Unraveling 5 Major Mysteries of Dementia: Insights from the Melanin Theory

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Abstract

Dementia, encompassing Alzheimer's disease (AD), Parkinson's disease (PD), and Lewy body dementia (LBD), remains a complex and multifaceted condition with many unresolved questions. We propose a novel perspective on the role of melanin in explaining the unanswered questions in neurodegenerative diseases. This poster explores five major mysteries in dementia -- energy metabolism in the brain, the role of inflammation, sudden worsening of symptoms, cognitive reserve mechanisms, and environmental and genetic factors -- integrating insights from our theory on the role of melanin in various dementias.

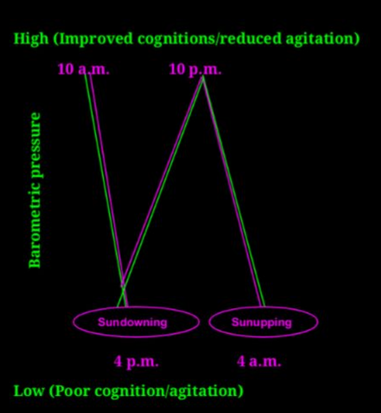
1. Energy Metabolism in the Brain

Glucose Metabolism: We theorize that melanin plays a crucial role in cellular energy production, influencing glucose metabolism. In fact, the specific areas of the brain where melanin loss is seen correlates with disease symptomology. We found that the energy retained in melanin appears to fuel cells in an inverse relationship with ATP production. Hence, alterations in melanin levels impact glucose metabolism. In addition, certain pathogens can decrease host blood glucose levels, which impairs the host's immune response, allowing the pathogen to persist and spread. One such strategy is to decrease the number of glucose transporters at the blood brain barrier (BBB), which is seen prior to the onset of AD symptoms.

Mitochondrial Dysfunction: Mitochondria are crucial for energy production in neurons. In dementia, particularly AD, mitochondrial dysfunction is a significant issue. Typically, neuromelanin increases as healthy people age but decreases in individuals with dementia. We theorize that elevated oxidative stress, which is often seen in neurodegenerative disorders, is related to a loss of melanin/neuromelanin. This oxidative stress is linked to mitochondrial dysfunction, contributing to the pathology of neurodegenerative diseases. Neuromelanin plays a role in mitigating oxidative stress.

2. Role of Inflammation

We theorize that symptoms of dementia are the result of inflammation, not plaques. The inflammation peaks and wanes, causing symptoms to increase or decrease. There is substantial evidence that dementia is caused by infection with pathogens entering the brain via the vagus nerve from the gut or the olfactory nerve and that the plaques are encapsulating the pathogens.



Sundowning involves increased confusion and agitation in the late afternoon or evening for people with dementia. This has been attributed to low lighting, quiet environments, and if waking at 4 a.m., disrupted circadian rhythms. We better explain sundowning (and sunupping) by cyclic twice daily changes in barometric pressure. Specifically, low barometric pressure allows for increased inflammation, and the lowest barometric pressures, on average, in a 24-hour period are at 4:00 p.m. and 4:00 a.m., as the sun sets and as the sun rises. In contrast, high barometric pressure reduces inflammation.

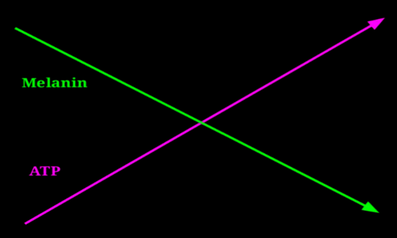
3. Sudden Worsening of Symptoms

We theorize sudden worsening of symptoms is caused by an acute inflammatory response resulting from a rapid onset of infection, such as seen with UTIs, via quorum sensing, triggering a coordinated attack of the host immune system and tissues to spread infection, increase virulence, form biofilms, and exchange genes to resist antibiotics; pathogens exiting dormancy; or even aggressive efforts by commensal microorganisms to regain balance, allergic response, heightened stress, or a sudden reduction of melanin.

4. Cognitive Reserve Mechanisms

Cognitive reserve (CR) in dementia is associated with neuroplasticity. Building and maintaining new neural networks and other brain adaptations requires large amounts of energy. There is a loss of glucose transporters at the BBB prior to symptom onset in individuals with later confirmed AD. Pathogens, including herpes simplex virus, which is linked to AD, can reduce the number of glucose transporters at the BBB via an inflammatory response. Hence, there is a loss of cellular energy prior to symptom presentation. Individuals with higher CR maintain memory better than their counterparts in the presence of AD-related glucose hypometabolism. Therefore, another energy source must be present to compensate for ATP production loss due to low glucose supply. We conclude that individuals with AD with high CR have higher amounts of neuromelanin, and likely, eumelanin, than those with significant symptomology. This may explain why CR is associated with participation in social activities and exercise, as they require cellular energy. Healthier individuals tend to eat healthier diets. Exercise and healthy diets, in turn, produce healthy gut microbiomes.

ATP production is inversely related to melanogenesis.
Click here for supporting evidence.



5. Environmental and Genetic Factors

Exposure to certain environmental toxins is associated with the development of dementia. We use glyphosate here to show, in the context of our theory, one way in which environmental toxins can contribute to the development of dementia. Glyphosate, the active ingredient in many commercial herbicides, has been associated with the development of neurodegenerative diseases, including AD and PD. Glyphosate targets the shikimate pathway, which is present in plants, bacteria, and fungi. Research suggests that more than half of the bacterial species in the human gut microbiome may be sensitive to glyphosate. Various neurodegenerative diseases present with a reduction in neuromelanin. The shikimate pathway plays a crucial role in melanogenesis by providing the necessary precursors for the synthesis of melanin.

The shikimate pathway is responsible for the production of aromatic amino acids, including phenylalanine and tyrosine. These amino acids are required for the production of melanin. We theorize that the reduction in neuromelanin in the brain reduces the energy necessary for a healthy immune response to pathogenic invasion. Reports also show increases in pro-inflammatory cytokines in blood plasma, increasing the expression of TNFα and soluble Aβ, after glyphosate exposure. This, too, under our theory, strongly suggests glyphosate-induced gut dysbiosis leads to subclinical infection and an inflammatory immune system response. Exposure to other environmental factors, for example smoking, may worsen symptoms by feeding pathogens. Many environmental factors associated with dementia are molecules that can be utilized by pathogens.

While there are many ways genes can be affected, in the case of glyphosate, as an example, the gut microbiome communicates with the brain through the gut-brain axis. Dysbiosis can disrupt this communication. This disruption can influence the regulation of genes involved in stress responses and hormonal pathways, which can impact melanogenesis. Further, gut dysbiosis can lead to an altered immune response, which can affect the expression of genes involved in inflammation.

Melanin: A unifying theory of disease as exemplified through various dementias

Melanins play important roles in the immune system. Diseases in which there is a loss of melanin, such as AD, PD, and LBD, are increasingly thought to have infectious etiologies. We theorize that under normal conditions melanin retains some of the energy it absorbs from electromagnetic radiation to fuel cells, and energy from ATP is used to compliment that energy supply in an inverse relationship. Therefore, the loss of melanin reduces the supply of energy to cells, which in the case of AD, PD, and LBD results in an inability to sustain immune system defenses to fight pathogens and remove the plaques encapsulating them. We further postulate that it is not the plaques that cause symptoms of dementia but, rather, inflammation in the brain resulting from the immune system's response to pathogens. Therefore, alteration of melanin levels may be at the core of dementia, and regulating melanin levels may offer new avenues for treatment development.

To read more about our theories, click here.