A brief review of the effects of alcohol on the brain

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Alcohol is a psychoactive drug that is consumed orally as a beverage. It's made by mixing yeast and sugar, typically a fruit, vegetable, or grain, together. This process produces ethanol, which is the primary psychoactive ingredient that causes the symptoms of alcohol use. It's considered a sedative-hypnotic drug as it acts as a depressant to the CNS (Central Nervous System) in greater amounts. It can also act as a stimulant when taken in smaller amounts, in which case the more typically associated effects of ethanol emerge such as "loose lips" and giddiness (Alcohol Advisory Council of New Zealand, 2012). It is a commonly used and widely accepted drug, though it is thought of negatively by certain groups and people (Liu et al., 2013). As such, it is relatively easy to purchase alcohol in several places, but it's most common at liquor or grocery stores. According to a 2018-19 national survey done by SAMHSA, 70.2% of Americans admitted to the use of alcohol within the year 2019, and 26% admitted to binge alcohol use within a month of the survey (SAMHSA, 2019). The numbers were higher in 2018, which may indicate a higher user percentage that's unreported. But what can be concluded from the reported numbers is that many Americans use this drug in particular, and it's purported that it's one of America's most widely used drugs. Both medical and societal consequences come with indulging in the beverage, yet there can also be some more rewarding aspects. And it may be because of those rewarding aspects that some develop chronic illnesses like AUD (Alcohol Use Disorder). The theory behind those rewarding aspects revolves around how ethanol, the psychoactive substance, acts on the human brain.

The chemical ethanol mimics many neurotransmitters in the brain, binding to their receptor sites, as well as acting as positive modulars that can bind to allosteric sites. The main neurotransmitters affected by ethanol are GABA, glutamate, serotonin, and dopamine. As previously stated, ethanol acts as both a stimulant and a depressant (Hendler et al., 2013) when

ingested, so its effects can vary greatly for each person and occasion. Likewise, according to Dr. Hendler and his associates, the risk of addiction to ethanol can also vary from person to person.

Dopamine & Serotonin

Dr. Hendler et al., states in their review that there's a consensus that ethanol's effect on the neurotransmitter dopamine is the underlying cause of ethanol's stimulant effects. And even though the depressant effects most likely include anxiolytic effects (an anxiety reducer), the stimulant effects are thought to be much more rewarding and pleasurable. Therefore, if one were to have a more diminutive depressant effect or a heightened stimulant effect, one might be more likely to keep drinking alcohol. The two reactions mentioned are currently the two central theories on how physical and cognitive responses to ethanol consumption could predict the risk of AUD (Alcohol Use Disorder) in an individual (Hendler et al., 2013). Both dopamine and serotonin are boosted in the brain due to ethanols' influence on the nucleus accumbens. Dopamine is the supposed cause of the stimulant effects of ethanol, and serotonin is a known contributor to feelings of happiness. However, too much ethanol can have the opposite effect, reducing both dopamine and serotonin levels, which can seriously affect many regions of the brain, especially the hippocampus. This could be caused by one; nearly all discovered presynaptic and postsynaptic serotonin receptors in the brain exist in the hippocampus, with serotonin playing a major role in the hippocampus's functioning (Berumen et al., 2012), and two; dopamine plays a major role in the hippocampus's abilities such as memory, learning, and attention (Nunes et al., 2019). And according to Nunes et al., memory, learning, and attention are all facilitated by a mix of cholinergic, GABAergic, and glutamatergic fibers.

GABA

GABA receptors are located within the hippocampus too and can affect the hippocampus by reducing the number of firing neurons altogether. The specific GABA receptor that ethanol primarily interacts with is GABAA, which can be found in 40% of all the synapses in the brain (Lithari et al., 2012). Ethanol similarly acts on GABA receptors by inhibiting neuronal functioning, and it's thought to be a major player in the effects ethanol has on the brain (Kulonen E., 1983). Abuse of the drug, according to Dr. Kulonen, weakens the GABA system over time, causing fewer and fewer GABA receptors to be present in the synapses. And concordant to Seilicovich et al. (1985), ethanol acts as both a binding agent and a positive modular. A positive modular is simply a chemical that can bind to an allosteric site, which once bound to, tells the receptor to stay open longer if it binds with a neurotransmitter or chemical. In this case, GABAA receptors would stay open longer if an ethanol molecule attached to an allosteric site and a receptor, allowing the neuron to take in more chloride and making it even harder for it to fire. In Seilicovich et al's study, a change in GABAA receptor activity was observed in the hypothalamus and cerebellum, where enhanced GAD activity was seen in the cerebellum and reduced GAD activity was seen in the hypothalamus. GAD or glutamic acid decarboxylase is the process of turning glutamate into GABA, which inhibits neural activity in the brain, or in this case, in the cerebellum. When GAD activity is heightened, the amount of GABA is increased, and when GAD activity is reduced, the amount of GABA also lessens (Seilicovich et al., 1985). In another study by Abrahao et al. (2017), the researchers looked into ethanol's effect on GABA receptor-mediated tonic currents. It was shown that ethanol consistently affects GABAA tonic currents, where it increases the postsynaptic GABA responses in the cerebellum, hippocampus, and thalamus. This same study also saw a pattern in how ethanol affects the brain, with ethanol often acting on one of the GABAA subunits (α, , γ, ε, θ, π, ρ). Subunit δ was seen to be

involved in many of the actions of ethanol involving the GABAA tonic currents. In a similar study by Xie et al., in 2019, the GABAA subunit α also proved to be important in ethanol's effect on the brain, potentially playing a role in alcohol-induced cognitive impairment. Another way ethanol affects GABA receptors is by inhibiting the process of nitric oxide synthase (Abrahao et al., 2017). The nitric oxide synthase process happens within the hypothalamus and pituitary gland and is responsible for stimulating the secretion of vasopressin. The peptide hormone vasopressin is responsible for salt balance and retention of water, so the inhibition of its production can cause a loose bladder.

