

An Introduction to Magtein™

A novel compound for cognitive health



Brain Aging and Cognitive Health

The brain naturally undergoes gradual structural and functional changes as we age, even in the absence of neurodegenerative diseases. Shrinking brain volume begins after age 25 when brain growth peaks. Cognitive health covers a range of conditions including memory loss, stress or anxiety management, dementia, Alzheimer's, phobias, sleep disorder and others. All of these are controlled by the health of the brain.

The good news is, the adult brain is capable of a greater degree of plasticity than scientists have previously believed. Old neurons, even in the brain regions involved in learning and memory, can restore synaptic density, leading to improvement of attention, working memory, short- and long-term memory, reduction of anxiety, and improved sleeping quality. Magtein™, a unique patented compound discovered by MIT scientists, has been shown in animal studies to restore the aging neurons to their youthful conditions.

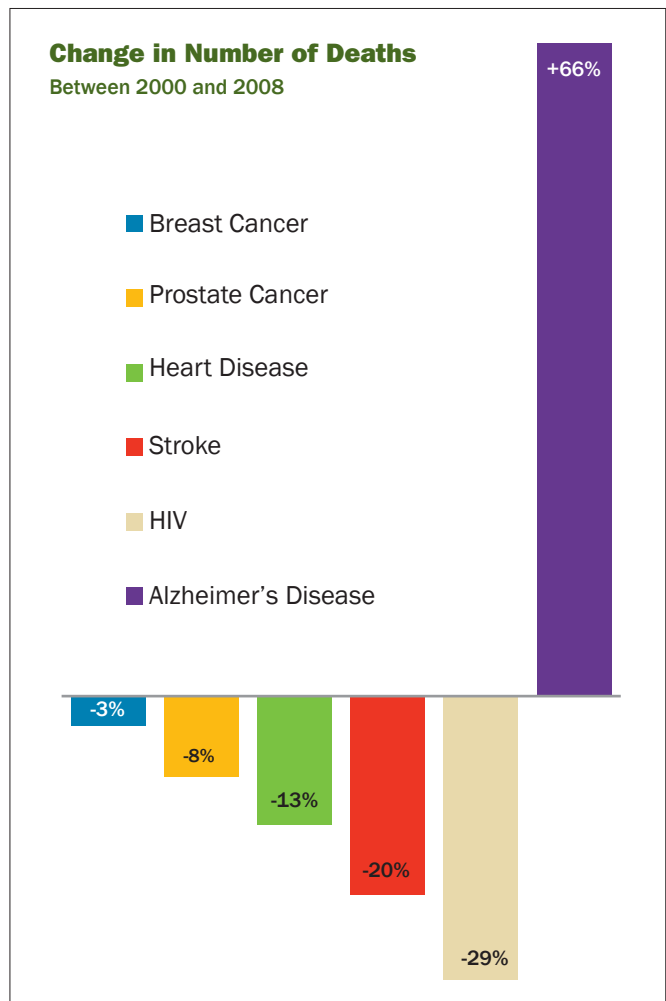
The Cognitive Market

Alzheimer's. As it currently stands, Alzheimer's disease (and related forms of cognitive decline) has no cure and very few effective preventative therapies. Alzheimer's is the world's most costly disease per patient and among the most feared, with major social costs. More than \$203bn was projected to be spent on total U.S. care for Alzheimer's patients in 2013, which presents a major cost to families and society. Alzheimer's disease is the sixth leading cause of death in the US. Deaths from Alzheimer have increased 66 percent between 2000 and 2008, while deaths from other major diseases, including the number one cause of death, heart disease, have decreased.

Anxiety and Stress. In the information age, each one of us is under more stress than ever before. Stress is a major factor affecting cognitive health. Millions of American's are afflicted with severe cases of anxiety. According to the National Institute of Mental Health, 18.1% of US Adults

have an anxiety disorder, of these, 22.8% are classified as severe.

Relaxation and Sleep. According to the National Institute of Health, more than 70 million people in the US are affected by sleep troubles. The prescription sleep aid market is now over \$2.0 billion and expected to grow as baby boomers advance in age, obesity rates climb and stress from the economy and longer work days grow.



Source: The American Alzheimer's Association. Based on preliminary 2008 mortality data.



