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Opinion

New Insights into Alcohol Addiction: Functional Impairment of Visual Circuits and The Underlying Cellular and Molecular Mechanisms

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Perspective on Eyes

The harmful use of alcohol has long been a serious global public health issue. Alcohol is causally linked to more than 60 different disease conditions [17,18]. Approximately 4% of the global disease burden is linked to alcohol, resulting in a level of death and disability comparable to that caused by tobacco and hypertension [18]. The pathological changes caused by alcohol addiction are present not only in the reward-related neural circuits of the brain [7,20], but also in the visual circuits [9]. *Xie, et al.* recently conducted a retrospective study using visual-related potential recording as the primary method, supplemented by global multivariate statistical data analysis. They observed significant differences in full-field flash electroretinograms (ffERG) and pattern-reversal visual evoked potentials (PR-VEP) between individuals with alcohol addiction and healthy controls [22]. These visual electrophysiological changes reflect functional impairments in the visual neural conduction pathways that occur early in alcohol-related vision loss. For example, in patients with alcohol addiction, the P100 wave latency is significantly prolonged in the two spatial frequency tests of PR-VEP, which assess optic nerve function.

Alcohol-induced dysfunction in the visual pathways can lead to retinal and optic nerve damage, ultimately resulting in vision loss [1,2]. While permanent vision damage from excessive drinking can be prevented, alcohol abusers often do not recognize functional impairment in their eyes until clinical symptoms or structural lesions develop. Current research on the effects of chronic alcohol use on visual pathways is limited, but it holds significant value [11,12]. Some studies suggest that chronic alcohol consumption initially causes functional disturbances, reflected in reduced photoreceptor sensitivity and weakened optic nerve conduction, without causing anatomical changes to the retina and optic nerve [9,16]. Furthermore, young individuals with a habit of weekly drinking already show signs of visual dysfunction compared to their peers in the same age group [1].

GABAergic Mechanisms

Alcohol consumption severely affects the brain. Chronic alcohol exposure can cause changes in gamma-aminobutyric acid (GABA) function within the brain, through two primary mechanisms: first, by acting on presynaptic neurons to increase the release of GABA [10], and second, by targeting postsynaptic neurons to enhance the activity of GABA receptors [13]. Considering GABA is the primary inhibitory neurotransmitter in the nervous system, it is reasonable to speculate that the molecular mechanisms affected by alcohol in the visual pathway may operate in a similar manner. GABA has three types of receptors: $GABA_A$, $GABA_B$, and $GABA_C$. Among these, $GABA_A$ and $GABA_C$ receptors play a predominant role in the retina [5,15]. Studies have shown that $GABA_A$ and $GABA_C$ receptors are abundantly expressed on bipolar cells located in the inner retina [6,8], where they transfer information from bipolar cells to retinal ganglion cells.

Research has confirmed the existence of a reciprocal regulatory mechanism between rod bipolar cells and amacrine cells. Glutamate released from rod bipolar cells activates GABAergic amacrine cells, which then release GABA to inhibit the bipolar cells that activate them [3]. Synaptic release of GABA mainly activates $GABA_C$ but not $GABA_A$ receptors in rod bipolar cells, because in the rat and rabbit retina, the proportion of $GABA_C$ receptor-mediated currents accounts for 63%-70% of total GABAergic currents [5,15]. Rod bipolar cells in $GABA_C$ receptor subunit ρ1 gene knockout mice do not express $GABA_C$ receptor-mediated currents. As a result, the b-wave amplitude of the dark-adapted ERG is higher in comparison to normal control animals, indicating a negative correlation between $GABA_C$ receptor function and bipolar cell activity [14].

Are the $GABA_C$ receptors in the retina of alcohol addicts persistently activated? Are the effects of $GABA_C$ receptor activation related to the alcohol-induced vision decline? Currently, there is no definitive answer; however, experimental evidence strongly supports this possibility. The scotopic ffERG responses in alcohol addicts show significantly reduced b-wave amplitudes and oscillatory potentials (OPs) amplitudes [22]. The b-wave amplitude primarily reflects the function of bipolar cells [19], while OPs mainly represent the functionality of amacrine cells [21]. It is currently known that amacrine cells can release GABA and inhibit rod bipolar cells by activating $GABA_C$ receptors [4]. The impairment of GABA-releasing amacrine cells may affect bipolar cell function. Thus, GABAergic synaptic transmission by amacrine cells and $GABA_C$ receptors on rod bipolar cells may play a crucial role in alcohol-induced bipolar cell depression.

Conclusions

Determining whether alcohol has functional effects on the retina and visual system is crucial for clinical diagnosis and treatment. The progressive vision decline in alcoholics exhibits a clinical progression from reversible functional decline in the visual pathway to irreversible deterioration or loss of vision. Irreversible alcoholic vision loss can severely impact patients' quality of life. Therefore, early prevention before permanent damage occurs is particularly important. This review aims to promote the visual health of individuals with alcohol addiction by discussing important examination methods and relevant findings. We particularly emphasize the role of GABAergic mechanisms involving bipolar and amacrine cells, as we believe these may be among the most significant factors at the cellular and molecular levels.

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