Neurodegeneration: You Have More Influence Than You Might Think

By Ben Shropshire

Consciousness is the most important aspect to your life; in the absence of it, you truly have nothing. You see, your experience of the world is created by your brain: the feeling of paper in your hands, the sight of a screen in front of you, the weight of your body against the chair, your feet in your shoes, and the smell of springtime air; these are all appearances in consciousness made possible by your nervous system. Even your childhood memories are appearances in consciousness created by your brain. Without your brain this would not be possible.

Your brain is structured to prioritize your attention by processing and categorizing all of your thoughts, internal feelings, and all information from your 5 senses. The generation of consciousness by the human brain has been quoted by many neuroscientists and theoretical physicists as the most complicated system in the universe. So what does it feel like when this system starts to break down? In other words, you still have consciousness, but your brain, a precious 3 pound glob of fat, protein and water, just isn't working the way it used to. Deborah Gould, a patient with Alzheimer's disease, may be able to answer this question. The following is her own account of the condition:

"Imagine yourself in a day in the life of someone suffering from Alzheimer's disease. Close your eyes. Now open them.

You awake in the morning, not feeling rested, and you don't know what day of the week it is, what the date is, what the month is or even what year it is. You don't remember what you had planned for the day. You get up and get dressed in one of the three outfits you wear regularly, ignoring all the other clothes in your closet. You go into the kitchen to make coffee, but you can't remember where the coffee is. You feed the cats. Or did you already? You take the clean dishes out of the dishwasher, but you're not sure where to put them.

You shrug your shoulders and go get the newspaper. You sit down with a cup of the coffee your loved one made and read the paper. You read the same article several times. You eat the breakfast your loved one made even though you are not very hungry.

You and your loved one go to your doctor appointment. During the twenty minute drive you ask him four times where you are going. At the appointment you are attentive and answer all the questions your doctor asks you. On the drive home you ask your loved one where you have been. When he reminds you of the doctor appointment you ask what she said. He reminds you the doctor is a man. You discuss what the doctor said, but you don't recall any of it.

You stop for lunch at a restaurant. You look over the menu for a long time. You eventually decide what you want to order. When the waiter comes you order something else. You eat half of it because it doesn't have much flavor.

When you get home you get anxious and start to have dark, negative thoughts. You cry. You feel angry. You feel depressed. Your loved one puts on some music and that, as it always does, lifts your spirits. You play games on your smart phone and time passes. You try to read a book, but you lose the narrative after a few pages and put it down.

When it's time for dinner, your loved one prepares the meal because you can no longer follow the recipe, unsure whether you already put that ingredient in or not. The dish just doesn't taste like it used to. Ice cream for dessert. Now that always tastes good.

After dinner you watch TV. Something on the news disturbs you. When the news is over you can't remember what it was, but the feeling still lingers. You and your loved one decide to watch a movie. It will be a comedy because dramas are hard to follow and sometimes leave you feeling low.

When the movie is over you get ready for bed. You forget to brush your teeth. Once in bed it takes a long time to fall asleep. Once asleep you awake in a few hours, then again later.

You awake in the morning, not feeling rested, and you don't know what day of the week it is, what the date is, what the month is or even what year it is."