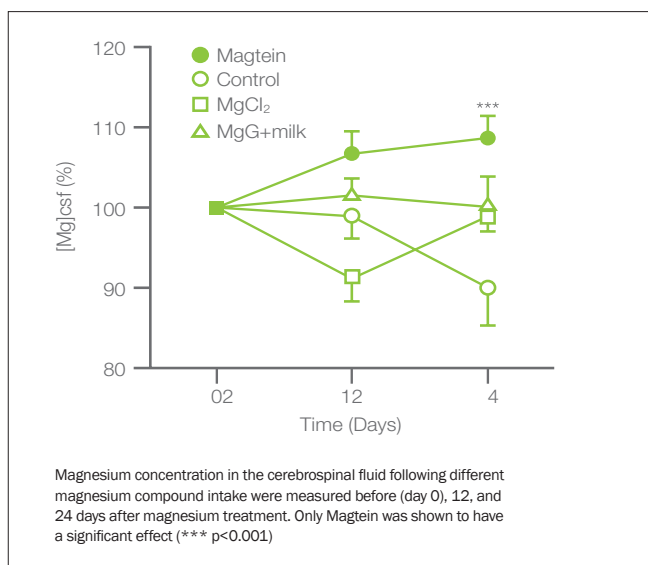
Magnesium is an essential cofactor for more than 300 enzymes involved in biosynthesis processes and energy metabolism. It plays an important role in many of the brain's functions. Only recently, a unique compound called Magtein was discovered by a group of scientists from MIT including a Nobel Prize laureate.

Magnesium has been implicated in many of the brain functions. However, most magnesium compounds have low brain bioavailability and severe gastrointestinal side effects. Magtein is the only magnesium compound that has been shown to effectively raise the brain's magnesium levels, which leads to enhanced learning abilities, working memory, and short- and long-term memory in both young and aged animals. In four published preclinical studies, Magtein was found to improve memory, alleviate anxiety and help prevent the decline and reverse the symptoms of Alzheimer's. These studies and finding will be reviewed in the next section.

Magtein Research

Magtein is the only magnesium forms to effectively increase the brain's magnesium levels

Figure 1: Evaluation of different magnesium forms in the brain



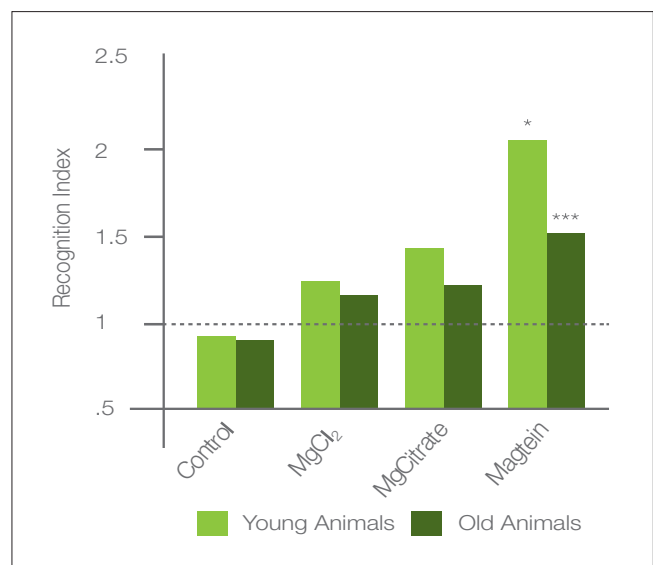
The ability to raise brain magnesium levels were evaluated among the most bioavailable organic and inorganic magnesium forms. Magnesium concentration in the cerebrospinal fluid was evaluated following treatment of different magnesium compounds available including Magtein and the most bioavailable inorganic magnesium, magnesium-chloride, and the most bioavailable organic magnesium, magnesium-gluconate in milk. After 24 days, Magtein was the only magnesium compound to raise the cerebrospinal fluid magnesium concentration with statistical significance. (Figure 1)

Magtein Memory Research. Learning and memory are fundamental brain functions affected by dietary and environmental factors. Here, we show that increasing brain magnesium using a newly developed magnesium compound (magnesium-L-threonate, Magtein) leads to the enhancement of learning abilities, working memory, and short- and long-term memory in rats.

Magtein Improves short and long term memory in young and aged animals.

