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Alcohol's Effect on Alzheimers: An Analysis of Alcohol as a Modifiable Risk Factor

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Abstract:

This review explores the negative effects of alcohol consumption, with a specific focus on Alzheimer's disease and neural health. Excessive alcohol intake has been associated with an increased risk of developing Alzheimer's disease. One proposed mechanism involves microglia, the brain's immune cells responsible for clearing amyloid-beta (Aβ) plaques. Chronic alcohol exposure may impair microglial function, leading to an accumulation of these plaques. In particular, an imbalance between the Aβ42 and Aβ40 isoforms — with Aβ42 being more prone to aggregation — contributes to neurotoxicity and plaque formation. Additionally, alcohol-induced inflammation can lead to the overproduction of cytokines. While cytokines are typically involved in cell repair, excessive levels can result in neuronal damage. In some cases, pro-inflammatory cytokines may disrupt neuronal membranes, further exacerbating neurodegeneration.

An Introduction to Alzheimers:

Alcohol plays an important role in getting dementia, as heavy drinkers were 8% more likely to develop Alzheimer's, and those who reduced their drinking from heavy to moderate saw a 12 percent decreased risk in Alzheimers.[1] In Alzheimers, neuron loss is a key symptom noticed in Alzheimer's patients. This neuron loss is due to the hyper-activation of the microglia which control a protein known as amyloid-beta. Due to the microglia's inability to remove the amyloid-beta proteins in an inebriated state, there leads to a higher ratio of amyloid-beta in the brain, and a lower ratio in the bloodstream, thus leading to cell loss.[2] This paper covers how neuron loss due to alcohol could lead to symptoms present in Alzheimers. State your research question/methodology: This

[1] Koch, M., Costanzo, S., Fitzpatrick, A. L., Lopez, O. L., DeKosky, S., Kuller, L. H., Price, J., Mackey, R. H., Jensen, M. K., & Muka-mal, K. J. (2020). Alcohol consumption, brain amyloid-β deposition, and brain structural integrity among older adults free of dementia. *J Alzheimers Dis*, *74*(2), 509–519. PMC7385407. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7385407/

[2]Hansen, D. V., Hanson, J. E., & Sheng, M. (2018). Microglia in Alzheimer's disease. *J Cell Biol*, *217*(2), 459–472. PMC5800817. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5800817/

review investigates how alcohol consumption leads to the death of neurons in the presence of amyloid-beta, and how this could affect Alzheimers. Firstly, this review will cover how amyloid plaques are formed, then the effects in terms of cell loss, and how this cell loss shows early symptoms of Alzheimers. This ends up showing how alcohol's inability to moderate the amyloid-beta cells could serve as a modifiable risk factor to Alzheimer's disease.

Section 1: The Hyperactivation of the Microglia

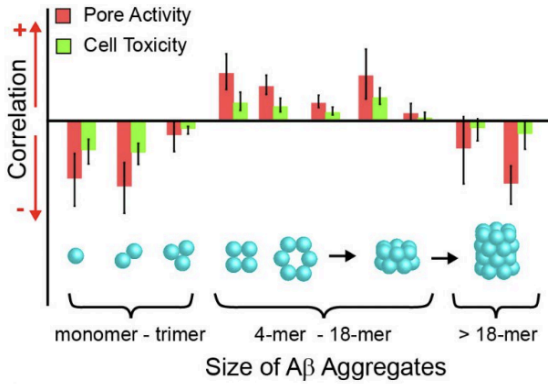
Alcohol has one main side-effect that pertains to the brain, which is the deactivation of microglia. Microglia are a type of glia cells that are similar to support cells. The main function of the microglia is to moderate cell debris, one of the main being the amyloid plaques. When one consumes alcohol and the microglia don't function as normal, the amount of amyloid plaques in the brain increase. High levels of amyloid-beta in the brain is bad, and due to the microglia's inability to filter the protein into the bloodstream, a low amount of amyloid-beta ends up in the blood plasma, another bad sign. Furthermore, acute or chronic neuroinflammation is caused due to the impaired cell function. This leads to gradual, yet apparent, programmed cell deaths and the loss of neurons. In a normal process of neuron death, the microglia would repair the dying neuron, and then would come the astrocytes.[3] However when one begins binge-drinking alcohol, the microglia become hyperactive and put out various disease response hormones. In terms of stimuli released, alcohol can release 1 or 2 stimuli. In both cases, variations of cytokines (CCL2) are produced. After the microglia exit the hyperactive state, they are then alerted to the high levels of cytokines, thus repairing healthy neural circuits, leading to unwarranted neuroinflammation and neural loss. [4]

[3] Khan, M. A. S., & Chang, S. L. (2023). Alcohol and the brain-gut axis: The involvement of microglia and enteric glia in the process of neuro-enteric inflammation. *Cells*, *12*(20), 2475. PMC10605902. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10605902/#:~:text=Proinflammatory%20Mediators%20in%20Activation%20of,other%20forms%20of%20cell%20death.

[4] Khan, M. A. S., & Chang, S. L. (2023). Alcohol and the brain-gut axis: The involvement of microglia and enteric glia in the process of neuro-enteric inflammation. *Cells*, *12*(20), 2475. PMC10605902. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10605902/#:~:text=Proinflammatory%20Mediators%20in%20Activation%20of,other%20forms%20of%20cell%20death.