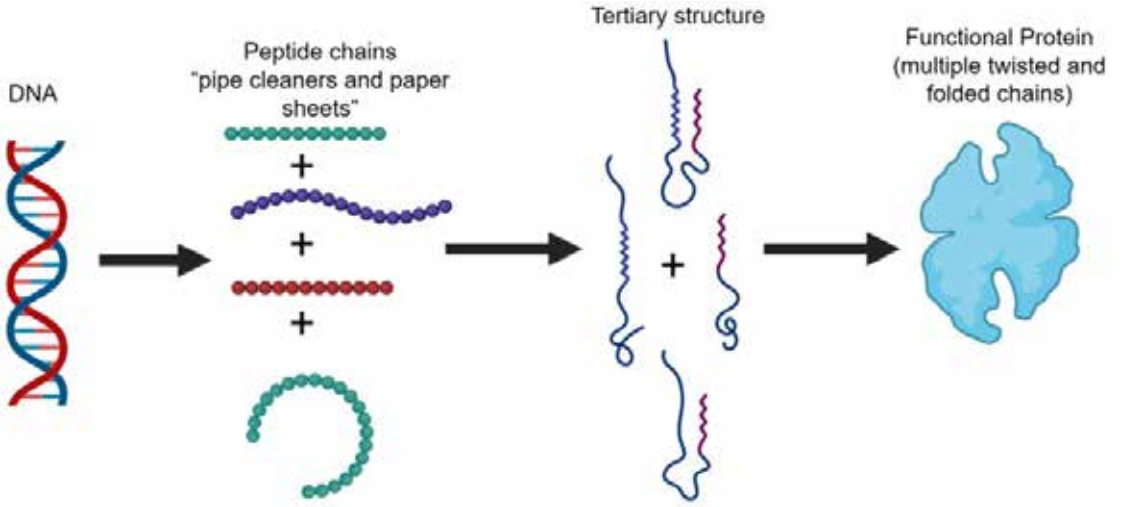

Figure 1*: Illustration showing the process of protein folding and misfolding, and how misfolded proteins can cause problems for the cell.*

The brain contains 86 billion neurons and about 9 times as many supporting cells, known as glia. This vast number of cells as well as the limited healing ability gives the brain some resilience. However, when the damage to our brian outpaces the rate of recovery we may begin to see signs of cognitive impairment. In the 65+ population, the range of cognitive impairment can be as high as 19%. It is also true that more than half of the population identified as cognitively impaired will progress to dementia [27]. The other half however remains stable. Why might this happen? Well, we know that the basis for this decline is often neurodegeneration [34]. And risk for this can be impacted by various factors. In this article, I will attempt to shed some light on the following questions to do with neurodegeneration and related diseases: How do neurons reach the point where they die? What role do glial cells play in this struggle? What factors do neurodegenerative diseases have in common? What can you do to help decrease your risk for neurodegeneration?

What is neurodegeneration?

Broadly speaking, the nervous system consists of neurons and glial cells. The neurons are primarily responsible for the communication of information in the form of electrical and chemical activity. Glial cells serve a wide variety of functions including but not limited to structural support, metabolic assistance, synaptic maintenance, clearance of waste products, management of the CNS immune response, storage of metabolites, and insulation of neurons and their axons [1]. While neurons are the star of the show, it is this codependent network of neurons and glia that gives rise to consciousness as you are experiencing it now. The neurons that form the incomprehensibly complex networks would not be able to generate anything worth experiencing without the proper assistance of the glial cells. Neurodegeneration is the progressive death and deterioration of the nervous system. This process often underlies a variety of nervous system diseases and can be devastating if left [5].

Statistically there is a good chance that you know at least one person who suffers from neurodegeneration, as in about 1 in every 5 adults over 65 in the US is at risk of developing diseases such as: Mild Cognitive Impairment (MCI), Alzheimer's, Parkinsons, multiple sclerosis, or Amyotrophic Lateral sclerosis (ALS) and others [84]. Depending on the nature of the neurodegenerative disease, not only are you suffering from a life threatening condition, your conscious experience of the world may be altered in a way that disturbs your sense of agency. For instance, a person suffering with Parkinson's or Huntington's disease slowly loses their ability to hold a pencil or walk without assistance. Those suffering from Alzheimer's disease slowly realize that the simple forgetfulness of "where did I leave my keys" has progressed to "I don't remember how to get back home". This experience of the world is frightening, but what causes the brain to make this transition?

Many of these diseases have individual genetic mutations that can predispose you to a particular disease such as APOE e4 for Alzheimer's, LRRK2 and PRKN in Parkinson's, HTT in Huntington's or C9ORF72 in amyotrophic lateral sclerosis (ALS) [28],[29],[30],[31]. There are other factors however, that contribute to their pathology and progression. Interestingly,

neurodegenerative diseases share many fundamental processes that lead to the progressive dysfunction and death of your brain. These include but are not limited to, protein misfolding, oxidative stress, insulin resistance, dysregulated waste recycling and removal, poor vascularization, and neuroinflammation [5]. In order to answer how we may reduce our risk for neurodegenerative diseases, it is important to understand what exactly is happening in the brains of individuals with these conditions.

Mechanisms of Neurodegeneration: How the Brain Falls Apart

Wrinkly Proteins are a Cellular Recipe for Disaster

Your body is composed of proteins that are assembled by your cells. Each protein has both a specific shape and job to do. The job of the protein depends on the shape of the protein. The protein gets its shape from a process called folding. Sometimes proteins misfold into the wrong shape. In this case, the protein cannot do its job and must be refolded or recycled, otherwise it will cause problems for the cell [5].

