

Luteinizing Hormone and Alzheimer's Disease: Impact and Possibilities of Treatment

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Abstract

Alzheimer's disease is a common neurodegenerative disease that is the 6th leading cause of death in the United States. An estimated 5 million Americans are afflicted nationwide and the cost to the economy is valued at 259 billion dollars. Additionally, unlike other major causes of death in the United States, there is no treatment for Alzheimer's Disease. Alzheimer's is a progressive disease and it is strongly tied to aging. In most cases symptoms make their first appearance in the late 60's and gradually worsen, eventually leading to a loss of cognitive function and death. The two outstanding changes in the brain associated with Alzheimer's disease are neurofibrillary tangles and beta amyloid plaque. The presence of these is used to diagnose Alzheimer's disease after death. Certain hormonal changes that are associated with age, such as a rise in luteinizing hormone levels, are strong contenders for the age-related causes of Alzheimer's disease. Elevated gonadotropin levels have been shown in studies to correlate with amyloid beta accumulation in human and animal brains. The precise mechanism of action and the causation are not yet fully understood. Nevertheless, some studies have shown that lowering levels of Gonadotropin-releasing hormone (which releases luteinizing hormone) through the treatment with Leuprolide acetate, a gonadotropin releasing hormone agonist, have led to lowered risk of mortality by Alzheimer's disease in both mice and humans. This paper will discuss the association between elevated luteinizing hormone levels and Alzheimer's disease as well as the possibility of a Gonadotropin-releasing-hormone blocking based treatment for Alzheimer's.

Introduction

Alzheimer's disease is named after Dr. Alois Alzheimer who first discovered the disease in 1906. Dr. Alzheimer had a patient with severe memory loss, aphasia, and unnatural behavior who died of complications related to her disease. Upon her death, he performed an autopsy and noticed two unusual features in the brain, tangles of fibers and protuberances. We now know these as neurofibrillary tangles and beta amyloid plaques. It is difficult to accurately measure tangles and plaques during the lifetime of a patient with the disease; therefore, Alzheimer's disease is diagnosed based on symptoms. The symptoms that are used to diagnose Alzheimer's disease today are much like those of Dr. Alzheimer's original patient. The common symptoms are memory related issues, trouble with organizational skills, getting lost, confusion, and personality changes. Eventually the deterioration escalates and the patient may hallucinate, become unable to recognize others, and then become unable to talk or eat. Lastly, the parts of the brain that directly control living processes are affected and death occurs. (National Institute on Aging, 2012)

The progression of Alzheimer's disease does not happen quickly, in fact Alzheimer's is a very slowly progressing disease, and there is usually 5-10 years between the first appearance of symptoms and death. This being the case, it is theorized that even before symptoms occur, perhaps years prior, there is a form of "pre-Alzheimer's". This can be defined as asymptomatic changes in the brain which are the true first steps of Alzheimer's disease. The ability to detect these changes would greatly assist in the struggle to find a cure and is currently being researched. (National Institute on Aging, 2012)

Unfortunately, it is not possible with our current level of technology to reliably detect the changes in the brain that are present in Alzheimer's, even advanced Alzheimer's. Although we have come a long way with neuroimaging methods, they are unable to determine Alzheimer's disease directly. Instead, after the onset of symptoms, brain imaging techniques such as MRIs and PET scans are used to rule out other probable causes of brain

dysfunction; such as stroke or other forms of dementia. If these are not indicated, a diagnosis of probable Alzheimer's is given until death and autopsy. Upon autopsy, if there are neurofibrillary tangles and amyloid plaques, the diagnosis is then confirmed (National Institute on Aging, 2015).

Neurofibrillary tangles and beta amyloid plaque are the two main physical phenomena that define Alzheimer's disease, but the mechanism that they use to influence Alzheimer's disease and cause the deterioration of the brain is not yet understood. Neurofibrillary tangles are also called tau tangles as they are composed and caused by defective tau proteins. Tau proteins are microtubule-associated proteins that are common in the central nervous system. In a healthy person, these tau proteins hold microtubules in place and keep them steady. However in Alzheimer's disease the tau proteins become hyperphosphorylated and they cease to support the microtubules. The microtubules unwind and collapse and the hyperphosphorylated tau builds up. Together they form filamentous clumps which are the neurofibrillary tangles of Alzheimer's disease. It is not certain if the tangles participate in the cause of Alzheimer's disease or are just an effect of it (C. Baner, 1989). However, the density of the tau tangles correlates with the extent of dementia and they are located in the affected brain areas. A possible mechanism by which the brain degenerates by neurofibrillary tangles is as follows. When disrupted microtubules are abundant, the neuron is weakened and it becomes unable to transmit impulses at a normal rate. The body's immune system detects compromised neurons and triggers apoptosis of the cells (Wang, Xia, Grundke-Iqbal, & Iqbal, 2013).

