Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer’s disease mouse model

What the researchers were trying to do

One of the hallmarks of Alzheimer’s disease (AD) is the accumulation of amyloid-β (Aβ) peptide in extracellular space. These accumulations are known as amyloid plaques.

The researchers wanted to investigate whether a temporary opening of the blood-brain-barrier could help clear some of the Aβ plaques in an AD mouse brain and in turn improve cognition and memory. To accomplish this, they decided to use repeated scanning ultrasound (SUS).

What they did

First the researchers established that SUS is a safe method to temporarily open the BBB.

Next, the investigators used two cohorts (groups) of APP23 mice for their study. APP23 mice have been specifically bred to have a large amount of Aβ plaque and deficits in spatial memory (memory related to one’s environment and orientation within that environment).

Cohort 1

Investigators treated 10 male APP23 mice with either SUS or sham treatment for 4 weeks. After 4 weeks, all of the mice underwent behavioral testing for 2 weeks. The goal of this behavioral testing was to analyze the mice’s spatial working memory functions in the Y-maze test, which is based on the preference of mice to alternate between the arms of a maze.

Cohort 2

Investigators analyzed 20 APP23 mice and 10 normal mice in the active place avoidance (APA) test, which is a test of hippocampus-dependent spatial-learning in which mice learn to avoid a shock zone in a rotating arena. After training all the mice in this test, the APP23 mice were then divided into two matching groups. These two groups received weekly SUS or sham treatment for 7 weeks. After 7 weeks, mice were retested in the APA test and given a novel object recognition (NOR) test.
What they found

The investigators found that SUS treatment:

1) Reduced Aβ and amyloid plaque load in APP23 mice.
2) Restored spatial working memory (as measured by the Y-maze test) to wild-type levels.
3) Improved short-term, long-term, and recognition memory as compared to non-SUS treated mice
4) Increased the following microglia-related functions* as compared to non-SUS treated mice: activation, uptake of Aβ into microglial lysosomes, and improved clearance of Aβ plaques
5) Did not lead to increased levels if inflammation when compared to non-SUS treated mice.

*microglia act as the primary immune cells of the brain

Conclusions

“SUS treatment engages microglia and promotes internalization of Aβ into microglial lysosomes, thereby reducing Aβ and plaque load in the APP23 transgenic mouse model of AD as well as restoring function in tests of spatial and recognition memory.”

What this means for the reader

Aβ levels are elevated in the AD brain for two reasons: increased production of the Aβ peptide and impaired removal. Recent therapeutic strategies have targeted both ends of this spectrum, but these approaches come with side effects.

The results of this study revealed that reduction of Aβ levels in an AD mouse model brain can be achieved through a method that is both safe and not dependent on the incorporation of additional therapeutic agents.

Furthermore, this study demonstrated that SUS treatment of the entire mouse brain was able to significantly improve the pathology of AD both biochemically and behaviorally, which paves the way for future therapeutic approaches using SUS in the treatment of AD and other diseases involving protein aggregation.
Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer’s disease mouse model (Gerhard Leinenga and Jürgen Götz)

LINK: http://stm.sciencemag.org/content/7/278/278ra33