Animals taking different magnesium forms were evaluated for their short-term and long-term memory by a novel object recognition test. Only Magtein subjects showed a significant increase in both short term and long term memory. (Figure 2)

Figure 2: Recognition index for different magnesium forms



Magtein Improves spatial working memory in young and aged animals

Young and aged laboratory animals' spatial long-term memory was evaluated in a T-maze setting. Animals were timed to find the hidden platform based on a spatial strategy. In both age groups, Magtein intake led to a

Figure 3: Enhancement of spatial working memory by Magtein.

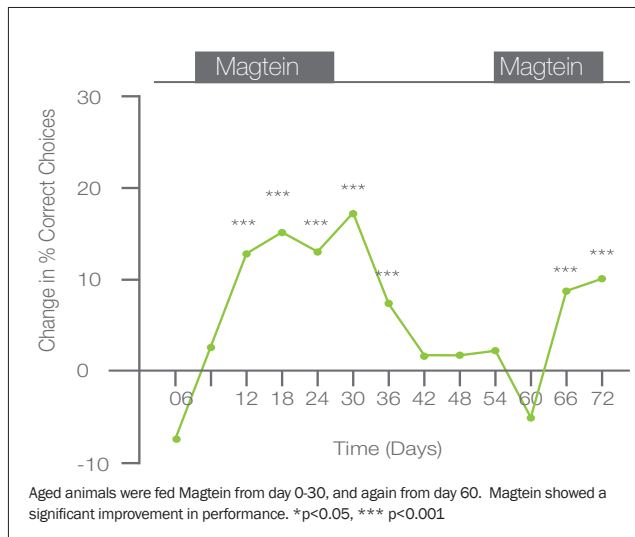
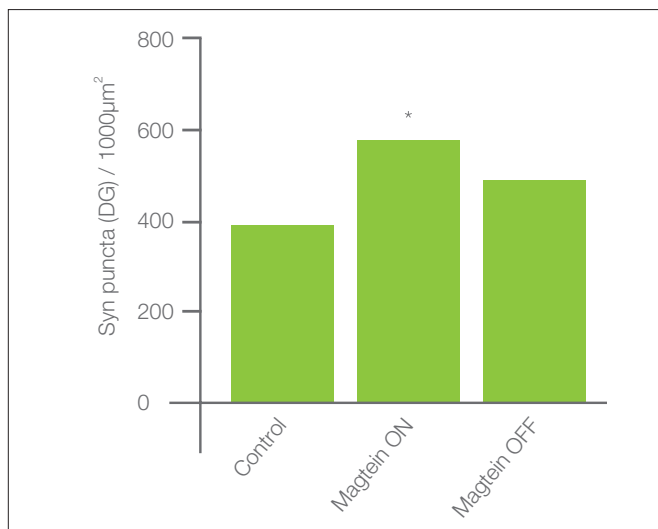
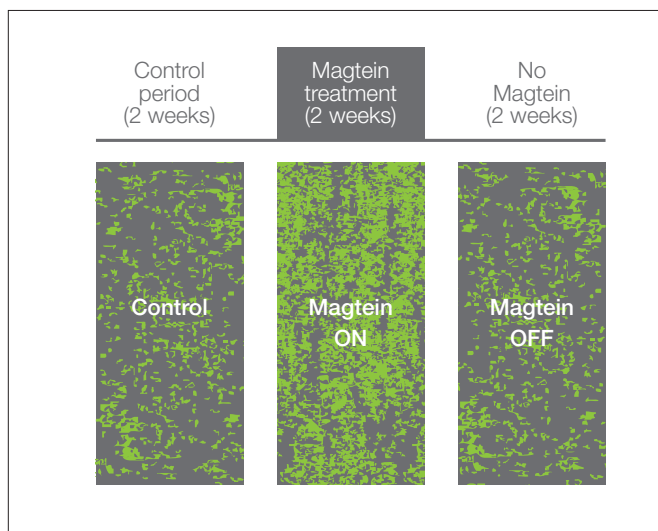


Figure 4: Correlations between Magtein treatment and synaptic density



Brain synaptic density increased when Magtein was administered. Ceasing use of Magtein decreased brain synaptic density. *p<0.05

statically higher spatial working memory. In addition, when Magtein intake was stopped at Day 24 in the aged group,, spatial working memory was reduced to the background level after two weeks. When Magtein intake was restarted at day 60, the effect of Magtein on spatial working memory was observed again. (Figure 3)

