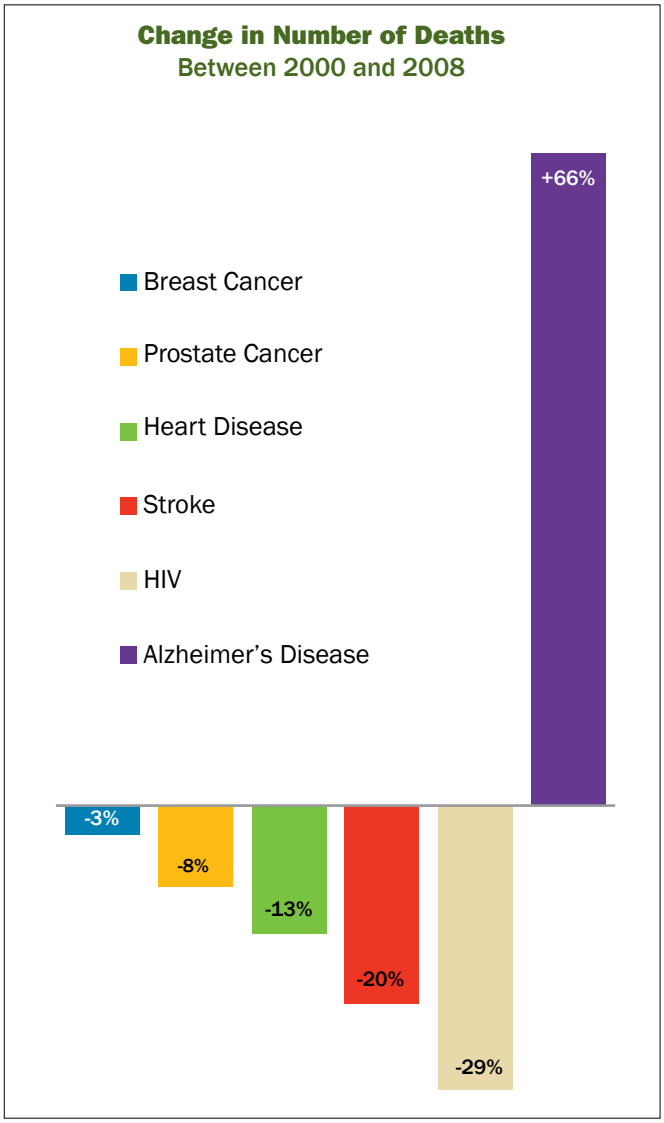
An Introduction to Magtein™

A novel compound for cognitive health

Overview of Cognitive Health

Cognition, by definition is the process of knowing and, more precisely, the process of being aware: knowing, thinking, learning and judging. The study of cognition touches on the fields of psychology, linguistics, computer science, neuroscience, mathematics, ethology and philosophy. Cognitive health covers a range of conditions including memory loss, stress or anxiety management, dementia, Alzheimer's, phobias and sleep. All of these are controlled by the health of the brain. One of the biggest challenges facing the aging baby boomer generation is the loss of memory and cognitive function.

Alzheimer's. As it currently stands, Alzheimer's disease (and related forms of cognitive decline) has no cure and very few effective preventative therapies. Symptoms of Alzheimer's in early stages include erratic behavior and loss of memory, but in later stages can become more severe and can include loss of bodily function control and ultimately death. Alzheimer's is the world's most costly disease per patient and among the most feared, with major social costs. More than $172bn was projected to be spent on total U.S. care for Alzheimer's patients in 2010, which presents a major cost to families and society. Finding natural, preventative solutions to this growing concern will have a significant impact on the industry. According to the Alzheimer's Association, Alzheimer's disease is the 6th leading cause of death in the United States and the 5th leading cause of death for those aged 65 and older. Alzheimer's is the only cause of death among the top 10 in America without a way to prevent, cure, or even slow its progression. 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.



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

Dementia and MCI. Memory loss crosses all age groups but is most predominant in the aged. Brain cells slowly die as we age. In the last century, life expectancy has grown to an average of 77 years from 47 years. With this dramatic increase, people are feeling the effects of aging. Mild cognitive impairment (MCI), is a brain-function syndrome involving the onset and evolution of cognitive impairments beyond those expected based on the age of the individual, but which are not significant enough to interfere with their daily activities. It is often found to be a transitional stage between normal aging and dementia. When memory loss is the predominant symptom it is termed "amnestic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease. Studies suggest that these individuals tend to progress to probable Alzheimer's disease at a rate of approximately 10% to 15% per year. Dementia is also a serious loss of global cognitive ability beyond what might be expected from normal aging. It may be the result of a brain injury or be progressive, resulting in long-term decline.

