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Association between alcohol use and retinal dysfunctions in patients with alcohol use disorder: A window on GABA, glutamate, and dopamine modulations

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Abstract

Background

Alcohol is the most widely consumed addictive substance around the world and have deleterious effect on the central nervous system. Alcohol consumption affect the balance of certain neurotransmitters like GABA, glutamate and dopamine. The retina provides an easy means of investigating dysfunctions of synaptic transmission in the brain. The purpose of this study is to assess the impact of alcohol consumption on retinal function using pattern electroretinogram (PERG) and flash electroretinogram (fERG).

Methods

We recorded PERG and fERG under scotopic and photopic condition in 20 patients with alcohol use disorder and 20 controls. Implicit time and amplitude of numerous parameters were evaluated: a- and b-waves for fERG, OP3 and OP4 for dark-adapted 3.0 oscillatory potentials fERG, P50 and N95 for PERG.

Results

Patients with alcohol use disorder showed a significant increase in N95 implicit time without a significant change in the amplitudes of oscillatory potentials.

Conclusion

The results of our study reflect the impact of alcohol use on ganglion cell function and could highlight alterations in glutamatergic neurotransmission inside the retina. We believe that ERG could be used as an early marker of alcohol consumption.

Introduction

Alcohol is a major public health issue and the most widely consumed addictive substance around the world. It has been estimated that approximately 43% of the global population are current drinkers, defined as individuals aged 15 years and older who have consumed alcoholic beverages in the previous 12 months (Peacock et al., 2018). Among young people, the percentages of current drinkers worldwide stand at 26.5% for 15-19 year-olds and 43% for 20-24 year-olds (“Global status report on alcohol and health

2018," n.d.). The repeated alcohol consumption of current drinkers can have consequences for health, with an increased risk of developing various diseases of the cardiovascular, digestive, muscular or nervous systems (Rocco et al., 2014; Boffetta and Hashibe, 2006).

Alcohol consumption can have a deleterious effect on the central nervous system (CNS). Ethanol can easily cross the blood-brain barrier so blood and brain alcohol concentrations equalize rapidly after drinking (Diamond and Messing, 1994). The neurons in the CNS are affected by the toxic, metabolic and degenerative effects of alcohol (de la Monte and Kril, 2014). The neurons transmit signals, mediated by neurotransmitters, between different regions of the CNS. Neurotransmitters are small molecules generally classified as either excitatory or inhibitory. Balance is critical for normal brain function and toxic substances can affect this balance. Alcohol is a toxic substance that affects both excitatory and inhibitory neurotransmitters. The most important excitatory neurotransmitter is glutamate, which increases the neuron signal activity and plays a major role in controlling brain function. Glutamate exerts an effect on cells through different types of receptors, all of which are inhibited by alcohol, but it has the strongest impact on the ionotropic N-methyl-d-aspartate (NMDA) receptor and more precisely the frequency and the opening time of its Ca2+ channel (Michalak and Bia, n.d.). NMDA is an important contributor to neuroplasticity and the synaptic changes responsible for learning and memory formation. The flow of Calcium ions from the Ca2+ channel of this receptor is inhibited by alcohol at low concentrations, around 0.03 percent (Gonzales and Jaworski, 1997), resulting in sedation and memory loss (Michalak and Bia, n.d.). Alcohol consumption results in decreased NMDA function, which reduces neuron excitotoxicity. NMDA receptor inhibition contributes to reinforcing the behaviour of alcohol consumption and encourages alcoholism (Gonzales and Jaworski, 1997). Furthermore, recent studies suggest that modification of glutamate concentration in the brain, especially as a result of NMDA receptor inhibition, may play a role in the development of psychiatric disease (Howes et al., 2015). Gamma-aminobutyric-acid (GABA) is the main inhibitory neurotransmitter, with two types of receptor: GABA-A, which inhibits chloride ion-mediated neuronal activity, and GABA-B. Alcohol consumption increases GABA-A receptor function,