Section 2: Amyloid Plaques and Cell Toxicity

Figure 1[5]:



Statistical Analysis:

The following image shows how medium sized amyloid-beta chunks show positive cell toxicity and more pore activity.

Analyzing the graph:

This highlights how in the presence of this cell toxicity, there becomes more holes in the neurons. These holes lead to neuron death, and eventual chronic neuron loss. This is because of what happens after the holes are opened. Calcium ends up entering the cell in unregulated amounts. This creates an uneven balance between calcium and other ions, thus leading to the neuron's death.

[5] University of Michigan News, "Understanding Alzheimer's: Study Gives Insights into How Disease Kills Brain Cells," *University of Michigan*, April 29, 2024, https://news.umich.edu/understanding-alzheimer-s-study-gives-insights-into-how-disease-kills-brain-cells/.

Section 3: The Attack on the Hippocampus and Cerebral Cortex

One of the most prominent progressive effects of Alzheimers is the loss of neurons, thus leading to memory loss. This specifically focuses on the hippocampus and cerebral cortex, both being regions which help recollect and create memories. [6]The cerebral cortex further plays a role in higher cognition, accounting for the lowered energy levels.

The loss of neurons in these regions is referred to as neurodegeneration, which is directly linked to the cognitive deficiency shown in Alzheimers. This deterioration within the brain impacts how neural networks function. Due to this, the link between neurons becomes weaker, leading to slower or even no information processing ability.

Although the loss of neurons is inevitable as one ages, alcohol accelerates the neuron loss through amyloid plaques and hyperactive microglia as explained above. As seen in Figure 1, the medium sized amyloid plaques end up breaking holes through the neurons, leading to weaker neuron interconnections and in cases even complete neuron loss. This shows how memory impairment in Alzheimers could be accelerated through consuming alcohol. [7]

Section 4: How Alcohol Links to Alzheimers.

An overconsumption of alcohol has various negative effects that come with it, however it affects the risk of dementia. Studies show that one's risk of Alzheimers could correlate with the amount of alcohol consumed. In some cases, chronic alcohol consumption could not only result in risking Alzheimers, but further contract Wernicke's encephalopathy, Korsakoff's syndrome.

Studies further suggest that moderate alcohol consumption affects the hippocampal volume and results in lower gray matter. This can be linked to the effects seen in Alzheimers, as neurons in the hippocampal regions die off, decreasing the volume.[8]

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[6] National Institute on Aging, "What Happens to the Brain in Alzheimer's Disease," *National Institute on Aging*, May 15, 2024, https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease.

[7] *University of Michigan News*, "Understanding Alzheimer's."

[8] Koch, M., Costanzo, S., Fitzpatrick, A. L., Lopez, O. L., DeKosky, S., Kuller, L. H., Price, J., Mackey, R. H., Jensen, M. K., & Muka‐mal, K. J. (2020). Alcohol consumption, brain amyloid-β

This shows how alcohol consumption links to the effects seen in Alzheimers. This suggests that if one reduces their alcohol consumption, it could further reduce the risk of Alzheimers and other syndromes.

Discussion: A Potential Research Avenue

Alcohol already has lots of research done on its relationship with Alzheimers, however there are still many potential research avenues. One that I found interesting could be experimenting with the relationship between alcohol and neuroinflammation, and how this affects the production of necessary hormones and proteins. This could further expand on the negative effects of Alzheimers, drawing more attention to this problem and also could explain how patients with Alzheimer's lack certain proteins

Conclusion:

Focusing on the brain, the consumption of alcohol has numerous side effects, impacting various aspects of cognitive function and overall health. While moderate alcohol consumption has been linked to some potential benefits, including reduced risk of heart disease and stroke, research increasingly highlights its detrimental effects on the brain. In terms of the risk of Alzheimer's disease, alcohol poses a significant and modifiable risk factor.

Studies have shown a clear correlation between excessive alcohol consumption and an increased risk of developing Alzheimer's disease, as well as a faster rate of cognitive decline in those already diagnosed. This is due to alcohol's ability to disrupt brain cells and their function, impacting regions vital for memory, learning, and overall cognition, such as the hippocampus and cerebral cortex.

Koch, M., Costanzo, S., Fitzpatrick, A. L., Lopez, O. L., DeKosky, S., Kuller, L. H., Price, J., Mackey, R. H., Jensen, M. K., & Muka-mal, K. J. (2020). Alcohol consumption, brain amyloid-β deposition, and brain structural integrity among older adults free of dementia. *J Alzheimers Dis*, *74*(2), 509–519. PMC7385407.

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National Institute on Aging. “What Happens to the Brain in Alzheimer’s Disease?” *National Institute on Aging*, May 15, 2024. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease.

University of Michigan News. “Understanding Alzheimer’s: Study Gives Insights into How Disease Kills Brain Cells.” *University of Michigan News*, October 16, 2012. https://news.umich.edu/understanding-alzheimer-s-study-gives-insights-into-how-disease-kills-brain-cells/.