Enhancement of synaptic density by Magtein

Previous studies indicate that synaptic connections in hippocampus decline during aging, and this loss of synaptic connections correlates with impaired memory functions. To further characterize the cellular changes that underline Magtein-induced memory enhancement, the effect of Magtein treatment on the density of presynaptic boutons in aged rats was examined. The synaptophysin-positive puncta in the DG hippocampus was significantly higher during the Magtein intake and the effect was diminished after Magtein was removed. These results indicate that Magtein increased the synaptic density in the hippocampus region of the brain. (Figure 4)

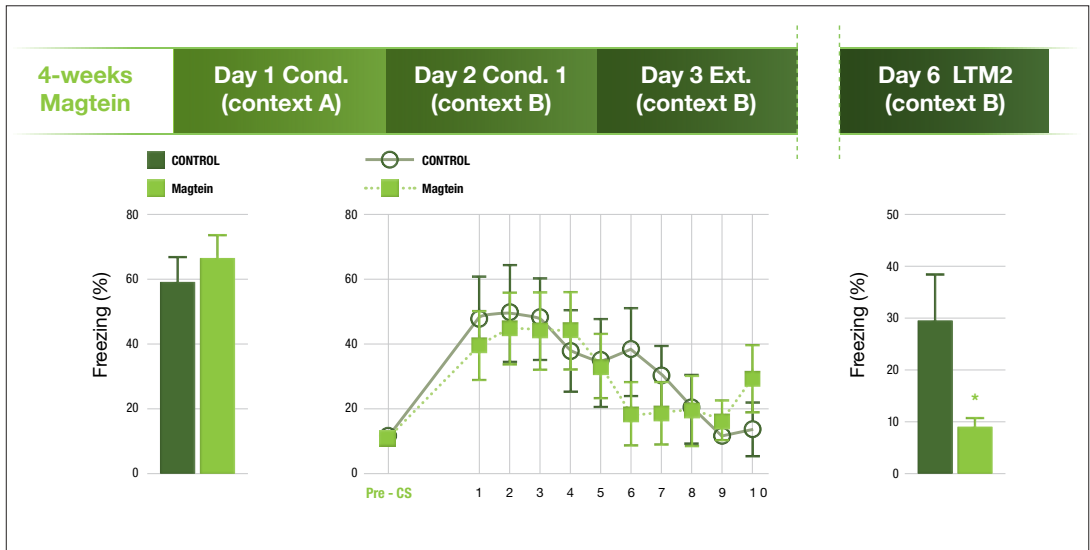
Conclusions: Magtein was shown to improve learning and memory functions in young and aged animals. Magtein-treated rats had higher synaptic density in DG and CA1 subregions of hippocampus that were correlated with memory improvement

Magtein Anxiety Research. Anxiety disorders, such as phobias and posttraumatic stress disorder, are among the most common mental disorders. Though fear-memories are important for survival, the lack of control over such memories increases the risk for affective and anxiety disorders. Cognitive therapy helps in treating these disorders; however, many cases relapse or resist the current therapy, which justifies the search for novel cognitive enhancers that could control anxiety disorders more effectively. Studies suggest that enhancement of plasticity in certain brain regions such as the prefrontal cortex (PFC) and/or hippocampus might enhance the efficacy of cognitive therapy. Magtein, a novel magnesium compound, was previously shown to increase brain synaptic density in hippocampus and facilitate short and long term memory. Thus, it is of great interest to investigate whether elevated brain magnesium has effect on different forms of fear-memories; and more importantly on the extinction and attenuation of fear memories.

Magtein treatment enhances the extinction of fear memory, but not the original fear memory acquisition

Figure 5a: Magtein treatment enhanced extinction learning and retention of the fear memory but not the fear memory acquisition

Magtein treatment enhanced extinction learning and retention of the fear memory.



Freezing behavior of Magtein-treated and control rats conducted 24 h after fear introduction (left) and during extinction learning (middle) and 3 d after extinction learning (right). Magtein-treated rats exhibited significantly lower freezing behavior than controls (n₈) on extinction learning and retention of the fear memory, while there is no difference on fear memory acquisition. *p_{0.05}. Data presented as mean_{SEM}.)

Laboratory animals were subjected to a series of established fear measurement protocols inducing trials with shock and tone. The generated fear freezing response was measured by established FreezeFrame2 software. Magtein was either administered prior to the introduction of the fear or after the introduction of the fear (Figure 5a). Freezing response was measured and brain synapses were examined.

