Alcoholic disruption of function in neurophysiological pathways and retrogressive development in size and capability of cognitive neurobiological structures throughcontinual exposure

Juan Bautista

Introduction

Alcohol (EtOH) as a chemical disruptor that impedes on neural development, nutritional and hormone regulations, but has low salience amongst contemporary cultures as being such. In many societies alcoholic consumption is the universal pastime. It is a particularly popular form of socialization amongst young adults (18-22 years old). Of full-time college students 54.9 percent admit to having drunk alcohol in the past month when surveyed in the 2018 National Survey on Drug Use and Health. Out of those who drank in the previous group mentioned 36.9 percent also admitted to binge drinking (having 5 or more alcoholic drinks on a single occasion) []. The high prevalence among young adults is particularly dangerous because their brains are still developing and alcohol may accelerate some deleterious effects and disrupt synaptic rearrangement of the later stages of neural maturation. The factors behind the alcoholic trend within campus communities are numerous from a bacchanalian culture to emotional isolation. The general attraction to alcohol is that it releases inhibitions and psychological pressures.

But, this article will take a glance at some of the immediate and long term effects of both continual and binge alcoholic consumption on the nervous system. From a molecular perspective, alcohol induced mechanisms create damaging toxic reagents that in turn cause cellular hypoxia and aggressive autoimmune responses in neural sensitive regions. As alcohol continues to be abused the effects of these faulty irregular pathways accumulate and structural brain damage, neuropathies, and even detriment to genetic viability become evident.

Ethanol and Its Metabolism

Alcohol is classified as a depressant drug because it reduces brain activity by blocking NMDA, GABA, Serotonin, and Acetylcholine receptors from their corresponding neurotransmitters.

The binding of EtOH on GABA receptors in particular dims neural activity by oversaturating postsynaptic neurons with chloride anions. This elongated period of ion influx reduces the rate of action potentials delaying neural stimulation. The apparent changes in cognition following an episode of excessive alcoholic intake include: difficulty speaking (slurred), poor memory, slowed movements, loss of balance (vertigo), incapacitated motor coordination, stupor (unresponsiveness), and in some cases loss of consciousness.

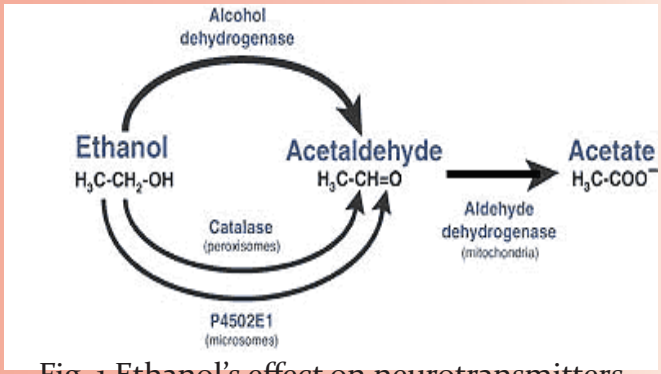

Fig. 1 Ethanol's effect on neurotransmitters

Ethanol (CH3CH2OH) is primarily metabolized in the liver by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Alcohol dehydrogenase breaks down alcohol into acetaldehyde (CH3CHO), NADH, and H+. Then aldehyde dehydrogenase reacts with water to further break apart acetaldehyde into acetate (CH3COO-) and more NADH and H+ by products. The accumulation of NADH and H+ disrupt the natural pathway of gluconeogenesis. If gluconeogenesis does not proceed normally, an insufficient amount of bicarbonate would form and oxygen delivery would be set back. In addition to the hypoxia this case would also have acetate build up which would decrease the blood pH which may develop into metabolic acidosis. Metabolic acidosis severely impairs breathing and requires medical attention. But, continuing on with our metabolism of alcohol, acetate can then be converted to acetyl CoA through contribution of ATP and coenzyme A in the mitochondria. Progression stops here though, before completing the citric acid cycle, because the excess saturation of NADH from previous steps blocks regulatory enzymes (isocitrate dehydrogenase and α-ketoglutarate dehydrogenase). Acetyl CoA and ATP are

produced, and CO2 is not released. The cells affected experience energy deficits and toxic retention which may lead to cellular death. Over time these recurrent irregularities can lead to fatty liver, alcoholic hepatitis and lastly cirrhosis. Each stage further weakens the liver's ability to filter toxins as the organ dies.

