment 1 by Western blot.

3.2 Experiment 1

In experiment 1, we first culture the three groups of mice for half a month under the same conditions, such as temperature, humidity, spaces, and food. After that, we take samples from the brain tissues of the mice of each group separately into tubes. Then, we add buffers and related antibodies to the tubes containing the samples. After loading equal amounts of protein into the wells of the SDS-PAGE gel along with molecular weight marker, we run the gel for proper amount of time at proper voltage. Finally, we can observe the intensity of each band and determine the protein levels of each segment (APP, SAPP, AICD, Aβ).

3.3 Experiment 2

After experiment 1, we begin experiment 2. The main method we use is RNA-sequencing. First, we also take samples from the brain tissues mentioned in experiment 1 and extract the total RNA. The next step is RNA-preparation, in which we purify the RNA by clearing rRNA out by the kits. Then we add related buffers and material to synthesize cDNA chains. After extracting the fragments, we use PCR amplification to proliferate them and, finally, compare the sequence of the HSV-1 infected group and HSV-2 infected group to the sequence of the control group to see which gene expression is changed.

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3.4 Experiment 3

In experiment 3, we use HSV-1 and HSV-2 infected mice brain tissues with mutant AICD separately. We take the samples of tissues with the mutant AICD and extract the total RNA. Then, we use them to do the RNA-sequencing as mentioned in experiment 2. Finally, we compare the result of the RNA-sequencing of the RNA with mutant AICD with the results of experiment 2 separately to see the change of the gene expressions.

4. Result and Conclusion

Because we have three related experiments, we start to talk about each small conclusion we reach from the possible results of each experiment. Then, we focus on the general conclusion we can draw from the experiments together.

In the first experiment, when we compare the fluorescence of the bands of the APP from the HSV-1 infected group and HSV-2 infected group with that of the control group, we can determine the relative intensity of APP. Suppose the intensity of APP will decrease while the intensity of SAPP, AICD, and Aβ will increase compared to the control group. In this case, we can reach the conclusion that The amount of AICD increases when the brain is infected by the herpes virus.

If we reach the conclusion mentioned above and we find that compared with the RNA sequence of the control group, there are some gene expressions changes in experiment 2 including nep, gsk3β, and other genes that are possible to have impacts on Alzheimer's disease, we can say that the infection of herpes virus will change some of the expressions of genes in brain .

Finally, in experiment 3, we may find the result that compared to the sequence of the control group, some genes change in both cases mentioned above, but some genes only change when the HSV-infected mise has normal AICD while the according genes of the HSV infected mouse with mutant AICD remain unchanged. What we can interpret from the result is that the genes that only change when the HSV-infected mice have normal AICD show that the changes are only due to AICD.

As a general conclusion, we can say that the AICD will worsen Alzheimer's disease if experiment 1 shows that amount of AICD increases when the host is infected by the herpes, and experiment 2 indicates that the expressions of the genes that related to the clearance of Aβ change when the host is infected by the herpes while experiment 3 provides a connection between the former two experiments by showing the changes of the gene expression are only due to AICD.

5. Future study

There may be an improvement of our experiment designs: if we perform some extra experiments that show some changes of gene expressions in human brain cells are similar to that of the mice when we treat the human cells in the same way we treat the mice as mentioned above, then we can say that the AICD really affects Alzheimer's disease.

In a word, our study may reveal an important fact that the change of AICD caused by the virus infection will contribute to the aggravation of Alzheimer's disease by reducing the proper clearance of Aβ, since the impacts of AICD on Alzheimer's disease are still unclear. Our study will contribute somehow to the vacancy in the research of the factors contributing to Alzheimer's disease. Also, we may lead to a new possible direction to treat Alzheimer for the researchers in the future, and we expect more future studies of the impacts of AICD on Alzheimer's disease will provide a clearer and more detailed answer.

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