Chronic Magtein intake was found to enhance prefrontal cortex/hippocampus-dependent but not amygdala-dependent fear-memory in rats. Interestingly, Magtein treatment enhanced retention of the extinction of fear memory, without enhancing, impairing, or erasing the original fear memory.

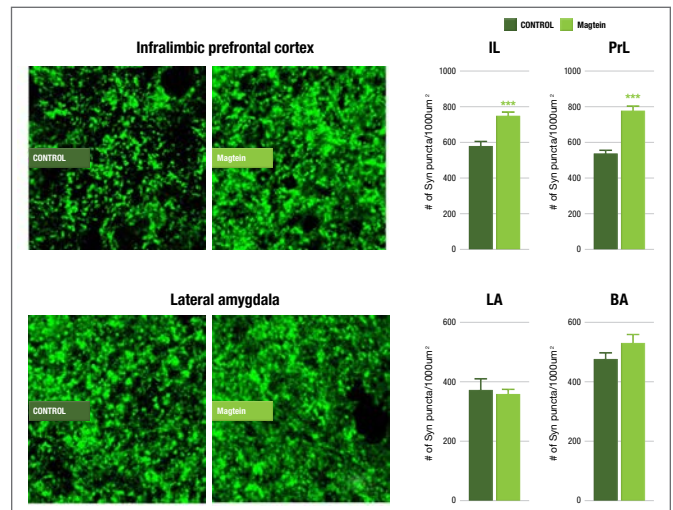
In addition to the fear memory tests, the cellular basis of the effects of Magtein treatment on fear memory was further examined. In the brain of these animals, Magtein intake increased synaptic NMDAR signaling in the infralimbic PFC, but not in the lateral amygdala, suggesting a difference in their sensitivity to elevation of brain magnesium. Consistent with these observations, the plastic density was also increased in the infralimbic PFC, but not in the lateral amygdala. These results suggest that elevation of brain magnesium might be a novel approach for enhancing synaptic plasticity in a regional-specific manner leading to enhancing the efficacy of extinction without enhancing or impairing fear memory formation. (Figure 6)

Emerging evidence shows that dietary factors might play a role in fear and anxiety-like behavior. For example, dietary

magnesium restriction was known to induce an increase in anxiety-like behavior in mice. Our studies suggest that long-term elevation of brain magnesium might enhance the brain regions involved in what was previously described as “top-down control over amygdala” and thus help to control the fear and anxiety. Our data suggest that Magtein might enhance the coping ability with aversive events and control of emotional responses, prerequisites for treatment of disorders such as depression and PTSD.

Magtein Taste Aversion Study. A newly published study (2013), performed by a research group at Baldwin

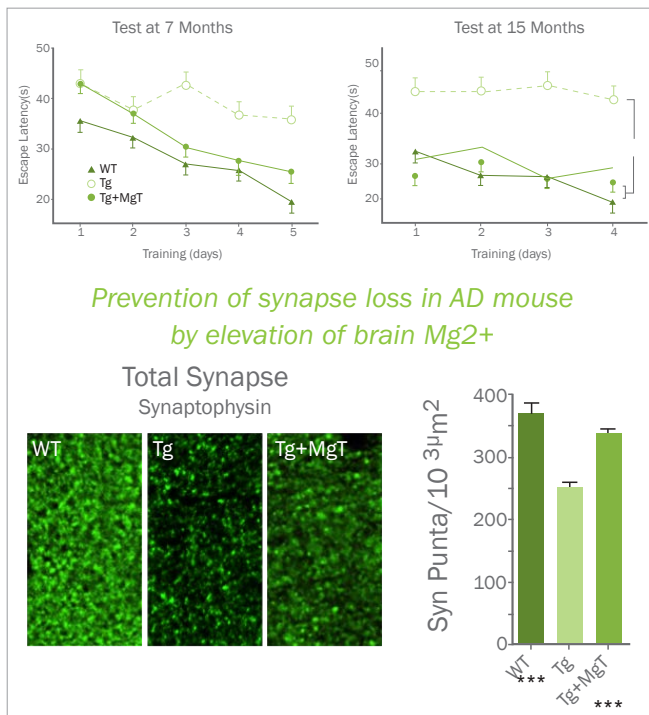
Figure 6: Effects of Magtein on presynaptic boutons in infralimbic prefrontal cortex and basolateral amygdala.