The more significant Alzheimer's disease marker is beta amyloid plaque. In the healthy brain, tangles and plaques are present in small quantities and pose no problem. It is when the beta amyloid amounts build up that issues arise. It is understood that this build up is the result of a difference between the amount of beta amyloid plaque that is formed and the amount that is removed. Beta amyloid plaque is formed by the breakdown of

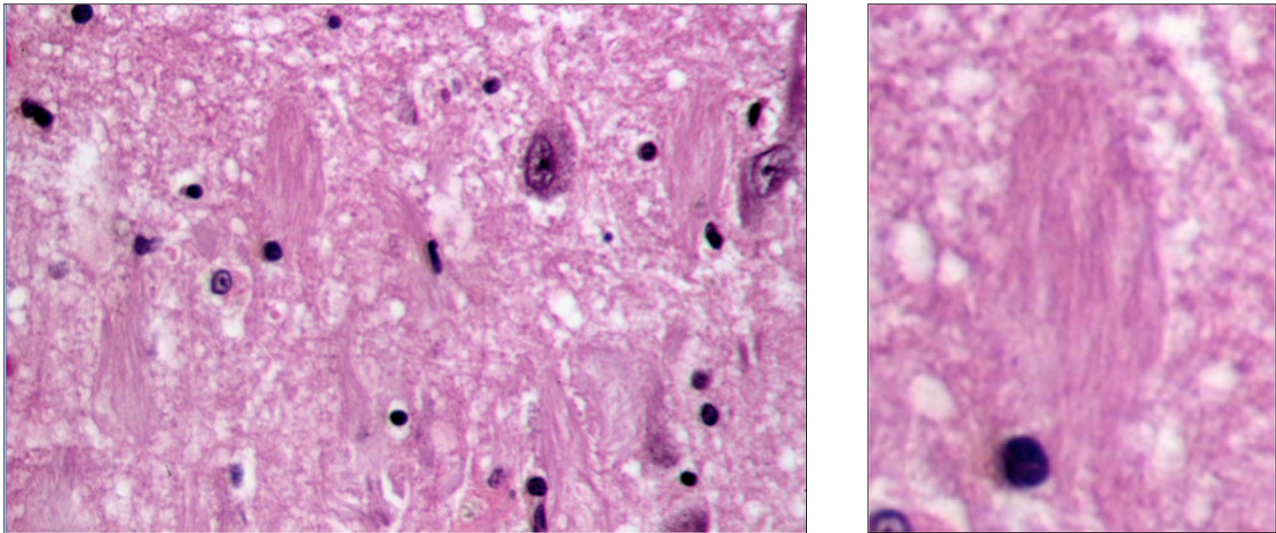


Figure 1: Neurofibrillary tangles in the Hippocampus of an elderly man with Alzheimer's related pathology. (Above: The tangle is enlarged and is visible above the dark stain) (Patho, 2015).

amyloid precursor protein (APP), which is present in the synapses of neurons. APP is present all over the brain and is thought to perform a function relating to neuron growth (Thinamaram & Koo, 2008). APP is broken down by several enzymes known as alpha, beta, and gamma secretase. When amyloid precursor protein is broken down by a combination of alpha and gamma secretase it forms a protein called α APP which may have effects that protect the brain (Krishnaswamy, Verdile, Groth, Kanyenda, & Martins, 2009). However, when beta secretase takes the place of alpha secretase, it forms beta amyloid, which is sticky and insoluble allowing it to form plaques. The process of how beta amyloid plaque is removed from the brain is not fully understood but it could be performed in a variety of ways including protein

transport through the blood or destruction by enzymes, such as insulin. Beta amyloid plaque is neurotoxic and it can inhibit synapse formation, disrupt mitochondrial action, contribute to inflammation in the brain, and promote the hyperpolarization of tau proteins which in turn causes neurofibrillary tangles. Beta amyloid plaques may be more important than neurofibrillary tangles and tau proteins in the onset of age related Alzheimer's. Other diseases have tangles but Alzheimer's disease is associated with plaque formation. (Lee, Goedert, & Trojanowski, 2001) Additionally, it is supposed that beta amyloid plaque forms earlier in the progression of Alzheimer's disease and contributes to the neurofibrillary tangles (Villemagne, et al., 2013). This theory, that beta amyloid plaque is the most significant factor in the

