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PERSPECTIVES

Could lysine supplementation prevent Alzheimer's dementia? A novel hypothesis

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Abstract: There is a growing body of evidence that implicates the herpes simplex type 1 virus (HSV-1) in the development of Alzheimer's dementia (AD). HSV-1 has been found to be present in the cerebrum of the great majority of older adults, and in many of the same areas of the brain that are affected by AD. When active, the virus may contribute to the formation of the neurofibrillary tangles and amyloid plaques characteristic of AD. Like AD, HSV-1 encephalitis may cause long term memory loss. HSV-1 replication is suppressed in lysine-rich/arginine – poor environments, and population studies suggest that diets high in lysine and low in arginine may be associated with lower rates of AD. There are no prospective studies of the efficacy of lysine supplementation to prevent or reduce the incidence of AD. Supplementation with adequate doses of lysine could prevent the development of AD.

Keywords: lysine, herpes, Alzheimer's dementia, HSV-1

Introduction

Progress toward an effective treatment to prevent Alzheimer's dementia (AD), or to retard its progression, has proven to be exceedingly elusive. In the last year alone, three promising drugs have failed to show clinical efficacy (bapineuzumab, latrepirdine, and semagacestat). Although current strategies directed at reducing or eliminating the production of amyloid plaques, or at eliminating plaques already produced, may finally lead to a solution, the time may have come to examine alternative approaches.

In 1982, Ball proposed that the herpes simplex type 1 virus (HSV-1) might be involved in the pathogenesis of AD and "degenerative" lesions of the normal aged human brain.[1] Ball noted that HSV-1 was well known to establish a lifelong presence in the trigeminal nucleus, and that the trigeminal nucleus has projections into the mesial temporal (limbic) areas of the brain that are affected in AD and in herpes encephalitis. A reactivated virus might therefore have access "downstream" to manifest as herpes labialis ("cold sores"), and "upstream" into the limbic regions of the brain.

In recent years, several researchers have made progress in developing what might be called a strong circumstantial case for Ball's hypothesis. Among these is the laboratory of Dr Itzhaki who has studied HSV-1 and AD for nearly 20 years. In a recent review article she summarizes some of the findings of her group and others,[2] noting that 1) HSV-1 DNA has been found in a high (90%) percentage of the brains of elderly people, including the brains of AD patients; 2) that HSV-1 can persist in an active or inactive state throughout a host subject's lifetime; 3) that intrathecal antibodies to HSV-1 have been identified in the cerebral spinal fluid (CSF) of AD patients and elderly normal controls, indicating that the virus had at some point become active;[3]

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4) that HSV-1 infection is associated with inflammation, and several mediators of inflammation have been identified that are common to both HSV-1 infection and AD;[4,5] 5) that HSV-1 may contribute directly to the formation of amyloid plaques and neurofibrillary tangles, the histologic hallmarks of AD;[6–9] 6) that HSV-1 infection leads to accumulation of cholesterol in infected cells, which has been found to be associated with the formation of amyloid;[10,11] 7) that acute HSV- 1 cerebral infection (encephalitis) affects the temporal and frontal cortices of the brain, but not the occipital lobes, which are many of the same areas affected in AD;[12] 8) that the long term sequelae of HSV-1 encephalitis include memory loss,[12] a clinical hallmark of AD; and 9) that HSV-1 confers a high risk of AD in patients who carry the APOE-4 allele, a well-established genetic risk factor for AD.[13] Interestingly, APOE-4 is also a risk factor for development of herpes labialis, a peripheral manifestation of HSV-1 reactivation.[14]

These and other findings demonstrate that HSV-1 is present in relevant cerebral regions and capable of causing the amyloid plaques, neurofibrillary tangles, inflammatory changes, and memory loss characteristic of AD. Although they do not constitute proof of causation, they are consistent with the hypothesis that HSV-1 may be responsible for at least some cases of AD. However, if the virus is present in such a high percentage of the general population, the question must arise, why is AD primarily a disease of the elderly? Why do many elderly develop the disease, but a majority do not? Or to put it another way, what are the changes that occur in later age in some people that are conducive to the reactivation of the virus and the subsequent development of AD? Two factors will be considered in the text below: the lysine to arginine ratio in the brain, and activity of the immune system.