Anxiety and Stress. In the information age, each one of us are under more stress than before. Stress is a major factor affecting cognitive health. People have stress and anxiety because of fear. It's natural to be afraid when you're in danger. It's natural to be upset when something bad happens to you or someone you know. Fear is essential for survival. However, having excessive-uncontrollable fear or experiencing strong fearful events can lead to anxiety disorders such as phobias and post-traumatic stress disorder (PTSD). 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. Relaxation drinks an over the counter remedies have also emerged as new product segments.

Magtein™

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.

Magtein is the only magnesium compound that has been shown to effectively raise the brain's magnesium levels, which leads to improved memory and cognitive functions. Magnesium has been implicated in many of the brain functions. However, most magnesium compounds have low brain bioavailability and severe gastrointestinal side effects.

Magtein was found to be able to increase brain magnesium, resulting in enhancement of learning abilities, working memory, and short- and long-term memory in both young and aged animals. It was recently found to relieve anxiety disorders and enhance the coping ability of adverse events in an animal study.

Magtein Research

Magtein Anxiety Research Review. 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 synapse 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.

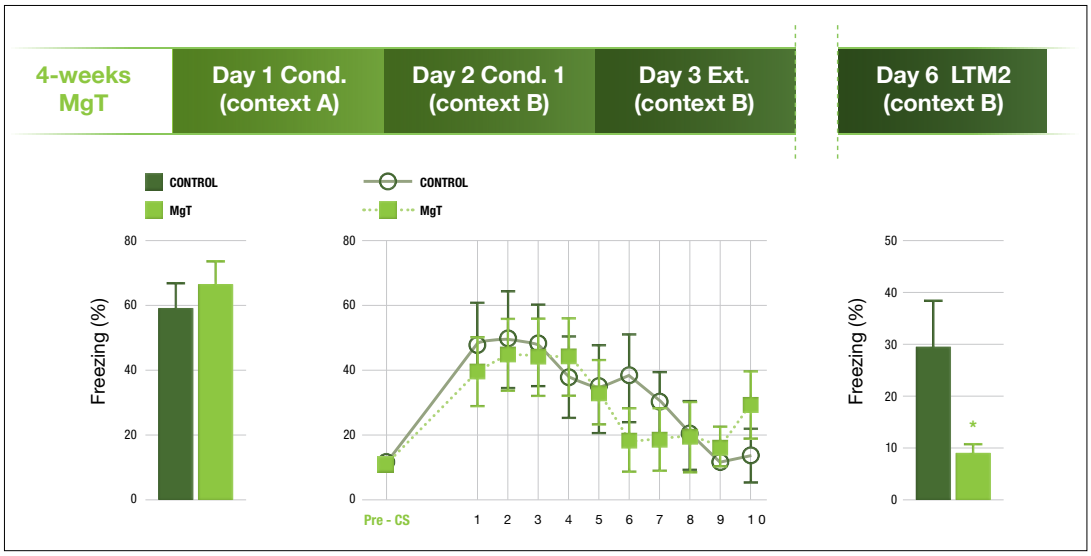
The research published in the *The Journal of Neuroscience*, October 19, 2011 (31 (42):14871–14881 • 14871) showed that elevating brain magnesium might be a novel strategy to dampen traumatic memories and treat affective and anxiety disorders in clinics. The enhancement of neural plasticity in hippocampus and PFC, brain regions responsible for highly processed emotional responses, could be the underlying mechanisms.

Laboratory animals were subjected to a series of established fear measurement protocols inducing trials with shock and tone. The generated fear response was measured by established FreezeFrame2 software. Magtein was both administered prior to the introduction of the fear and after the introduction of the fear (Figure A&B). Freeze response was measured and brain synapses were examined.