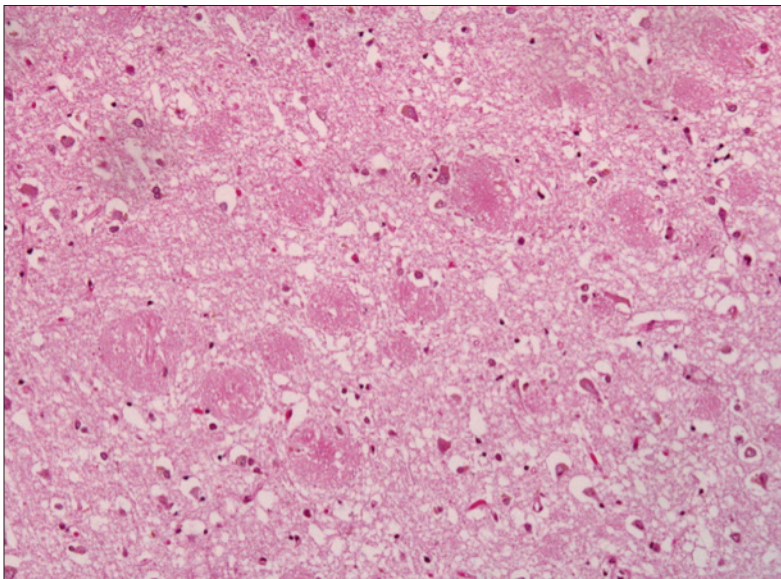


Figure 2: Cerebral autopsy specimen of a patient diagnosed with Alzheimer Disease. In the HE stain numerous plaque formations within the neuropil background are visible. (Neurofibrillary tangles in the Hippocampus of a person with Alzheimer-related pathology, HE 1.JPG) (Patho, 2015)

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pathogenesis of Alzheimer's is called the "amyloid hypothesis" (Burnham & Thornton, 2015).

There are two forms of Alzheimer's and they have inherently different causes. Early onset Alzheimer's is when Alzheimer's disease occurs to people under 65. Most people with this form of the disease have a mutation in one of three genes, APP, PSEN 1, and PSEN 2. These mutations run in families and create a disposition to suffer from early onset Alzheimer's. (Bird, 2015) This is a genetic disease but it is far less common than late onset Alzheimer's disease and it accounts for about 5 percent of total Alzheimer's cases. In late onset Alzheimer's disease, there is also a genetic component connected with the APOE gene but the main risk factor is age. The older someone is, the more they are at risk of late onset Alzheimer's disease. The reasons why age should increase risk for Alzheimer's disease are not yet understood. Research is being done into the natural changes that occur in the body with age as possible contributors to Alzheimer's disease. The age-related changes to the hypothalamic/pituitary/gonadal feedback loop that regulates sex hormone levels in the blood is a strong candidate for this research.

The sex hormones are produced in the context of a feedback loop with Gonadotropin-releasing hormone in the hypothalamus and the gonadotropins, luteinizing hormone and follicle stimulating hormone which are released by the pituitary gland. In a healthy individual, Gonadotropin-releasing hormone is released from the hypothalamus in surges in response to internal and environmental factors. It travels to the anterior pituitary gland where it stimulates gonadotropic cells to produce luteinizing hormone and follicle stimulating hormone. These hormones travel to the gonads, the testicles and the ovaries, and they stimulate them to release testosterone and estrogen

respectively. To prevent too much of these hormones from being made, testosterone and estrogen in sufficient quantities provide negative feedback that discourages the further production of GnRH by the hypothalamus. However, with advancing age the process changes. Testosterone levels fall gradually in men, and in women estrogen drops rapidly after menopause. Without the negative feedback of the endpoint, gonadotropin levels tend to rise, although this is not true in all cases. (Jones, 2012)

For many years it was thought that the lowered levels of testosterone and estrogen that come with age were involved in the cause of Alzheimer's. It was assumed that these hormones had neuroprotective properties and their absence allowed Alzheimer's disease to creep in. However, it was found that giving testosterone or estrogen directly did not lower risk for Alzheimer's disease and in fact raised it. (Manly, et al., 2000) Since supplementing with testosterone/estrogen was not useful in preventing or understanding Alzheimer's disease, the next logical step was to look at the heightened levels of gonadotropins that relate to the lower sex hormone levels. However, even in this case distinctions must be made.