Why do Proteins Misfold?

The specific cause of protein misfolding is not always clear; however, current research posits that oxidative stress, genetic mutations, and random error may be root causes [5]. Genetic mutations are rare, uncontrollable, but often are identifiable. Random error occurs when your body accidentally builds the wrong protein. Oxidative stress is directly linked to metabolic health, which includes factors such as blood sugar, waist circumference, and blood pressure and mitochondrial health [19,39,40]. These three root causes contribute to the individual's loss of control over their oxidative stress levels.

What is Oxidative Stress?

Understanding oxidative stress first requires an understanding of the process that generates the most of it, cellular respiration. The human body creates energy at a cellular level by oxidizing metabolites in your food and using that stored chemical energy to create ATP, a standard energy currency for your body. This process happens in your mitochondria, small generators located in almost all cells in the body. They have many functions but none as important as the generation of ATP through the process of cellular respiration. Cellular respiration generates a compound known as reactive oxygen species (ROS) as a byproduct. If cellular respiration can be likened to a fire for energy, then ROS is the smoke that rises from the flames. A poorly burning fire generates a lot of smoke and not a lot of heat. ROS are exactly what its name would lead you to believe: reactive. These compounds contain an extra electron that causes damage to cellular membranes and proteins. This reaction can cause proteins to misfold and eventually result in mitochondrial and cellular dysfunction. Oxidative stress occurs when the levels of ROS increase beyond what your body is capable of managing; after this threshold, it is highly likely that cellular damage will occur [10],[35]. In another apt metaphor, ATP generation is similar to warming your house with a fire but ROS causes the chimney to be blocked, which in turn causes toxic smoke to be trapped in your house, putting you at risk of becoming sick.

Why is this process so important?

The brain is one of the most energy-hungry organs in the body. While at rest, it comprises 2% of the body's total weight and uses 20% of the body's oxygen [41]. Continuing with the fire analogy, the fire (ATP) in your house provides warmth and food; without it you'd starve and freeze in

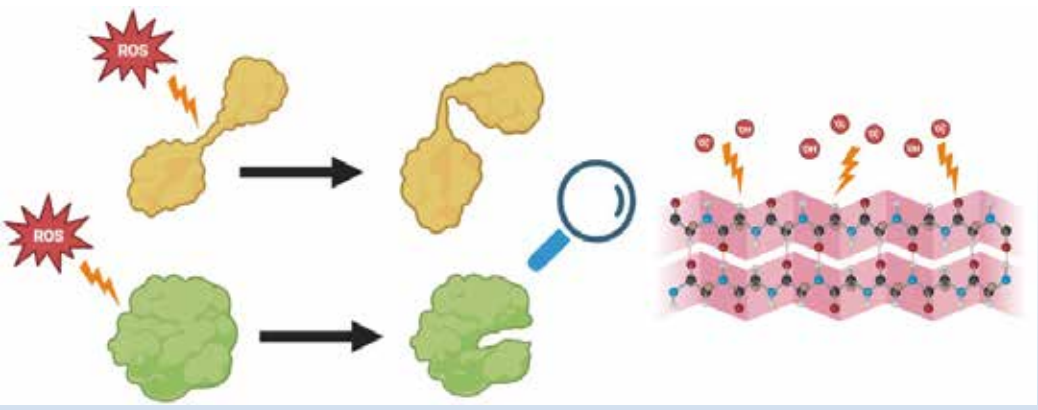

***Figure 2**: The process of cellular respiration leading to the generation of reactive oxygen species (ROS) and resulting oxidative stress.*