Wallace University, independently demonstrated that proprietary ingredient Magtein, lead to the consolidation and retention of conditioned taste aversion (CTA) in rats. This study, which was not commissioned by AIDP, provided verification by independent research of previously published functions of Magtein in a different behavior system that has been known to use the same brain signaling pathways.

The purpose of the study was to examine the ability of Magtein to affect the extinction and spontaneous recovery (SR) on conditioned taste aversion (CTA). Researchers created an aversive memory that caused the rats to refuse the conditioned stimulus (CS) of saccharin. This aversion memory was then slowly extinguished by repeated exposure to saccharin alone. Magtein treated rats exhibited a faster rate of extinction than the control group. The clinical trial results indicate that the effect of Magtein on memory enhancement as well as fear memory control was verified in a different system by an independent third party research group, since all these functions are controlled by the same pathways of the brain

Figure 7: Decreased Memory & cell synaptic density



Prevention of memory deficits in mice treatment. The Magtein treatment group in both ages had a statistically better response than the transgenic mice. *p<0.05

In AD mice with Magtein treatment, the synapse density is statically significantly improved over the controlled AD mice and comparable to the wild type mice. ***p<0.001

Alzheimer Research. Profound synapse loss is one of the major pathological hallmarks associated with Alzheimer’s disease (AD) and might underlie memory impairment. Magtein has been shown to enhance synaptic density in brain regions control memory and cognitive function, suggesting a possible role in Alzheimer’s disease (AD) management. In a recent publication in Journal of Neuroscience, Magtein was investigated for its ability to ameliorate the AD-like pathologies and cognitive deficits in a transgenic mouse model of AD.

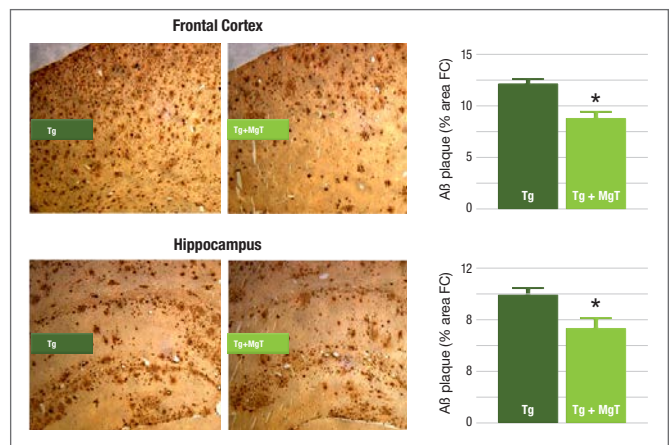
Magtein treatment prevented memory defect and synaptic loss in Transgenic Alzheimer’s mice.

The prevention of memory deficits was tested by a water maze learning test which concluded that Magtein administration improved the memory of Alzheimer’s animals. The prevention of synapse loss was statistically significant for the Magtein treated group (Figure 7).

Magtein treatment reduced amyloid plaques in Transgenic Alzheimer’s mice.

Neurotic plaque is extracellular deposits of beta amyloid in the gray matter of the brain. These Aβ plaques are characteristic features of Alzheimer’s disease. When transgenic Alzheimer’s mice were fed Magtein and the brain sections were compared to the non-treated controls, Aβ plaques were significantly reduced in the transgenic mice on Magtein in both the hippocampus and the frontal cortex (Figure 8).