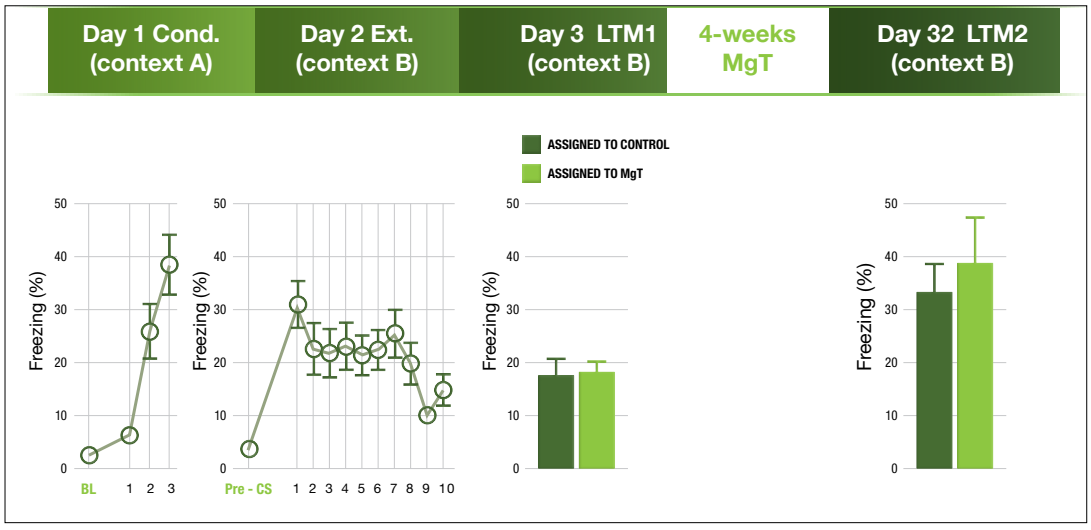
Using a fear conditioning paradigm, chronic Magtein intake was found to enhance prefrontal cortex/hippocampus-dependent but not amygdala-dependent fear-memory in rats. Interestingly, Magtein treatment enhanced retention of the extinction of fear memory, without enhancing, impairing, or erasing the original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

In addition to the fear memory tests, the molecular basis of the effects of Magtein treatment on fear memory were 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 (Figure C). 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

A: Effects of Magtein on extinction learning, retention and retrieval. Freezing behavior of Magtein-treated and control rats during and after extinction.



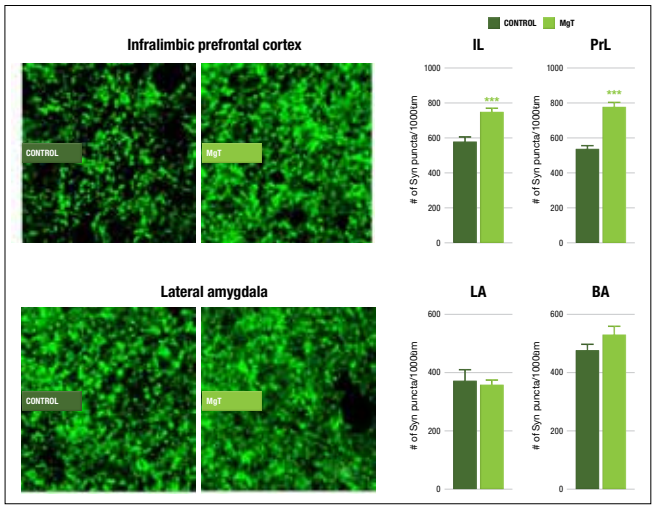
B: Effects of Magtein on retention of extinction when treatment was given after conditioning for 4 weeks.



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.

Emerging evidence shows that dietary factors might play a role in fear extinction and anxiety-like behavior. For example, dietary magnesium restriction induces an increase in anxiety-like behavior in mice. Our studies suggest that long-term elevation of brain magnesium might enhance NMDARs functioning selectively in brain regions involved in what was previously described as "top-down control over amygdala" (Rauch et al., 2006) and might help to enhance the efficacy of fear extinction. Our data suggest that Magtein might enhance the coping ability with aversive events and control of emotional responses, prerequisites for treatment of affective and anxiety disorders such as depression and PTSD.

C: Effects of Magtein on presynaptic boutons in infralimbic and prelimbic prefrontal cortex and basolateral amygdala.