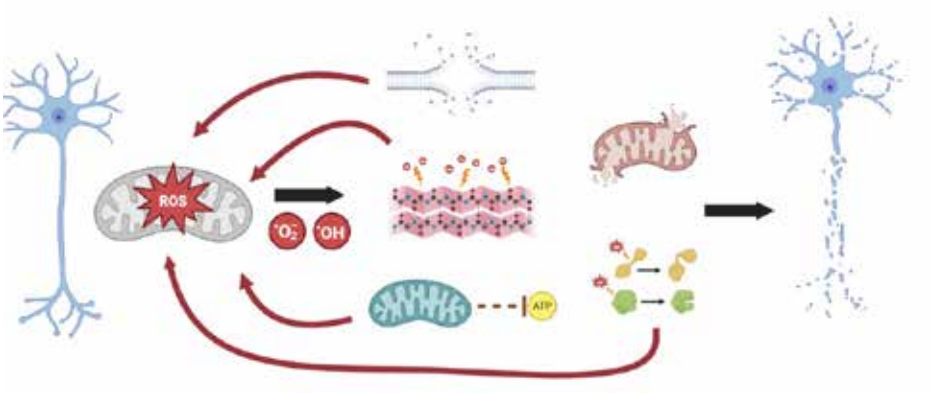

***Figure 3**: Cellular respiration generates reactive oxygen species (ROS) as a byproduct, causing oxidative stress. This results in damage to cellular membranes and proteins, leading to dysfunction of mitochondria and cells.*

the winter. The process of keeping all your neurons alive and working requires thousands of mitochondria within each cell [42]. An inefficient mitochondria will produce more ROS (smoke), which, if left unchecked, will lead to more damage to the mitochondria and its eventual death. Your body has smoke alarms in place that will start the process of shutting down the mitochondria if they are producing too much ROS. When this happens en masse, mitochondrial death, in a similar fashion will signal the death of a neuron. [10],[35].

Particular proteins, such as Amyloid-beta, Tau protein, and alpha-synuclein, have been implicated in Alzheimer's and other neurodegenerative diseases [5]. When these proteins misfold they often cluster in tangles or plaques, creating blockages outside and within neurons. So, not only are the proteins not performing their original job, but because they are misfolded, they also now obstruct the molecular flow and communication between and within neurons [5].

Why would all of this information be relevant when thinking about preventing neurodegenerative disease? You might be thinking " I would know if my brain started degenerating." The truth is, this is not always obvious. Protein misfolding, which underpins neurodegenerative diseases becomes present before the onset of symptoms. People suffering from Parkinson's can lose up to 80% of their movement initiating neurons before they recognize they are symptomatic [43],[44]. As mentioned earlier, the beauty of the brain is that its complexity and richness allows for compensatory mechanisms (such as synaptic plasticity and cognitive reserve) to stave off the effects of neurodegeneration as certain areas begin to falter [43],[44],[45],[46]. Unfortunately, the mechanisms of neurodegeneration often lead to processes that cause further deterioration of the brain [47].

Brain Inflammation: Another Neurodegenerative Culprit

Neuroinflammation is implicated in the progression of almost every neurodegenerative disease [32],[49],[50]. By understanding it we can attempt to limit the impact it may have on us. Inflammation is a protective response against external pathogens and/or a healing response to damaged or sick cells. Inflammation can be triggered by pathogens, foreign substances, trauma, toxins, and cause physical damage to cellular structures. Taking the perspective of a cell in your body, the presence of inflammation is akin to the activation of EMS and also having the National Guard patrolling your neighborhood. This is a huge relief if your city was just hit by a natural disaster or if their homes were invaded by a rioting mob. They come to clean up the damage and clear out the invaders. The downside is that this system in your body can get confused. For instance, what if the National Guard mistakes you for the invader that brought them to the scene?

The main components of

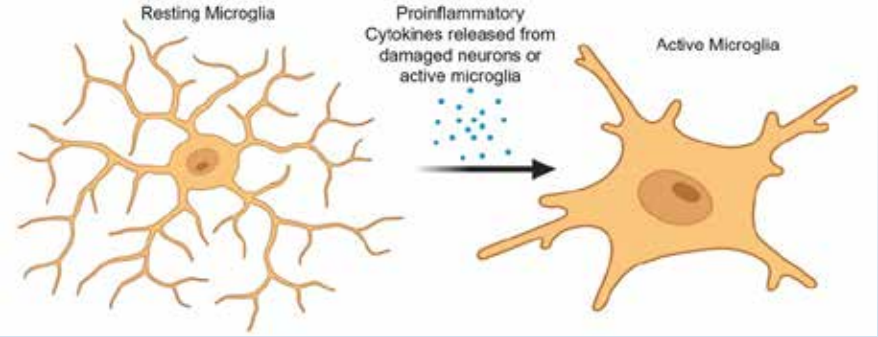

***Figure 4**: The inflammatory response within the brain involves microglia and cytokines, this process activates microglia to respond accordingly.*