Figure 8: Reduction of amyloid plaques in AD mouse with MgT treatment

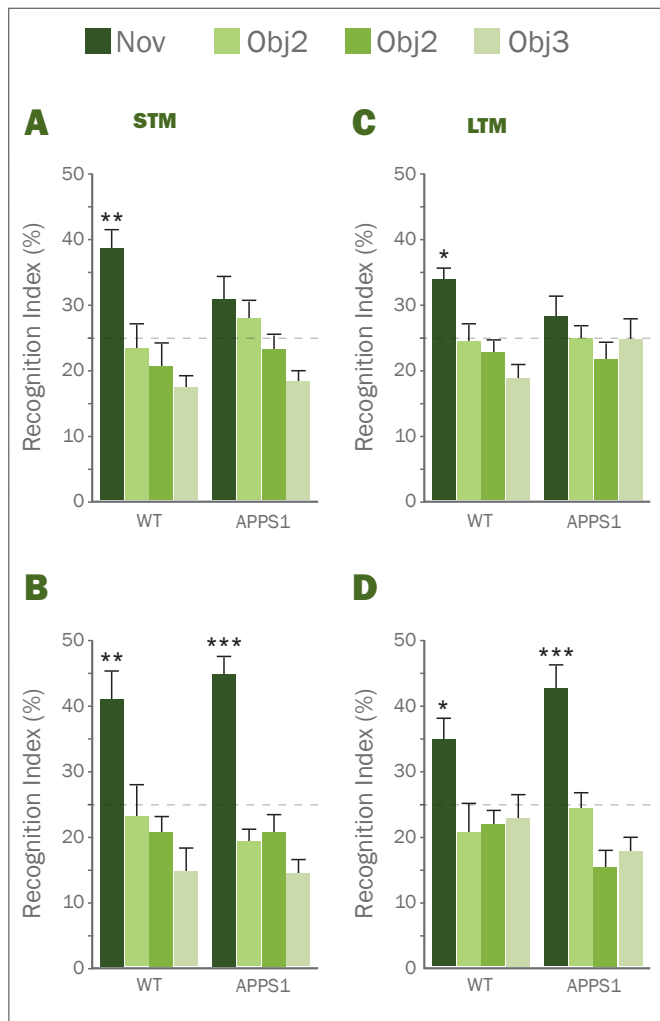


Amyloid plaques were significantly lower in Tg+MgT mice in Hippocampal as well as the frontal cortex *p<0.05.

Reversal of learning and memory deficits and synapse loss in aged Tg mice by Magtein treatment.

If synaptic loss in AD is reversible as demonstrated, Magtein treatment may also be able to reverse memory deficits even when given at end stage AD mice. To test this possibility, 23 months old end of stage AD transgenic mice were treated with Magtein for 1 month and then re-evaluated their memory abilities. As expected, before treatment, Tg mice did not show any preference toward the novel object in short term memory (STM) and long term memory (LTM) tests (Figure 9A&C). After one month of Magtein treatment, strikingly the same Tg mice exhibited significant improvement in their memory test performance (Figure 9 B&D).

Figure 9: Reversal of memory deficit in end-stage of AD mice



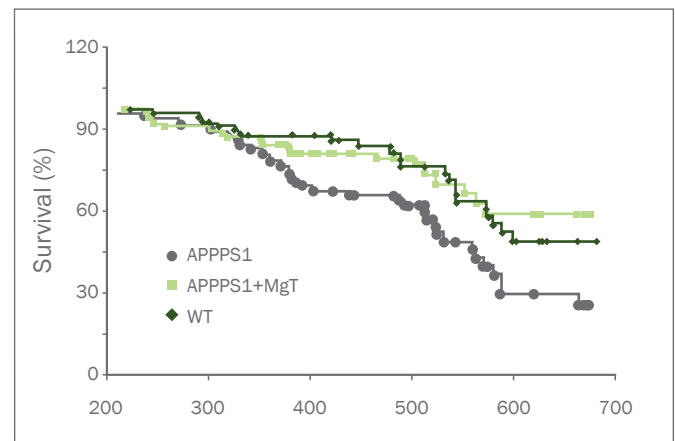
Recognition index of the novel object (Nov) and other familiar objects (Obj 1-3). Repeated on the same mice after Magtein treatment was given to Tg mice after one month. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$

Magtein treatment reduced amyloid plaques in Transgenic Alzheimer's mice.

In addition to the progressive impairment in cognitive abilities, the lifespan of Tg mice was significantly lower than the WT. Magtein treatment prevented the premature death of Tg mice (Figure 10). This longevity with more normal cognitive function highlights the overall beneficial effects of Magtein treatment on body health, at least in mice.

Conclusion: The results demonstrated that elevating brain magnesium was effective at preventing/reversing learning and memory deterioration in transgenic mice, a model of AD-like pathologies. The most striking finding in the present study was that elevation of brain magnesium was effective at restoring synaptic density at the end stage of AD-like pathological progression in transgenic mice, which might be responsible for the restoration of cognitive functions. In addition, Magtein treatment prevented the premature death of transgenic mice. This longevity with more normal cognitive function highlights the overall beneficial effects of Magtein treatment on body health.

Figure 10: MgT increases lifespan of AD mice mice



Survival curve of WT and Tg+Magtein mice over the 678 day lifespan.