Luteinizing hormone and follicle stimulating hormone are both released by the anterior pituitary gland in response to Gonadotropin-releasing hormone. Structurally, LH and FSH are similar. They both are heterodimeric glycoproteins and are composed of an alpha and beta subunit. The alpha subunit of luteinizing hormone and follicle stimulating hormone are identical, however, the beta subunit is different and this is how they connect to different receptors and have a different scope of action. In men, luteinizing hormone is released throughout the day and stimulates Leydig cells to produce testosterone. Follicle stimulating hormone stimulates Sertoli cells which help sustain the

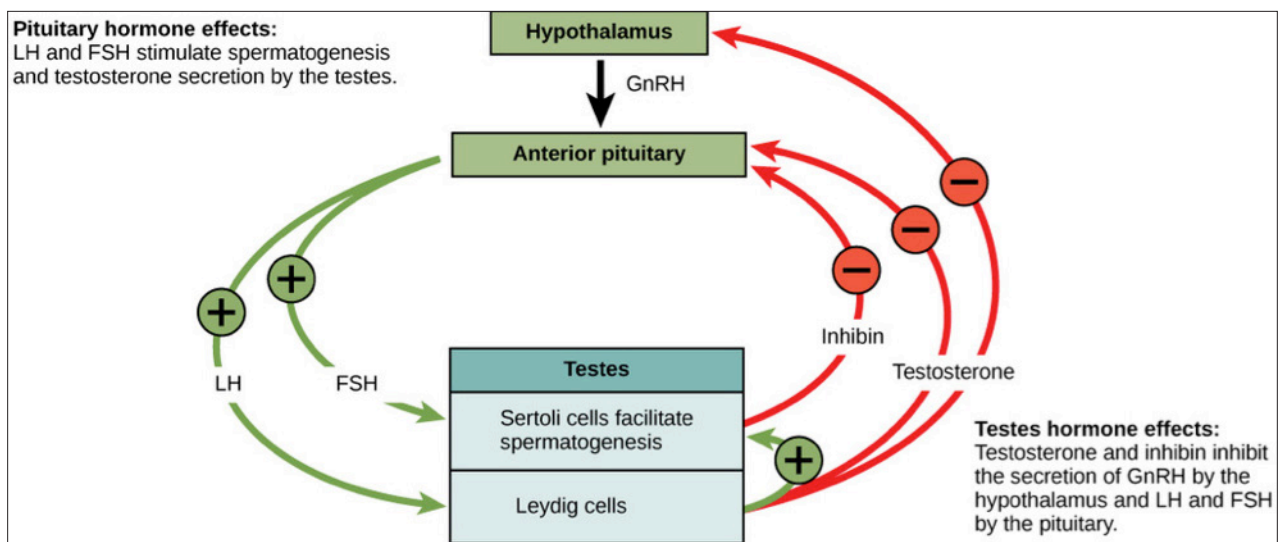


Figure 3: A feedback loop regulates the Hypothalamic – Pituitary – Gonadal axis (Boundless.com, 2017).

maturing sperm cells. In women, follicle stimulating hormone stimulates growth of the follicle in the ovary which increases production of estradiol and estrogen. When the follicle is mature, there is a critical level of estrogen that is reached and that stimulates a surge in luteinizing hormones, which in turn causes the release of the egg from the follicle. LH and FSH are different in both structure and function and how they interact with amyloid plaque as well. Many studies have shown links specifically between luteinizing hormone and the levels of beta amyloid plaque in the brain and this will be presented and evaluated.

