NEUROPHYSIOLOGY

Amyloid-β betta get outta here

A study found that local injection of gene editing proteins significantly improved the commonly observed neuroanatomical and behavioral changes associated with Alzheimer's disease. Moreover, these findings advance the field of research investigating gene therapy as a novel method of treatment for neurodegenerative diseases.

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Every 66 seconds someone is diagnosed with Alzheimer's disease[1]. Alzheimer's is a disease which causes degeneration of the brain through a complex process where plaques accumulate within the brain causing memory dysfunction amongst other deficits, leading to death in many cases[2]. Furthermore, it is estimated that by 2050, diagnoses will increase to every 33 seconds[1]. Currently, Alzheimer's disease is the 6th most common cause of death and has already deaths caused by stroke, heart disease, and prostate cancer combined[1]. This results in over $236 billion dollars a year in health care fees[1]. These statistics express the necessity for rapid development of treatments for Alzheimer's disease. Fortunately, Hanseul Park and colleagues published in Nature Neuroscience this year investigating how gene therapy may be a treatment for people with Alzheimer's disease. They found that their novel delivery technique of gene editing proteins significantly decreased toxic levels of the proteins clumps associated with Alzheimer's disease. These findings suggest a new delivery method to the brain for many neurodegenerative diseases, resulting in more effective and precise prevention or treatment.

Alzheimer's disease is an irreversible neurodegenerative disease resulting in memory dysfunction and hippocampal degeneration due to the accumulation of plaques called **β**-amyloid plaques and tau tangles, amongst other etiologies[3,4,5]. These **β**-amyloid plaques accumulate after the metabolism of **β**-amyloid precursor protein (APP) by ***γ***- and **β**-secretases[6] (Figure 1). Therefore, targeting **β**-secretases activity serves as an important therapeutic target for preventing the accumulation of **β**-amyloid. Although **β**-amyloid accumulation does not account for the entirety of the neurodegenerative properties of Alzheimer's disease, it has been shown to be one of the greatest contributions to the neurodegeneration[7]. Current complications with developing treatments is delivery to the brain. This is because the vascular system of the brain forms what is known as the blood-brain-barrier (BBB)[8]. The BBB selectively allows compounds into the internal structures of the brain. Many drugs are unable to pass the BBB and therefore, treatments, no matter how effective in cell culture, are not effective *in vivo*[8]. Thus, recent studies have been testing novel methods of treatment delivery across the BBB.

The study most recently published has explored the efficacy of amphiphilic nanoparticles. These nanoparticles contain the gene editing proteins collectively known as the amphiphilic-CRISPR-Cas9 construct or nanoparticles for short[2] (Figure 1). An amphiphilic molecule is one that has a side of the membrane which is water soluble and the other side of the membrane is water insoluble, meaning that the particle is able to pass through water-insoluble membranes while holding water soluble components within the vesicle[9] (Figure 1). Hanseul utilized the properties of the amphiphilic nanoparticles to deliver his drug across the BBB. The nanoparticle he

developed contained a CRISPR Cas9 construct which targeted beta-secretase 1 (*Bace1*) and silenced the gene[6,10,11] (Figure 1). The nanoparticles were injected into the hippocampus of mice which were genetically modified to reflect the pathophysiology of Alzheimer's disease[2]. This method of administration allowed for direct administration of the construct in a controlled and localized manner. Through use of these novel methods, they found astonishing results.