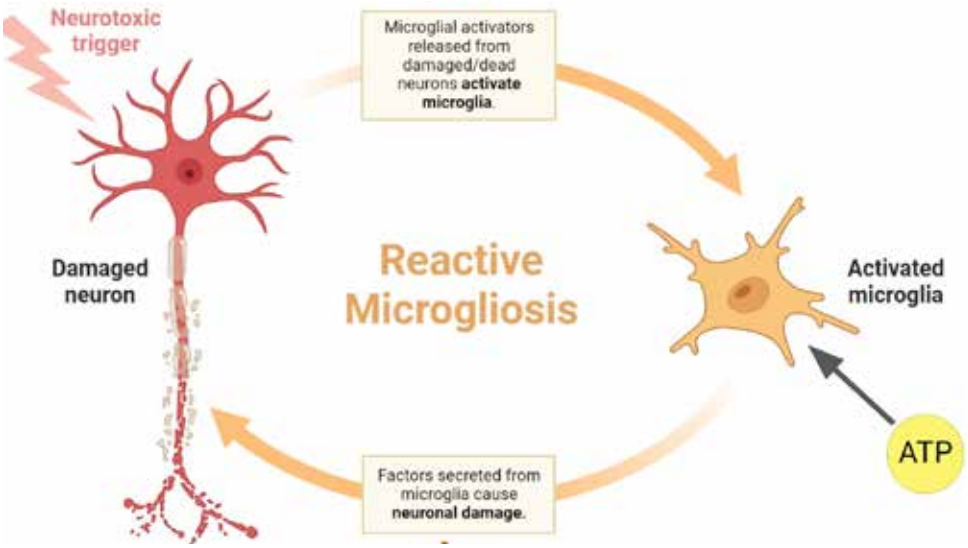

***Figure 5**: TThe process of microglial activation triggered by the presence of damaged proteins can lead to helpful inflammation and clearance of misfolded proteins in the early stages of neurodegeneration.*

an inflammatory response within the brain are the microglia, and cytokines [50]. The microglia are the EMS and National Guard. Cytokines are small communication molecules with a unique signature used to attract microglia to a particular area. When microglia receive the signal of a potential emergency they begin to crawl over to the source of the signal, following the trail of cytokines, while leaving behind their own trail of similar molecules [51].

The presence of damaged proteins is often the trigger for microglial activation. The neurons sense the disruption being caused by the misfolded proteins and send out signals for help [5],[50]. The microglia do not recognize the clusters of misfolded protein and begin to secret factors to destroy them and the neurons that contain them. In the early stages of neurodegeneration, the inflammation is helpful and can lead to clearance of the misfolded and clustering proteins. However sustained activation of microglia is taxing on the brain. Microglia use up valuable resources, are energetically demanding, and the chemicals that they secrete to clear unwanted substances damage healthy neurons. As these conditions persist, the microglia become less efficient and begin to cause more harm than good by targeting the wrong cells [52]. It's as if they forget which cells are supposed to be cleared and which ones are still working. Additionally, these microglia activate other glial cells called astrocytes that are meant to be supporting the neurons. Once activated, they lose their ability to support neurons resulting in the death of neurons as well as other supporting cells [48]. Unfortunately, what started as a helpful clearance of damaged hardware becomes a degenerating cycle of uncontrolled self sabotage.

Alzheimer's: Type three diabetes?

Another factor implicated in neurodegeneration is insulin resistance. Unless you are diabetic or care for someone with diabetes, you may not know what insulin is or how it works. Simplified, insulin is a hormone that is released in response to the consumption of food. A small amount is produced in response to fat, and a stronger response is seen in the presence of amino acids and sugars. This is to ensure that the calories that you consume make it to the intracellular space where they can be utilized. Insulin resistance occurs when your cells require more and more insulin in order to open up the gates to receive the calories from your bloodstream. This happens when insulin levels are intensely and chronically elevated. Your cells become desensitized to the effects of the hormone, leading to the overproduction of insulin, further dulling your cells sensitivity. This leaves your blood sugar elevated for lengthy periods of time while reducing the cell's ability to absorb calories, resulting in tissue damage [11],[19]. Insulin resistance puts your cells in a state of oxidative stress and is seen in Alzheimer's, MCI, Parkinson's, and even Huntington's [13],[14],[15],[16],[38]. It is no surprise that we see major problems when the most energetically demanding organ in the body can't get enough fuel.