If increased levels of luteinizing hormone contribute to Alzheimer's disease, it would be useful to have an explanation for how it does so. The presence of luteinizing hormone in the brain is not expected as it is not lipid soluble and in theory cannot cross the blood brain barrier. However luteinizing hormone is found in the brain and it has been found that LH can pass through this barrier in small amounts (Lukacs, Hiatt, Lei, & Rao, 1995). It is also a possibility that luteinizing hormone is synthesized in the brain itself. LH receptors are found not only in the gonads but also in the brain which would imply that it may be active there as well. It may be that signals which are mediated by luteinizing hormone receptors affect the processing of APP and influence it so it is more likely to be cleaved by beta secretase than alpha secretase. This would result in a higher level of beta amyloid plaque formed relative to α APP and could trigger a cascade of beta amyloid plaque buildup and ultimately Alzheimer's disease.

Possibility of Treatment

Since elevated levels of luteinizing hormone could be a factor in the pathogenesis of Alzheimer's disease, they are also a target for prevention or reversal of the disease. By lowering levels of luteinizing hormone in the blood, the contribution luteinizing hormone is making to the disease could be negated. A potential medicine that could be effective in this therapy is leuprolide acetate. Leuprolide, also called leuprorelin, is a synthetic hormone that is currently prescribed under the name Lupron to treat prostate cancer, sex hormone imbalance, and even less serious issues such as early onset of puberty (World Health Organization, 2015). Leuprolide acts as an agonist to the Gonadotropin-releasing hormones. It binds to the Gonadotropin-releasing hormone receptors in the pituitary gland and interrupts their stimulation. This results in a downregulation of luteinizing hormone and follicle stimulating hormone. Leuprolide is delivered by injection and it can be self-administered after training. It has mild short-term side effects including dizziness, itching, and headaches. As a long-term treatment, it can weaken bone density (Norsigian, 2005). However, with the research we currently have, the long-term side effects do not seem to be very significant, specifically when weighed against the pathology of Alzheimer's. The effectiveness of Leuprolide as

a treatment to lower luteinizing hormone levels, improve cognition, and prevent or even reverse the accumulation of amyloid plaque will be discussed in this paper.

Methods

All the information that was used in this article was gathered from online using the Touro Library search and Google Scholar. The search terms that were used were leuprolide acetate, leuprorelin, Alzheimer's disease, beta amyloid plaque, luteinizing hormone, gonadotropins, hormone, gonadotropin releasing hormone. The articles were drawn from accepted and peer reviewed scientific journals and are all available online. Websites that were used were selected from dependable sources, government websites or scientific institutions.

Discussion:

Alzheimer's Disease and Heightened Luteinizing Hormone Levels in Humans

In one study, plasma samples were taken from 284 patients seen at a tertiary care center and measured for concentrations of luteinizing hormone and follicle stimulating hormone. The patients were divided into three groups, 134 with probable Alzheimer's disease, 45 with frontal temporal dementia (FTD), and 105 cognitively normal controls. The researchers logged each patient's score on the Mini-Mental State Examination (MMSE) to measure severity of dementia. They recorded length of sickness, the sex and age of the subjects, and, in the case of women, if they were taking an estrogen supplement. It was found that there was no relationship between follicle stimulating hormone levels in men between the controls and the Alzheimer's disease group and although there was one with luteinizing hormone, it was not significant when controlled for age. The important finding was that in the women who were not taking estrogen, a significant difference in luteinizing hormone level was observed compared to the controls after a univariate analysis (Figure 4)

In women who were not taking any form of estrogen, this study found elevated levels of luteinizing hormone and follicle stimulating hormone compared to controls. The luteinizing hormone levels were higher in the Alzheimer's group compared to the frontotemporal dementia group which indicates that they were not just an effect of dementia or brain deterioration. There was no significant difference found for women who were taking estrogen but that is not unexpected, considering that estrogen is part of a negative feedback loop that limits luteinizing hormone production. Within the men, there was no difference found between the FTD group and the Alzheimer's disease group. It is possible that this is due to the small sample size. An important part of this study found that in estrogen free women, there was a connection between elevated levels of gonadotropins and Alzheimer's disease.