enhancing inhibitory neurotransmission (Michalak and Bia, n.d.) and causing motor incoordination, sedation and anaesthesia and lowering seizure threshold (Mihic and Harris, 1997). Chronic alcohol consumption affects the GABA-A receptors, reducing the number on each neuron. This induces tolerance to alcoholic beverages and contributes to the process of dependence (Mihic and Harris, 1997). The modification also affects tolerance to all substances that use the GABA-A receptor, such as benzodiazepine (Mihic and Harris, 1997). Lastly, some studies suggest that GABA-A reduction may play a role in developing alcoholism (Mihic and Harris, 1997). The neurotransmitter dopamine plays a major role in the motivational control and reinforcement process by modulating regions that depend on the reward circuit, such as the ventral tegmental area (VTA) and the nucleus accumbens (NAc). Alcohol consumption influences dopamine release via 5-HT receptors in the VTA and NAc that mediate the reward effect of alcohol (Michalak and Bia, n.d.). Dopaminergic neurons contained in the NAc are extremely sensitive to alcohol; the result is a dopamine spike each time alcohol is consumed. Repeated alcohol consumption therefore causes a dopamine release adaptation and contributes to reinforcing alcohol behaviour, cravings and compulsive alcohol consumption (Di Chiara, 1997). Current drinking also has an impact on all these neurotransmitters.

A variety of biomarkers are used to assess the degree of impact of alcohol intake in current drinkers. For example, gamma-glutamyl transferase indirectly shows the impact of alcohol on the liver, and liver transaminases, alanine transaminase and aspartate transaminase are used to indicate liver damage (Lees et al., 2020). These biomarkers are all useful in clinical practice, but most of the time they show the impact of alcohol intake after many years of chronic consumption, and they only reflect its impact on the liver. As it is important to measure the impact of alcohol consumption at an even earlier stage for prevention and screening, we focused on neurotransmitters modulated by alcohol. The brain is a complex system, and it is difficult to measure individual neurotransmitters directly; an indirect approach is also needed, therefore. The retina provides an indirect means of investigating brain function in psychiatric and addictive disorders (Hoon et al., 2014; London et al., 2013). An anatomical and developmental extension of the central nervous system (Hoon et al., 2014), the retina is a neural network

consisting of several layers of neurons with similar properties to brain neurons (London et al., 2013). Retinal neurons, organized in several distinct cell layers, are subject to influence by glutamate, GABA and dopamine neurotransmitters (Pourcho, 1996). In the retina, photoreceptors (rods and cones) convert light into an electrical signal, which modulates the release of neurotransmitters. Photoreceptors then transmit the signal to interneuron cells, the horizontal cells that modulate synaptic transmission along with bipolar cells. Amacrine cells, which are also interneuron cells, then modulate the excitation of ganglion cells, whose axons form the optic nerve (Demb and Singer, 2015; Schwitzer et al., 2017b). In response to light stimulation, the photosensitive ganglion cells will express an action potential which will be transferred to the visual cortex. Photoreceptors and bipolar cells release glutamate while horizontal and amacrine cells mainly use GABA. Yang et al., in 2004 review the organization of glutamate and GABA receptors in the retina. They show that the main receptors affected by alcohol consumption, the NMDA-type ionotropic glutamate receptors and the GABA-A and GABA-B receptors for GABA, are mainly expressed by amacrine cells and ganglion cells (Yang, 2004).

Retinal neuron function can be assessed using an electroretinogram (ERG) (Lavoie et al., 2014), a test that records light-evoked electric potential from the retina in response to different types of stimulate (Schwitzer et al., 2015). The recording of retinal neuron signaling reflects changes in the level of neurotransmitters through the retina (Hoon et al., 2014). Using the N95 amplitude of a pattern electroretinogram (PERG) we can assess the response of central retinal ganglion cells, which is influenced by glutamate transmission (Holder et al., 2010). Amacrine cell function is influenced by dopaminergic neurotransmission and can be measured via oscillatory potential, using a flash electroretinogram (fERG) (Witkovsky, 2004). We also contend that the retina can be used for indirect investigation of the effect of alcohol consumption on cerebral neurotransmission, which is also suggested by Arden and Wolf's study. They shew indeed low levels of alcohol would change the standing potential of the eye so this work may support at least that ethanol can reach the outer retina (Arden and Wolf, 2000). To measure the effect of alcohol on cerebral neurotransmission, we used ERG under photopic and scotopic conditions.

Our study aimed to measure retinal function using PERG and fERG in current alcohol drinkers with alcohol use disorder versus control. We hypothesised that repeated alcohol consumption among patients with AUD modifies retinal function by modifying glutamate, GABA and dopamine neurotransmission.