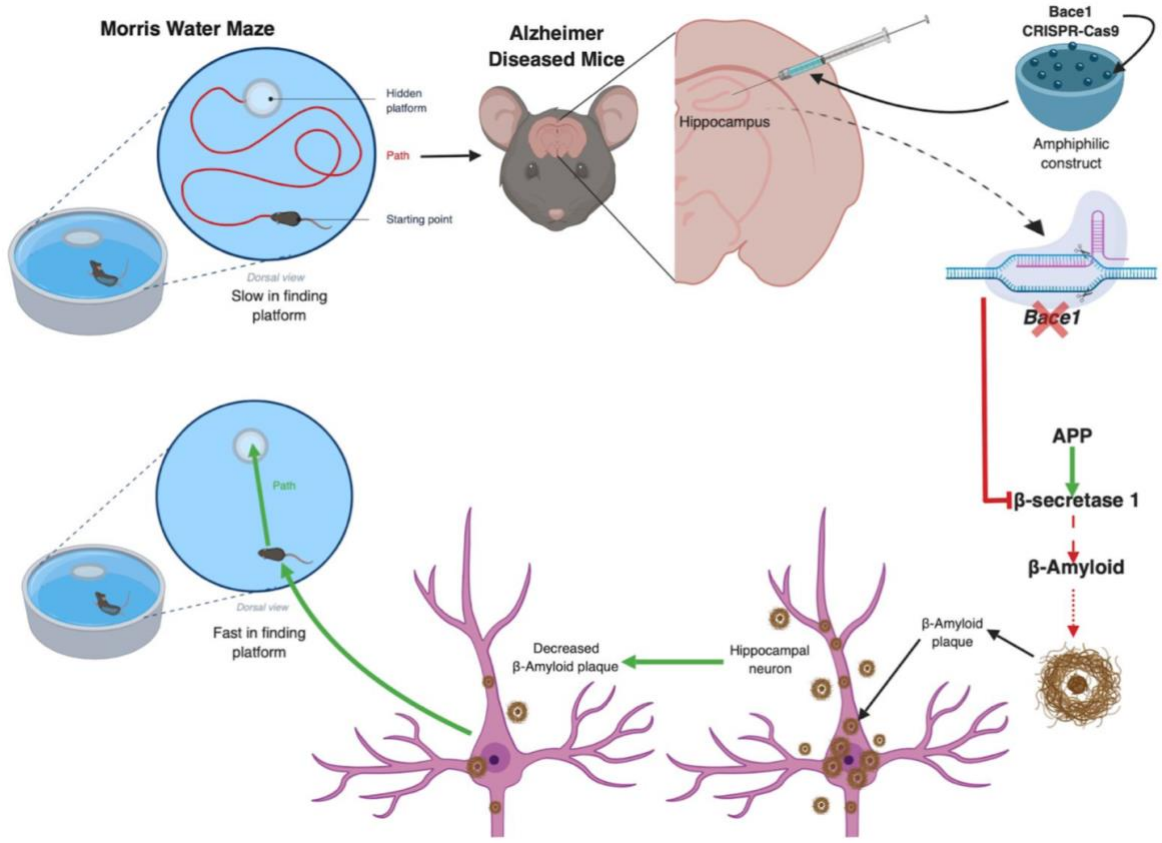

Figure 1: Nanoparticle injection into the hippocampus of Alzheimer diseased mice significantly reduced β-amyloid plaques and improved time to find platform with Morris Water Maze Test. Use of amphiphilic-CRISPR-Cas9 construct to genetically silence the function of **β**-secretase 1 expression significantly reduced the conversion of APP to **β**-amyloid leading to a reduction in **β**-amyloid plaque accumulation. APP = amyloid precursor protein. CRISPR = clustered regularly interspaced short palindromic repeats. Cas9 = CRISPR Associated protein 9.

Upon injection of *Bace1*-Cas9 construct into the hippocampus they reported a 70% reduction of *Bace1* expression[2]. Then, they wanted to evaluate the phenotypic result from the reduction of *Bace1*. Hanseul Park had the mice perform various memory tasks such as the water maze and spontaneous alternation Y-maze test which both demonstrated a significant improvement in memory and learning in the nanoparticle treated mice compared to the Alzheimer's diseased mice (Figure 1). These results are extremely important and clinically relevant as the mice only had to receive one low dose injection with significant reduction in both the plaque accumulation and memory deficits. Although these results are very reassuring for the advance of CRISPR-Cas9 applications, there are remaining concerns yet to be completely evaluated.

One of the concerns by the field is that there will be chronic off-site binding of the CRISPR-Cas9 system which would cause random mutations with unknown effects. Park addressed this concern in his paper by using whole-genome sequencing, whole-exome sequencing and Digenome-

sequencing and found that there was a low percent difference between the sham and nanoparticle treated mice[2]. This thorough examination reassures immediate concerns, however, there have yet to be studies on the chronic effects of the system. Although Park reassured the reader by a study he performed, where he found that the Cas9 system was undetectable in the brain three weeks post-injection[2]. Lastly, after the injection there was no observed increase in inflammation, cell death or microglia recruitment[2].

In conclusion, this work greatly advances the reality of using gene therapy as a possible treatment for neurodegenerative disorders. As Park stated, the novel delivery system may also be used to treat localized neurodegenerative disorders. This opens the future field of research not only to the capabilities at attenuating the effects of Alzheimer's disease but also other diseases such as Parkinson's disease. This study greatly increases the likelihood of remediation of this extremely serious and prevalent disease. Future studies will likely evaluate the effects in higher-order mammals prior to human trials.

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