In a previous study by the same authors, a difference was

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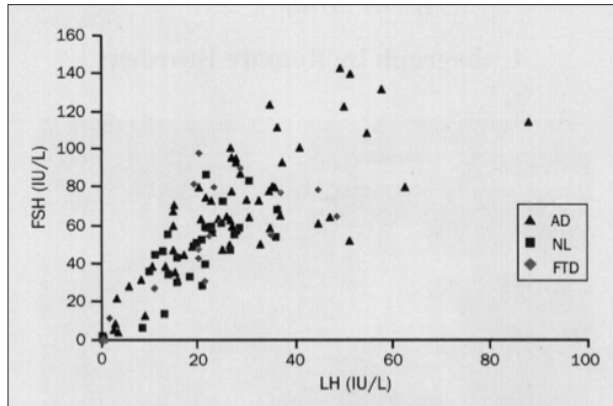


Figure 4: Follicle-stimulating hormone (FSH) vs luteinizing hormone (LH) levels in women not taking estrogen. Note that some patients with Alzheimer disease (AD) (triangles) have both higher LH and FSH levels compared with cognitively normal (NL) controls and patients with frontotemporal dementia (FTD) (Short, Bowen,, O'Brien, & Graff-Radford, 2001).

found for men as well. The study tested 40 males who were diagnosed with Alzheimer's disease in a long-term care center and compared them to 29 controls. The study found that the Alzheimer's disease patients were significantly higher in both luteinizing hormone and follicle stimulating hormone levels relative to the control group. (Bowen, Isley, & Atkinson, 2000).

In another study, 585 normal and healthy men between the ages of 70 and 87 years were tested for luteinizing levels to try to find a relationship between luteinizing hormone levels and issues with memory recall. Men were chosen specifically because in previous studies, this correlation had not been demonstrated for men as strongly as in women. The study found that higher levels of luteinizing hormone were related to worse performance on CVLT-II which is a test for immediate recall (Hyde, et al., 2010).

In an even larger study that evaluated the effects of elevated levels of gonadotropins on cognition in elderly women, 649 women without dementia were given cognitive testing and blood samples were taken. Plasma levels of luteinizing hormone, estradiol, follicle stimulating hormone, and beta amyloid were recorded. The study found that elevated levels of luteinizing hormone were associated with worse cognitive performance and depression (Rodrigues, et al., 2008).

In the Australian Imaging Biomarkers and Lifestyle study of aging, more than 1000 people were assembled to conduct a longitudinal study to aid understanding Alzheimer's beginnings and progression. The subjects were given full cognitive evaluation, their blood was analyzed and many of them had their brains imaged by MRI machines and various brain imaging technology. The participants were grouped by cognitive issues. The categories were healthy, subjective memory impairment, mildly impaired, and Alzheimer's patients. It was not the primary focus of the study to

test specifically for gonadotropin levels. Nevertheless, the blood that was taken was tested for it amongst other things. Some researcher reviewed the data with an eye on luteinizing hormone and it was found that increased levels of luteinizing hormone in the blood were correlated with beta amyloid presence in the brain as measured by imaging techniques. This was only found in the subjective group, which suggests that the most important link between luteinizing hormone and beta amyloid plaque is in the preliminary stages of Alzheimer's disease (Ellis, et al., 2009).

Animal Trials

In studying disease pathology, and possible treatment options, it is not always possible to use humans as some potential treatments may have negative side effects, it is therefore better to first test their potential with animals. Mice are often used because of their biological similarities to humans. Some researchers have studied ties between luteinizing hormone, beta amyloid plaque, and cognition in transgenic mice that have genes that lead to Alzheimer's disease development. To test for cognition in mice, researchers use a test known as 'spontaneous alternation'. It is a behavioral test which tests spatial learning and memory. In this test, the animal is put in the center of a maze and can move freely. Spatial memory is tested by observing whether the mouse remembers which arms of the maze it has already explored. It should be noted that the test results can also be influenced by factors such as attention or sensory stimuli (Hughes, 2004).

In a study of 21, one month old transgenic Tg2576 mice, the effects of high luteinizing hormone levels in the mice on amyloid beta plaque deposition were tested. The animals were bred to over-express human APP to ensure that there would be beta amyloid plaque buildup. In this breed in general, beta amyloid plaque grows throughout the first 6 months of age and by the time they are 10 months old, the level of beta amyloid plaque is enough to form an accumulation. The mice were randomly split into two groups. One was a control group that received saline solution and the second group received leuprolide. The mice were tested with mazes to examine spontaneous alternation and their blood levels of luteinizing hormone were assayed to evaluate the effects of leuprolide. The brains were sliced on the sagittal plane and preserved to find the amount of beta amyloid deposition. The mice that were treated with leuprolide were found to have significantly lower levels of luteinizing hormone compared to the saline group especially 3 months after the treatment. The leuprolide-treated mice performed better on the maze task than the control group. Additionally, the leuprolide-treated mice had lower levels of beta amyloid plaque and this correlated with the improved cognition (Casadesus, et al., 2006).