Lysine treatment of herpes labialis

It has been known since 1968 that HSV-1 requires arginine for replication,[15] and that lysine inhibits HSV-1 replication by competing with arginine.[16] These findings led to the use of lysine as a treatment for the common condition known as herpes labialis which, as noted above, is known to be caused by HSV-1. Seven randomized, double-blind, placebo-controlled studies have examined the effectiveness of lysine in preventing outbreaks of herpes labialis and reducing the severity of outbreaks that do occur. Six of these studies found lysine to be effective in preventing or decreasing outbreaks, and only two found that lysine reduced the severity of outbreaks. The first study, conducted in 1978, employed a dosage of 500 mg/day of lysine and found it to be ineffective.[17] A 1984 study specified 1,000 mg of lysine, given once a day, and also measured serum lysine levels. Lysine was found to be effective in reducing outbreaks when serum lysine concentration was greater than 165 nmol/mL, but not when it was less than this.[18] Another study, also published in 1984, found that a dosage of 1,248 mg/day was effective in reducing outbreak frequency, but that 624 mg/day was ineffective.[19] A 1987 study studied lysine 1,000 mg three times a day, and found it to be effective in reducing both the frequency and severity of attacks.[20]

It seems beyond question, then, that lysine in sufficient concentrations relative to arginine suppresses reactivation of HSV-1 in vivo, at least in so far as it is manifested peripherally as herpes labialis. It has been shown to be effective in reducing frequency of herpes labialis attacks, and possibly the severity of attacks, when given in dosages of at least 1,500 mg/day in divided doses.

Lysine: arginine in the CSF

Lysine is an essential amino acid, and the most highly conserved of all amino acids. The average adult diet supplies 6–10 g/day of lysine. Following absorption, it is transported across the blood–brain barrier by a basic amino acid carrier, and competes with arginine for transport. There are very few reports about this transporter, although there is evidence that the cat-1 transporter is responsible for the movement of lysine and arginine across the blood–brain barrier.[21] From the point of view of the current discussion, this is a pivotal point: the relative concentrations of lysine and arginine will depend on their transport across the blood–brain barrier, as well as their rates of efflux from the central nervous system. Lysine, unlike arginine, as an essential amino acid, cannot be made within the central nervous system. If lysine is not consumed in the diet in adequate quantities relative to arginine, or if it is not transported across the blood–brain barrier in adequate quantities relative to arginine, conditions may evolve in the central nervous system that are favorable for the reactivation of HSV-1.

It is not known whether activity of the lysine transporter declines with age. It is known, however, that CSF levels of amino acids are not constant, and may change with disease states. For example, CSF amino acid levels, including lysine and arginine, vary in patients with Parkinson's disease relative to normal controls.[22]

It is known that older age is associated with dietary changes, and these may reduce the amount of lysine available to be transported. Many factors have been proposed to explain this shift, but in general elders consume fewer calories with

advancing age, and dietary choices move away from protein and energy dense foods such as meats, and towards foods that are less protein and energy dense, such as grains.[23] This is a change, in general, from foods that have a favorable lysine to arginine ratio to foods that do not. As a result of diminished total caloric intake, and a change to foods with less lysine relative to arginine, it is likely that over time an environment more favorable to reactivation of HSV-1 evolves.

There are, then, at least two factors in older age that might shift the lysine to arginine ratio in favor of arginine, and thereby favor the reactivation of HSV-1: first, the activity of the basic amino acid transporter and second, the quantity of lysine acquired through the diet.

Activity of the immune system in suppressing reactivation of HSV-1

Since 2005 evidence has been accumulating that points to CD8+ T cells in maintaining HSV-1 latency.[24,25] Immunosenescence, or the decline of the immune system with age, appears to be related to involution of the thymus over time, with subsequent imbalance in T cell subtypes. There are no published reports specifically addressing the question of immunosenescence and HSV-1 reactivation in humans, although interestingly it has been reported that in mice the immune response to herpes simplex encephalitis is modulated by vitamin E.[26] Vitamin E, of course, has long been the object of scientific interest in the search for a means to retard the progression of AD.