Simple tips to reduce your risk for neurodegeneration

The tips within this article will not individually prevent the formation of a neurodegenerative disease. However, that doesn't mean that all hope is lost! When used synergistically and consistently, they will likely decrease your risk for neurodegeneration and associ-

ated diseases. These are meant to be simple and affordable suggestions to potentially help you live an improved quality of life. When making any large life changes, it's always best to ask your physician.

Hit the Sauna

Psychological stress, environmental toxins, and obesity can all increase oxidative stress, and thus inflammation, which as we know potentiates protein misfolding [25],[53],[54],[55],[56]. In response to these stressors, and to prevent protein misfolding, your body activates what is called heat shock factor 1 (HSF1) [6]. HSF1 is a signaling protein that tells your cells to make other proteins, offering protective effects for the cell [6]. The general name for these are heat shock proteins (HSP), the most studied of which is HSP70. HSPs, also known as chaperone proteins, help new proteins to fold properly [57]. When activated by outside stress, HSPs prevent protein misfolding and aggregation. Numerous studies have shown that expression and overexpression of HSP70 is neuroprotective in the face of chronic and acute stress or injury to the brain [6,12].

Studies of sauna bathers suggest that increased sauna bathing duration and frequency decreased one's risk of dementia, although the results are not definitive [7]. As their name suggests, one of the best ways to stimulate HSPs is through exposure to elevated temperatures. Through passive heat bathing in a sauna, you might increase your HSP70 expression [6]. This is one of the proposed mechanisms by which chronic heat exposure is thought to protect against neurodegenerative disease. Another mechanism is through increased blood flow and cardiovascular elasticity, as cardiovascular health is linked to neurodegeneration [8, 85]. Heat therapy is an inexpensive way to improve your overall health and reduce your risk for neurodegeneration.

A Brain-Healthy Diet

Studies on the "western diet," a diet consisting of high sugar and fat content, lead to mitochondrial dysfunction, specifically a disturbance in the quality control mechanisms that signal for the mitochondria to recycle themselves. This leads to a build up of poorly functioning mitochondria that leak reactive oxygen species into their host cell [9],[10],[35],[58].

But what is it about food that impacts the mitochondria and may go on to increase your risk of neurodegenerative disease? Food is normally perceived as a means by which to get fuel—an input/output equation of sorts. From a certain perspective, that holds completely true. However, in the context of neurodegeneration, certain foods may have beneficial effects, while the over consumption of other foods may have negative consequences. Thus, it becomes clear that all food is not created equal. Research over the past few years has begun to uncover evidence for the benefits and detrimental effects of certain foods on the health of the brain. Recent research has found that a "Western diet" (WD) induces mitochondrial dysfunction, obesity, metabolic disorders, and systemic inflammation. This leads to accumulation of misfolded proteins such as and increases one's propensity for memory impairment [58],[59],[60].

Recall from earlier that insulin resistance is detrimental to the brain. It deprives the brain of access to fuel while at the same time causing damage and inflammation to the vasculature

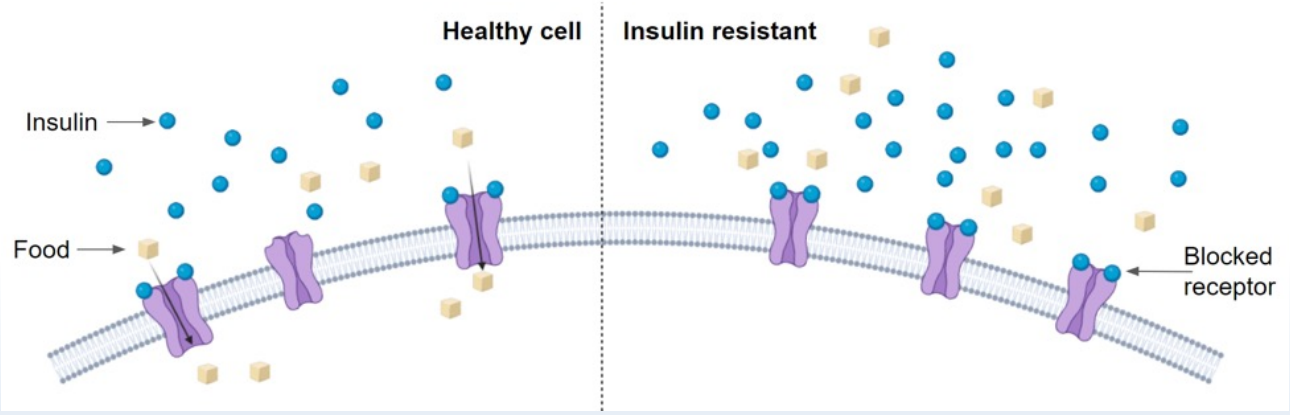

Figure 6: *A comparison of a healthy cell and an insulin resistant cell, illustrating how insulin resistance impairs the ability of cells to absorb calories from the bloodstream, leading to tissue damage and oxidative stress.*