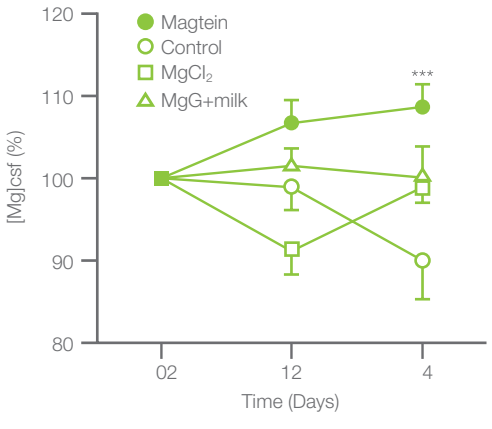
Magtein Memory Research. Learning and memory are fundamental brain functions affected by dietary and environmental factors. Here, we show that increasing brain magnesium using a newly developed magnesium compound (magnesium-L-threonate, Magtein) leads to the enhancement of learning abilities, working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

Phase I: Evaluation of Magnesium forms.

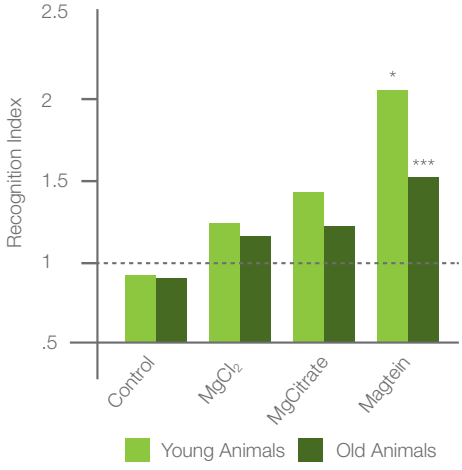
Magnesium concentration in the cerebrospinal fluid was evaluated following treatment of different magnesium compounds. Widely used magnesium forms were evaluated including magnesium-chloride, magnesium-citrate, magnesium-gluconate in milk and Magtein. After 24 days, Magtein was the only magnesium compound to raise the cerebrospinal fluid magnesium concentration with statistical significance.

The animals taking the four magnesium forms completed short-term and long-term memory tests by a novel object recognition test. Only Magtein subjects showed a significant increase in both short term and long term memories in both young and aged animals.

Phase I Research:
Evaluation of Magnesium forms



Four Magnesium products were evaluated for short term memory in young and aged animals. Only Magtein was shown to have a significant effect. ***p < 0.001.

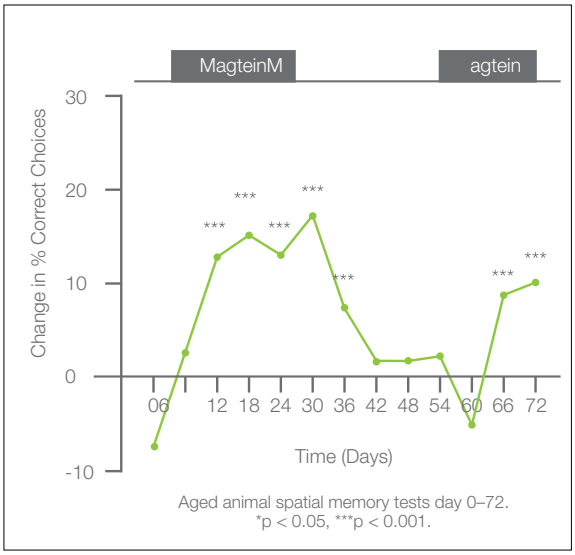


Three compounds were evaluated for long term memory in young and aged animals. Only Magtein was shown to have a significant effect. *p < 0.05, ***p < 0.001.

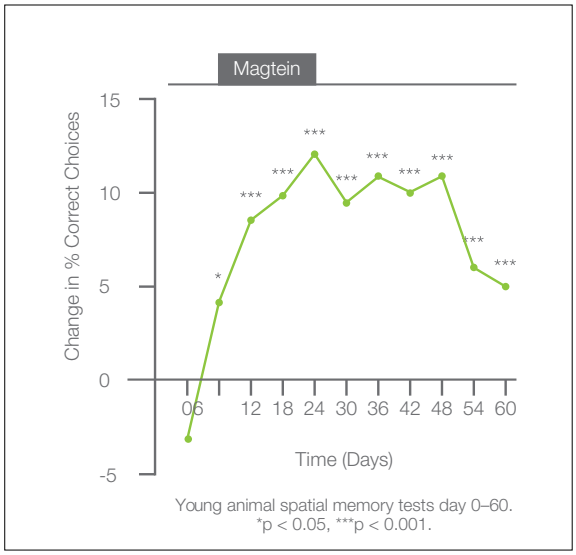
Phase II: Spatial working memory tests.

