

## Why do Neurons Die so Fast?

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Neurons have special shapes and sizes. Their shape resembles that of an insect (spider), and in the human brain, billions of these “spiders” are skillfully clustered in different areas, like on each floor of a department store. In a department store, there are food shops in the basement, cosmetics shops on the first floor, clothes shops on the second floor, and a restaurant complex on the eighth floor, and the function of each floor is separate. The brain is organized in the same way. Basement spiders are responsible for “emotion”, the spiders on the first floor are responsible for “exercise”, and the spiders on the second floor are responsible for “memory”, so the spiders on each floor have their own unique and important functions to perform.

The legs of each spider on each floor of the department store extend not only to every corner of the floor, but dozens of meters around the wall and beyond the ceiling. In other words, nerve cells have abnormal legs compared to the size of their ‘torso’. Legs like hairs extend over dozens of meters. Moreover, there are so many spiders in the department store. Their legs are intertwined in a complex way, yet arranged in an orderly fashion. There is a nucleus containing DNA in the torso, and there is a chemical plant (rough ER), called Nissl body, that produces neurotransmitters and cell constituent proteins around it. Proteins produced in this “chemical plant” are transported by trucks on small rails to the tips of the legs extending to every corner of each floor. Receptors, channels, and some neurotransmitters are typical of such proteins. When each protein ceases to function and ages, it is brought to a recycling factory called lysosome around the nucleus by a “truck”. In this recycling factory, it is broken down into amino acids which are then taken back to the rough ER to make protein again. In other words, old and new proteins are going back and forth between the spider’s torso and the antennae that are several tens of meters away. This is how neurons support brain activity.

As long as the trucks are functioning properly, the spider is kept alive and working properly. However, the rails get rusty with aging, and various problems also occur with the transport vehicles. When a problem occurs with the trucks bringing “protein waste” back to the spider’s torso, stairs and elevators which connect each floor of the department store will fill up with garbage. Then, store employees can no longer carry goods through the store, and shoppers cannot move around inside it. Imagine, if an excess amount of garbage were to pile up on one certain floor of a department store, shopping on that floor would be impossible.

The same thing occurs in the brain. In other words, when garbage collects, certain functions of the brain, such as “memory” or “attention”, are disrupted so that meals can no longer be enjoyed on the restaurant floor. Then, humans can’t get new information, and can’t do clean up chores well. If meals can’t be enjoyed on the restaurant floor for many years, there will soon be very few customers, so management will slump and the store will go bankrupt. The same in the brain, at first, you might think you’re just making mistakes or careless mistakes, but then you start to lose track of today’s date and place. This is known as “early dementia”.

So why do the transport vehicles running around the department store break down in the first place? That’s the problem! The reason is, the wheels of the trucks get rusty with age. When the wheels get rusty, the trucks are derailed and they overturn. Yet if we keep lubricating with

good oil and maintaining the axles so the wheels do not rust, derailments will not occur. Rusting in the brain is due to the reactive oxygen species, but there are antioxidants which can prevent it. For example, vitamin E, polyphenols and  $\gamma$ -oryzanol. In particular, astaxanthin which is a component of the red pigment found in salmon, shrimp and crab has more than 500 times the antioxidant activity of vitamin E, and is a health supplement which has been drawing attention in recent years. Both department stores and brains have many trucks. When the trucks get rusty, it corresponds to “forgetting things or loss of concentration”; when trucks are derailed here and there, scattering garbage all around and the department store is closed, that corresponds to “mild cognitive impairment”; and when the whole store goes bankrupt, that corresponds to dementia”.

Aldehyde dehydrogenase 2 (ALDH 2) is an enzyme that we expect will offer even better prevention of Alzheimer’s disease than the above antioxidants. The human population is divided into three types: humans with a pair of this gene, those with only half, and those with none at all. In East Asia, approximately half of people have an enzyme-inactive ALDH2 corresponding to the latter two. As these people have a hard time decomposing acetaldehyde, the causative agent of hangovers, when they drink alcohol, they immediately go “red in the face”, and even if they consume dregs of “sake” (Japanese rice wine), they get “heart palpitations”. Statistical data show people with this inactive ALDH2 tend to get Alzheimer’s disease only 1.6 times more than those with the active gene. However, the situation is more serious in humans who have apolipoprotein E (ApoE) type 4, since they are 3 times more likely to develop Alzheimer’s disease. Moreover, people with both inactive ALDH2 and ApoE4 genes can’t drink alcohol at all, and their risk of Alzheimer’s disease is a whopping 30 times higher.

Why is it that humans with low ALDH2 and APOE4 enzymatic activity are likely to develop Alzheimer’s disease? Well, according to my reasoning, the answer is very clear. It’s because they don’t have sufficient enzyme activity to detoxify hydroxynonenal, the agent that causes neurons to die. (The suffix “-nal” is actually another name for “-aldehyde”). A person with a physical constitution that can’t break down acetaldehyde would not be able to detoxify hydroxynonenal derived from vegetable oil. Therefore, this neurotoxin accumulates in the brain little by little, and in parts of the brain related to memory like the hippocampus, temporal lobe and cerebellum, it keeps on doing decisive oxidative damage, known as carbonylation, to the heat shock protein 70 (Hsp70). Hsp70 is a molecular chaperone and protects integrity

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of the lysosomal membrane. As a result, by the age of 65, neurons in the hippocampus and the precuneus degenerate by the lysosomal permeabilization, finally leading to Alzheimer's disease.

Looking at the incidence of Alzheimer's patients worldwide, the incidence is overwhelmingly high in Japan. In Japan, the number of people with Alzheimer's disease is more than twice, compared to the United States and the EU countries in terms of the ratio of the population. The reason for this is that mountain areas occupy the

majority of the country's land area, and electromagnetic waves and exhaust gases that cause oxidative stress are concentrated in narrow plains where the majority of the people live. Besides, most Japanese people like foods containing a large amount of hydroxynonenal such as tempura, fried potatoes & fish, cutlets and fried chicken cooked in vegetable oil. However, I believe that the major reason is that Japanese people are racially weak in the enzyme activity of ALDH2, and cannot detoxify this cytotoxin, hydroxynonenal, derived from vegetable oil.