Additional Research

Ongoing Magtein research is continuing to uncover a variety of new applications. This unique form of magnesium is being evaluated by the research communities for Alzheimer's, dementia, longevity, sleep, mood and other aging conditions. AIDP is ew in Magtein research for greater market potential and the discovery of future benefits. For memory and cognitive health, Magtein is the category standard. No other magnesium compares. Human studies are currently under development.

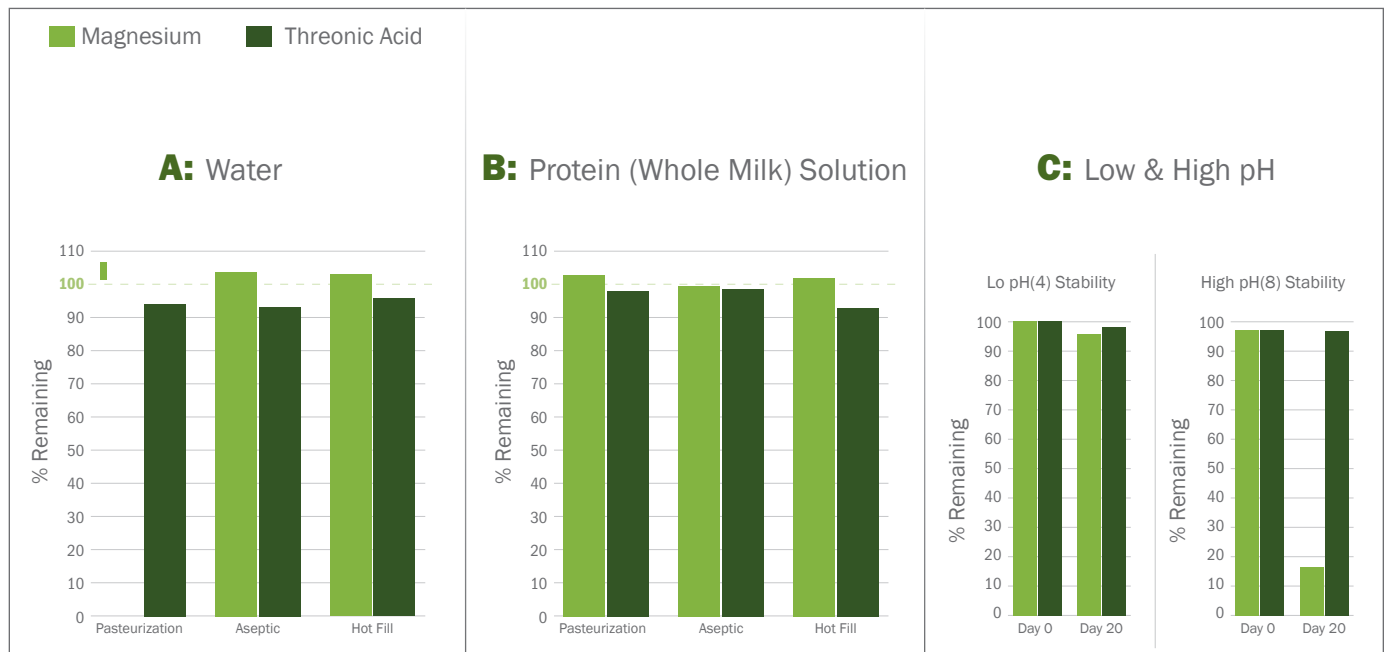
Quality Assurance

- Magtein is self-affirmed GRAS
- Magtein is a non-GMO
- Magtein is produced and distributed exclusively by AIDP, Inc. a NSF certified GMP facility

Ingredient Qualities

Magtein is ideal for the nutritional and functional beverage market. It is completely soluble, colorless and tasteless. In an application study, Magtein was shown to successfully withstand hot fill, aseptic and pasteurization, all commonly used heating conditions in the beverage industry, with little stability loss in both water and milk solution (Figure 11). It also performs well in low pH solutions. This broadens the market for Magtein beyond supplements and pills.

Figure 11: Magtein Stability



Magtein was evaluated under typical beverage manufacturing conditions to determine stability. One gram of Magtein was added to 8 oz. of water (A) and one gram of Magtein was added to 8 oz of whole milk (B) and subjected to several common manufacturing processes. Both magnesium and threonic acid were measured and presented as percentage remaining vs. control solution.

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