Glutamate

Lastly, alcohol acts on glutamate receptors, specifically the NMDA (N-methyl-D-aspartate) type. Glutamate is the main neurotransmitter in the body that controls the excitatory effect on neurons like GABA controls the inhibitory effect. NMDA is a g-protein receptor that has a vital role in neurological functions such as the respiratory system, voluntary movement, learning and memory, and neuroplasticity. Ethanol binds to NMDA receptors, shifting the hippocampal GABA/glutamate balance, and inhibiting glutamate from acting on neurons (Nunes et al., 2019). Abuse of alcohol can lead to an increase in NMDA receptors in the brain, which causes withdrawal-induced glutamate excitotoxicity, and necrosis-mediated (cell death) neurodegeneration and seizures occur as detoxification take place (Nunes et al., 2019; Crews et al., 2014). Nunes et al., have also stated that glutamate excitotoxicity's role in necrosis is associated with tissue loss specifically in the prefrontal cortex. Like NMDA receptors, Nunes et al., found that ethanol also inhibits AMPA and kainic ionotropic glutamate receptors, which are both responsible for mediating glutamate neurotransmission, and the release of nitric oxide in

particular for AMPA. This would mean that messaging between cells and the production of vasopressin is inhibited by ethanol, as it is with GABAA receptors.

Areas of The Brain

All of the neurotransmitters and receptor sites discussed above affect various areas of the brain. In some cases, all are acting on the same area, such as the hippocampus, which is affected by serotonin, dopamine, GABA, and glutamate in different ways with similar effects. The main sites of the brain affected are the prefrontal cortex, the cerebellum, and the nucleus accumbens. The prefrontal cortex is involved in social behavior, planning, and personality, and when inhibited can cause abnormalities in behavior (such as no philter when speaking), poor decision making, and apathy. Glutamate excitotoxicity's role in the degeneration of the prefrontal cortex (Nunes et al., 2019) was already mentioned, but a study done in 2014 details how ethanol's influence on the brain butchers the prefrontal cortex. Erdozain and others used H&E staining to study ethanol damage in the prefrontal cortex in 2014 and uncovered the nuclei of the cortical and subcortical neurons' cytoskeleton had been significantly reduced, and the subcortical neurons, in particular, were impeded. Subcortical neurons are thought to be vital to the circuit wiring connecting the motor, oculomotor, dorsolateral prefrontal, orbital frontal, and anterior cingulate circuits (Starosta et al., 2016). Another area responsible for possibly the more famous effects of alcohol consumption is the cerebellum. The cerebellum is involved in voluntary movements such as coordination, speech, and walking. Damage to the cerebellum processes causes difficulty with movement, loss of coordination, adiadochokinesia, tremors, etc… Erdozain et al., again detail the specific area of the cerebellum that ethanol acts on, the Na+/K+/ATPase pump. By partially inhibiting the Na+/K+/ATPase pump, it is thought to result in a rapid onset of dystonia-parkinsonism and cognitive impairment, and it may also contribute

to behavioral issues shown by patients with AUD (Erdozain et al., 2014). Finally, alcohol acts on the nucleus accumbens by stimulating dopamine and serotonin secretion, producing a pleasurable effect (Hendler et al., 2013).

The Good

While there aren't many good effects of alcohol other than the immediate effects seen during consumption, the few that are known are remarkably good. Heavy alcohol consumption causes dreadful health problems, but light to moderate consumption has been shown to be effective at lowering the risk of cardiovascular disease, cognitive decline, dementia, and diabetes (Liu et al., 2013).

The Bad (and The Ugly)

Potentially a far more expansive list is the bad effects of alcohol consumption. GABA receptor-mediated tonic currents, a crucial part of maintaining the hippocampal circuitry balance, are inhibited by ethanol intake, specifically in adolescents (Crews et al., 2014). This interferes with neurotransmissions and memory creation, which in chronic abuse causes permanent damage and is seriously debilitating. Effects of ethanol like glutamate excitotoxicity are linked to neurodegeneration, especially in the prefrontal cortex as well as severe hippocampal neurogenesis in adolescents (Crews et al., 2014). This is made all the more concerning when SAMHSA reported that approximately 26.7% of Americans aged 12-17 have drunk alcohol at least once in 2019.

To reiterate, Alcohol is a psychoactive substance that affects the pre-frontal cortex, cerebellum, and nucleus accumbens. Specifically, it affects GABA and glutamate receptors, and the neurotransmitters serotonin and dopamine. It is a widely accepted drug in America, and can easily be purchased by anyone above the age of 21. It's most commonly associated with social

gatherings and AUD and has both positive and negative health effects. If used in moderation, Alcohol can be a beneficial drug with minimal negative consequences. However, due to limited regulations, it is easily abused in America. If possible, it would be good to find a way to achieve the positive effects of alcohol while reducing the negative aspects like the addictive properties. There are already many studies on what exactly makes alcohol addictive and how to reduce withdrawal symptoms, so it may not be so far-fetched.

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