Young and aged laboratory animals' spatial long-term memory was evaluated by a water maze. Animals were timed to find the hidden platform. Subjects were evaluated one hour and 24 hours after training. In both age groups, the Magtein group performed at a statically higher rate. In addition, when partial removal of extra-cues was imposed, the Magtein aged rats were able to find the hidden platform. Interestingly, the aged rats when taken off Magtein had a drop in spatial long-term memory, but were able to regain this once Magtein was reintroduced.

Phase II Research:
Spatial Working Memory Tests



Aged animal spatial memory tests day 0–72.
*p < 0.05, ***p < 0.001.

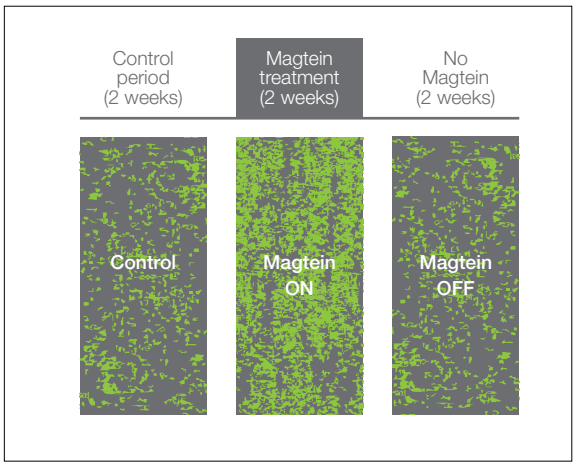


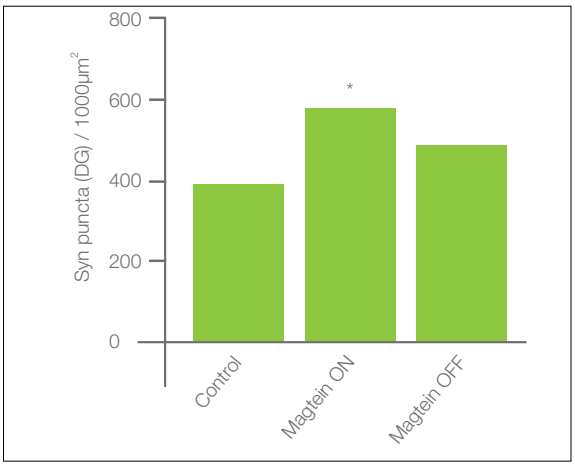
Young animal spatial memory tests day 0–60.
*p < 0.05, ***p < 0.001.

Phase III: Brain synapses evaluated.

To further characterize the potential cellular mechanisms that underline Magtein-induced memory enhancement, the effect of 1 month of Magtein treatment on the density of presynaptic boutons in aged rats was investigated. The synaptophysin-positive puncta in the DG hippocampus was significantly higher in the Magtein group vs. control. A similar pattern of changes was observed in another presynaptic protein, synaptobrevin. These results indicate that Magtein increased the synaptic density in the hippocampus region of the brain.

Phase III:
Brain Synapse Evaluation





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

Conclusions. Magtein enhances both short-term synaptic facilitation and long-term potentiation and improves learning and memory functions in young and aged animals. The pattern completion ability was improved in aged rats. Magtein-treated rats had higher density of synaptophysin-/synaptobrevin-positive puncta in DG and CA1 subregions of hippocampus that were correlated with memory improvement. Functionally, magnesium increased the number of functional presynaptic release sites, while it reduced their release probability. The resultant synaptic reconfiguration enabled selective enhancement of synaptic transmission for burst inputs. Coupled with concurrent upregulation of NR2B-containing NMDA receptors and its downstream signaling, synaptic plasticity induced by correlated inputs was enhanced. Our findings suggest that an increase in brain magnesium enhances both short-term synaptic facilitation and long-term potentiation and improves learning and memory functions.

Additional Research

Ongoing Magtein research is continuing to uncover a variety of new applications. This unique form of magnesium is being evaluated by research communities for Alzheimer's, dementia, longevity and other aging conditions. AIDP is investing 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. Preliminary results are likely in 2012.

Quality Assurance

- Magtein is self-affirmed GRAS.
- Magtein is a non-GMO, natural compound.
- Magtein is produced and distributed exclusively by AIDP, Inc., an 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. It also performs well in high pH solutions and low pH solutions. This broadens the market for Magtein beyond supplements and pills.

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