Mice which were bred to have an elevated level of amyloid beta precursor proteins had higher levels of luteinizing hormone and faster cognitive decline. The group that was treated with leuprolide, to help lower luteinizing hormone levels, had

less beta amyloid plaque deposition and better cognitive performance than the controls.

In another study done with mice, Tg2576 mice that were bred to express the human amyloid precursor gene were crossed with mice that had the genes for luteinizing hormone receptors removed, so that they couldn't use luteinizing hormone. There were two control groups. One of the control groups were APP expressing mice that were not crossbred. A second control group was mice that had luteinizing hormone receptors and did not express the human APP gene. Finally, a group of normal mice was a third control. The animals were raised for 16 months, sacrificed, and then their brains were sectioned. An imaging software was used to compare the beta amyloid concentrations in the brains of each group. The most important finding in this study was that there was significantly less beta amyloid plaque in the mice which had luteinizing hormone receptor knockout compared to the mice with APP that did have luteinizing hormone receptors. (Lukacs, Hiatt, Lei, & Rao, 1995)

The studies mentioned above all find a correlation between elevated luteinizing hormone levels and Alzheimer's disease or beta amyloid plaque deposition. If luteinizing hormone is a part of the cause of Alzheimer's, it presents exciting treatment possibilities through the lowering of luteinizing hormone levels especially to prevent deterioration in those at risk for Alzheimer's. A promising candidate for a medication that can accomplish this safely is leuprolide.

Leuprolide as a Treatment for Alzheimer's Disease

Leuprolide interferes with GnRH in humans and therefore brings about lower levels of luteinizing hormone. It is not an approved treatment for Alzheimer's disease as of now. However, since leuprolide is an approved treatment for prostate cancer, some studies have observed the effect that leuprolide has had on Alzheimer's disease in the patients using it for other reasons. Clinical trials are currently underway to test this possibility under the code ALADDIN which is an abbreviation for Antigonadotropin-Leuprolide in Alzheimer's Disease Drug Investigation

One study of the impact of leuprolide on Alzheimer's disease in patients with prostate cancer was done in 2010. The study looked at the risk of death by Alzheimer's disease in 6,647 men who were treated for prostate cancer. In the study, 1700 men who were treated with leuprolide were compared to 4,947 controls who were treated using other drugs that do not limit luteinizing hormone production. After 4 years of follow up, 81 of the group in the study had died from Alzheimer's disease. Those who died of Alzheimer's were found to be from the control group rather than from the group of patients who took leuprolide for at least 4 months (D'Amico, Braccioforte, Moran, & Chen, 2010).

The results were that Leuprolide can aid in slower regression and improved cognition in Alzheimer's patients. Voyager Pharmaceuticals is not currently pursuing further research into Lupron and most likely will not do so in the future as it declared bankruptcy in 2012. In an interview for medicalresearch.com, Richard Bowen cited lack of marketability to account for the dearth in leuprolide research. "Unfortunately, there is no intellectual property protection for this treatment making it unlikely that a pharmaceutical company will take the lead." (R. Bowen). It is vitally important to find a cure for Alzheimer's and perhaps the funding will come from a government the government or foundation, and leuprolide research will be continued.

Conclusion

Alzheimer's disease is a common debilitating disease that is one of the main leading causes of death in the United States. One of the main changes detected in the brain of a patient with Alzheimer's disease is beta amyloid plaque. These plaques can only be detected after death, upon autopsy. Studies have shown that a rise in luteinizing hormone is linked to increased beta amyloid plaque and Alzheimer's. Studies have been done to lower Gonadotropin-releasing hormone levels through the treatment of Leuprolide acetate, a Gonadotropin-releasing hormone agonist. This treatment is not being financially backed and is therefore on hold for the time being; however, the possibility of this treatment for Alzheimer's disease is somewhat promising and deserving of more research.

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