New article in the Journal of Alzheimer’s Disease proposes metabolic events that precede Alzheimer’s disease, along with potential methods for early diagnosis, treatment, and prevention.

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Alzheimer’s disease (AD) remains the only disease in the top ten causes of death for which there are no effective treatments or definitive preventive measures. Understanding the underlying mechanism that causes the brain to develop AD has been elusive. A new article in the Journal of Alzheimer’s Disease lays out a hypothesis which could open the door to new methods of diagnosis and treatment, as well as the possibility of stopping AD before it has a chance to begin.

The memory loss and cognitive decline associated with Alzheimer's disease (AD) takes many years to develop. The “neuroenergetic hypothesis,” describes how the aging-related decline in the transport of glucose from the blood into the brain may be the key. More specifically:

- The process that leads to AD is brought about when the brain no longer receives enough energy to fuel its various functions. Glucose is the main source of energy used by the brain.

- We always have glucose in our blood, but the brain does not have direct access to this resource.

- Before it can get to the brain, the glucose in the blood must pass through the body’s blood-brain barrier (BBB), a protective layer of cells designed to allow only specific substances into the central nervous system where the brain resides.

- The ability of glucose to cross the BBB and provide fuel for the brain declines as we age. This occurs in everyone, even those who never develop AD. The ability can be further impaired by diseases involving the blood vessels (our vascular system), diabetes, hypertension, obesity, and heart disease.

- Bottom Line: While there is always plenty of glucose in our blood, the situation can develop as we age where the brain no longer receives the amount it expects (and requires) to provide for all its energy needs.

- **How does the brain react when it does not have access to the energy it needs?** First, we must recognize humans are not the only organisms that rely on glucose for energy. Glucose is a prime fuel for microorganisms, such as bacteria and viruses. Successful microorganisms are ones that can out-compete their host for essential resources, such as glucose. Humans have the advantage of an immune system designed to detect and combat unwanted microorganisms, although in some cases we must turn to antibiotics or other drugs to help turn the tide.
• Returning to our discussion, we have the situation where there is plenty of glucose in our blood, but there is a developing energy-deficiency in the brain because, as we age, less-and-less glucose is able to cross the BBB.

• Evidence suggests that this energy disparity is interpreted as a microbiological attack on the brain - not enough energy there, but plenty elsewhere - and this sets off a cascade of events.

• First, our body’s main defender, the immune system, gets the call. It responds, bringing its army of compounds and causing inflammation, which is widely reported to accompany AD.

• Next, the brain starts making one of its own antimicrobial weapons. One such weapon is amyloid-beta, the same substance that forms the plaque associated with AD. Amyloid-beta gets made by changing the way a certain protein gets broken down. When the brain has enough energy, one enzyme does the job, the product being harmless and able to depart the brain through the BBB. But when glucose is inadequate (and the brain reacts as though it is under attack), a different enzyme does the work, and amyloid-beta gets produced. Amyloid-beta does not efficiently exit the brain. This makes sense as you would not want your antimicrobial weapon to be able to depart from the field of battle. Figure 1 in the paper provides an illustration of this.

• But because the energy deficiency in the brain is not being caused by a microbial attack, the defensive steps being taken do not make to the problem go away. The inflammation and the generation of amyloid-beta continue, and this leads (gradually) down the road toward AD. Low-glucose in the brain is also associated with the formation of tau, another protein produced in excess with AD.

Are there Solutions?

• Tests can be designed to track the ability of glucose to cross the BBB and identify at what point in life the energy resources for the brain become inadequate. These tests can reveal when we pass that energy turning point – which would be well before AD has a chance to get established. From that point on, steps can be taken to assure that the brain has the energy it requires. This could involve dietary, lifestyle, and pharmaceutical interventions, including alternate (non-glucose) sources of energy that the brain can use when not enough glucose is available.

• There is also an important message regarding food and lifestyle. A healthful, plant-based, whole foods diet, along with an active lifestyle, lowers the risk of a variety of diseases including those involving the vascular system, diabetes, hypertension, obesity, and heart disease. Both healthful diets and lifestyles have long been associated with a lower risk of AD. The neuroenergetic hypothesis now provides a plausible rationale for adding AD to the list.

• The paper discusses other theories and evidence relating to AD, including epidemiology and the impact of genetic risk factors.

• The neuroenergetic hypothesis presents approaches to detect and treat the metabolic events associated with the Alzheimer’s disease process before any onset of cognitive symptoms. It may also offer hope for those already in the grips of this devastating disease.

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