Alcohol Use Disorder and Neuroimmunity

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Immunology

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Abstract

Alcohol Use Disorder is a disease that results from uncontrolled ethanol ingestion and compulsive alcohol intake. It is a disease that is of epigenetic importance involving system wide contributions inclusive of the immune system, specifically neuroimmune responses. Most patients present with episodic chronic relapse. While the physiological impacts are most commonly associated with the hepatic system post ethanol exposure, it's now known that the disorder is initiated in neurological regions before ingestion of ethanol occurs. Attention is refocused towards neuropathology of Alcohol Use Disorder, most recently, the neuroimmune system and its genetic regulation therein. Current experimental intervention includes a neuroimmune modulator drug, Ibudilast, which inhibits heavy drinking disorders and sequential behaviors, but no known prevention is available to cease neuromolecular onset entirely. This paper highlights possible immune targets to perpetuate potential approaches regarding applications for future medicinal treatment modalities (US Department of HHS, n.d.).

Alcohol Use Disorder is an epigenetic disease involving the molecular function of immune response contributors system wide. The disease involves immune inflammatory responses and alters pathways and cascades of adaptive and innate neuroimmunity, ultimately seen in post-mortem alcoholic brain tissue. As the signaling cascade alters due to ethanol exposure for individuals genetically susceptible to Alcohol Use Disorder, the result is a neuroimmune response of pleiotropic proportions. Pathologically, the effects are seen in the individual as a whole, evidenced both in behaviors and physical health deterioration. The known cause of this disease is initial ethanol ingestion which potentially progresses in symptomatology over a span of decades to a lifetime if intervention does not occur and alcohol ingestion is not ceased entirely. Prevention of underlying causation from neurogenetic onset is the most logical approach. Neuroimmune factors such as NF-κB along with its cofactors are the focus of interest in the following.

Nuclear factor kappa beta (NF-κB) is a light chain enhancer of activated B cells. It is a multi-factoral immune regulator and signaling contributor with a crucial role in pleiotropic transcription factors of the innate and adaptive immune response. Its omnipresence in cells dictates cyto-behaviors and is controlled by two structural termini. Based on the canonical and noncanonical pathways of NF-κB, alongside its kinase and protein associates, it will dictate responses such as inflammation, growth and apoptosis leading to this emphasis of importance. NF-κB signals indicate the onset and progression of diseases and conditions and can be targeted when considering more specific diseases related to neuroimmune function (O'Neil et al, n.d.).

Focusing on the neuroimmune system, and NF-κB gene induction therein, of people with Alcohol Use Disorder, the critical role of these signaling pathways is proven to be vital. Ethanol exposure induces the regulatory expression of innate immune response causing cytokine

elevation, further stimulating this response in glutamate excitability, resulting in alcoholic neurodegeneration due to the contribution of compulsive behaviors and lack of ability to regulate alcohol intake. The longevity of the effects of neurobiological effects of neuroimmune signaling not only increases binge and heavy drinking behaviors, but reciprocal results occur where the flexibility to change these behaviors is repressed due to neuroimmune signals of the alcoholic brain. NF-κB controls the functions and consequences sequential to the oxidative stress response from immediate to prolonged ethanol ingestion (Banks et al, n.d.).

The neuroimmune system signaling cascade of the Toll-like receptor (TLR) family is induced via pairing with high mobility group box 1 protein (HMGB1) causing inflammation and generating reactive oxidation species (ROS). These events cause downstream activation of the transcription factor NF-κB inducing ROS and transferring NF-κB to the nucleus, causing proinflammatory gene expression to TLR and interleukin targeted genes. Upregulation and expression of TLRs and HMGB1 is found in post-mortem brain tissue of individuals with Alcohol Use Disorder. These findings are paralleled with the upregulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression. Pharmacologic and genetic blockades of neuroimmune signaling can possibly prevent the ethanol induced neuroimmune gene factors and neurodegeneration. However, as of May 2021, there exists only four pharmacological interventions or medicinal therapeutic for Alcohol Use Disorder and the heavy drinking behaviors associated therein.

Ibudilast is a translational pharmacologic which has been warranted for more review as it has been seen in randomized trials to reduce heavy drinking and cue-elicited neural activation induced by alcohol for individuals on the more severe end of the Alcohol Use Disorder spectrum. Because this is a neuroimmune modulator drug, it emphasizes the critical role the neuroimmune

system plays in the development and progressive pathology of Alcohol Use Disorder. Its mode of inhibition involves neuroinflammatory processes via regulatory inflammation responses of microglia. Post mortem brain tissue of individuals with Alcohol Use Disorder samples of the microglial tissues have been evidentiary of Alcohol Use Disorder because of insidious inflammation presence when compared to controls (Grodin et al. 2021).

In conclusion, Alcohol Use Disorder treatments have a long history of multifaceted approaches which have proven lesser than adequate in efficacy. Innovative and creative ways of preventing onset are necessitated. The neuroimmune system and the aforementioned subsets within show potential for research on a biomolecular therapeutic level. Attention is warranted to alleviate suffering of the individual with Alcohol Use Disorder, their associated family and society as a whole.

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