of the brain, which is critical for maintaining optimal brain health [17],[18],[19]. One thing you can do to potentially reduce your risk of neurodegeneration is to adjust the timing of your meals to be within an 8 hour period to increase insulin sensitivity and decrease blood glucose [61],[62],[63]. In the context of neurodegeneration, refined carbohydrates will spike blood glucose much higher than proteins or fats. Over time, this may lead to vascular damage and potentially insulin resistance. It may be better to consume foods which do not spike blood sugar as much, such as fish, olive oil, nuts and seeds [22],[23].

Fish, such as salmon, mackerel, and sardines, contain a critical omega-3 fatty acid known as DHA. Development of the human brain is dependent on DHA as it helps form many of the protective membranes that insulate your neurons [82], [83]. It is present in high levels in nervous tissue and exhibits neuroprotective effects by upregulating antioxidant pathways. Some research has even shown alleviation of Alzheimer's symptoms [28],[64],[65],[66].

Consuming Antioxidant rich foods

Your body produces antioxidants in order to balance the ratio of oxidants to antioxidants. Antioxidants are compounds that are able to receive an extra electron and remain chemically stable, protecting the cell from damage [67]. Your body makes antioxidants, but you can also get them from foods. Evidence suggests that antioxidants from food interrupt both the oxidative pathway as well as the inflammatory pathway, and likely play a role in reducing one's risk for neurodegeneration [68],[69],[70],[71],[73]. Due to the novelty of the field, current evidence for the clinical efficacy of dietary whole food antioxidants is limited, there is one food that is promising. Your sunny-yellow breakfast drink is more than just a drink to wash down your pasture-raised, cruelty-free, organic eggs. An overview of the scientific literature found orange juice consumption likely to be effective in reducing markers of inflammation [72],[74]. So the jury is still out on just how effective antioxidant rich food may be at reducing oxidative stress and inflammation, but it can be recommended that consumption of these foods in place of the high fat, high sugar, "western diet" will decrease your risk for neurodegeneration

Move your body, protect your mind

Outdated biology textbooks may report that the number of neurons you have once you reach adulthood is set in stone. We know this is no longer the case. Your brain can create new neurons when stimulated by a hormone known as brain derived neurotrophic factor (BDNF) [75]. This is promising news for neurodegeneration! What is the fastest and most effective way for anyone to increase their levels of BDNF? Exercise. Ok so I'm not saying that you can literally run away from dementia. But, I am saying that exercise is effective in improving executive functioning skills and cognition in people suffering from cognitive decline, even more than mental training [37],[76].

It creates new connections between neurons and places the brain in a state optimal for learning even after a single bout of exercise [77]. Consistent exercise leads to improvements in memory, even for people in cognitive decline [24].

The brain-boosting benefits of exercise are multifaceted. It promotes the creation of new blood vessels in the brain [78]; clears out and recycles damaged proteins, increases insulin sensitivity, and improves sleep [26],[36]. It upregulates the neuroprotective Heat Shock Protein [79]. Exercise stimulates the production of your body's own antioxidants, promotes the birth of new mitochondria and improves mitochondrial efficiency [36].

There are lots of ways to exercise and all of them will benefit you. The most effective for brain health appears to be aerobic exercise; which may be 30-60 min of 5 min efforts at medium intensity followed by 5 min of light intensity [37],[80]. Keep it simple. While complexity can be fun, simple is effective.

Take Away

As a larger percentage of the world's population reaches old age, more and more individuals will experience neurodegeneration. The sad irony is that these conditions steal the very things that make a long life enjoyable: remembering, thinking, moving, deciding, and feeling [49],[81]. You now know that neurodegeneration is not just up to fate; preventative measures can be proactively taken. As you finish reading this article, take a moment to ponder the beautiful complexity of your brain and your experience of the world.

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