At present there is little that can be done to prevent or slow the process of immunosenescence. However, this does not necessarily apply to the lysine to arginine ratio in the CSF. The question arises, given that lysine is effective in suppressing HSV-1 activation as manifested by herpes labialis, would it also suppress HSV-1 activation in the temporal and frontal cortices leading to AD? There are no data describing the prevalence of AD in older people who have taken at least 1,500 mg/day of lysine continuously over a period of years. However, given that it is known that diets rich in lysine and poor in arginine suppress HSV-1 replication, it would be instructive to know whether such diets are associated with lower prevalences of AD. The Mediterranean diet is one such diet. It emphasizes grains, but also emphasizes fruits, vegetables, cheese, yoghurt, and fish, all foods high in lysine and low in arginine.[27] Perhaps more than any other food, weekly consumption of fish is associated with a lower risk of AD.[28] This is generally attributed to omega-3 fatty acids in fish; however, it is also true that fish have a high lysine to arginine ratio.

A study published in 2001 described what may be the lowest incidence rates of AD ever found, in the Northern Indian rural community of Ballabgarh: 4.7 per 1,000 person-years, compared with 17.5 per 1,000 person-years in the Monongahela Valley, Pennsylvania.[29] The authors do not speculate on why this may be so. The residents of Ballabgarh are farmers, remain physically active into older age, and obesity is essentially unknown. They also eat a diet proportionally high in dairy products, which have a very high lysine to arginine ratio.

Conversely, unlike fish and dairy products, tofu has a high arginine to lysine ratio. It was recently reported that high tofu intake among elderly Sudanese and Javanese, a population much like that of Ballabgarh, was unexpectedly associated with an increased risk of cognitive impairment.[30]

These observations are consistent with the hypothesis that if HSV-1 causes some cases of AD, a diet high in lysine relative to arginine may help prevent this from occurring by preventing reactivation of the latent virus in vulnerable regions of the brain.

Conclusion

To summarize, AD is a disease process, not a natural result of the aging process; HSV-1 is present in 70%–90% of the brains of older adults; HSV-1 has been identified in the tissue of patients with AD at autopsy; acute HSV-1 encephalitis affects many of the same regions of the brain that are affected by AD, and leads to long term memory loss; HSV-1 is known to reside in a latent form in the trigeminal nucleus, which projects to areas of the brain known to be affected by AD; there are indicators of an inflammatory process associated with AD, suggesting the possibility of an infectious etiology, possibly as a result of immunosenescence; activated HSV-1 virus is associated with formation of plaques and tangles, which are histologic hallmarks of AD; it is also associated with elevated cholesterol levels, also considered a risk factor for AD. Finally, there are indications that diets high in lysine and low in arginine may be associated with lower prevalences of AD.

This leads to the following hypothesis: HSV-1, latent in brain, becomes activated when in older age the ratio of lysine to arginine in the CSF favors arginine, providing a medium conducive to viral reactivation, and the process of immunosenescence releases the virus from immune system surveillance. Active HSV-1 then in turn causes AD. This process may be prevented or attenuated by increasing lysine, either in the diet, or as a supplement, or both. Studies of lysine treatment of herpes labialis suggest that supplements of 1,500 mg twice a day or more are effective for this purpose.

Much of this, of course, is highly speculative. However, as noted above, the time may have come for thinking "outside of the box" in our approach to this terrible disease. The hypothesis as described above is highly testable, although it would require a very large study over many years to reach a definitive conclusion. Some would argue that it would be preferable to test the efficacy of the antivirals, rather than lysine supplementation. It cannot be argued, however, that the risk to patients posed by treatment with lysine is negligible, and the potential benefit enormous: a safe, inexpensive approach to the prevention or attenuation of AD.

Disclosure

The author reports no conflicts of interest in this work.

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