Oxidative Stress and Cellular Response

If alcoholic intake exceeds the oxidation rate of the stomach and liver enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) respectively, then other enzymes across the body will metabolize the alcohol and cause toxic products to linger in regions where they can do the most damage. The particular pace of oxidation in the average human body is roughly 100 milligrams of liquor for each hour per kilogram of body weight. To place this in context, about 8 grams of liquor will be discharged in an hour in the event that you weigh 180 pounds (81.6 kilograms), and 5 grams of liquor will be broken down in an hour if you weigh 110 pounds (50 kilograms). The oxidation rate is modified by sex, ethnicity/genetics, and health of the liver []. Once consumed alcohol is rapidly absorbed into the bloodstream. 20 percent enters from the stomach and the other 80 percent seeps in through the linnings at the beginning of the small intestine []. Because of this chemical's high solubility in fat and water, it does not need to be broken down to readily circulate and permeate across the blood-brain barrier. The brain is 75% water by mass and the diffused alcohol has an almost immediate effect in it[U.S. Department of Health and Human Services (1990)].

In the brain, the enzymes catalase and CYP2E1(Cytochrome P450) metabolize alcohol; this pathway is therefore called the cytochrome P450-dependent pathway. This pathway creates aldehydes and acetates similar to the primary alcohol metabolism

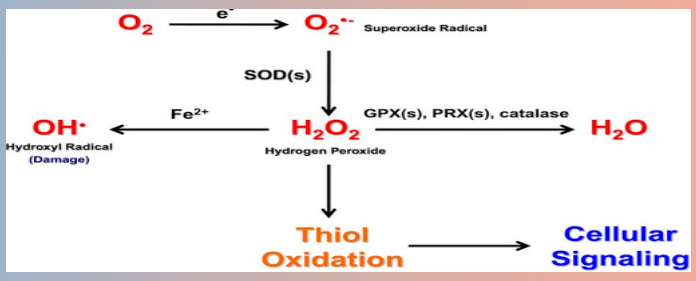

Fig. 2 Reactive Oxygen Species

pathway in the liver but differs in that it converts NADPH into NADP+ by implementing oxygen which forms oxidative free radicals in the brain. Free radical-mediated interactions occur within proteins, lipids, and dna. Oxidative degradation of omega 3 and omega 6 some polyunsaturated fatty acids undergo lipid peroxidation induced by ethanol intake (Burke and Ludden 1989).

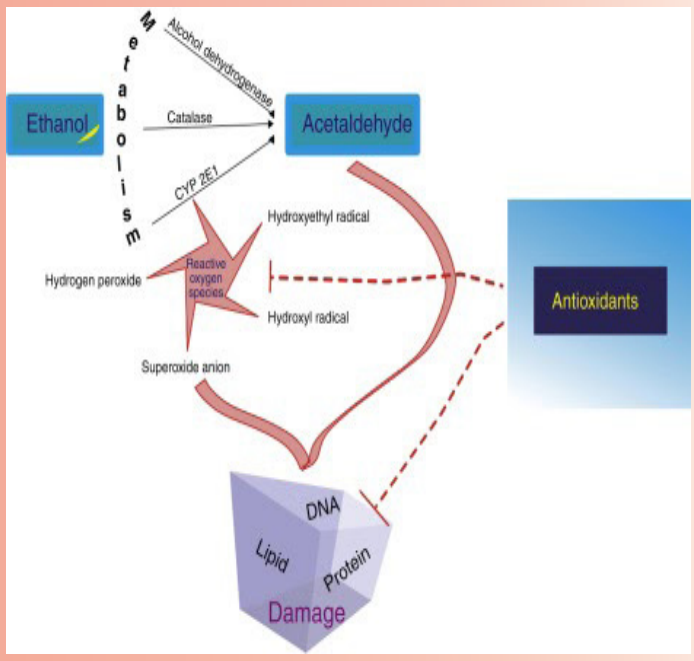

Fig. 3 Antioxidant Treatment and Alcoholism. In Molecular Aspects of Alcohol and Nutrition

Acute and chronic intoxication created Acetaldehyde is very unstable and forms covalent adducts with the surrounding constituents. This should be done within the liver as it decreases enzymatic activity, inhibits microtubule assembly, and increases catabolism of proteins (Lieber; Sorrel and Tuma). Acetaldehyde condensates can incur detection by the immune responsive proteases and thereby damage the conjugated tissue (Israel et al., Lin et al). Aldehyde also activates production of acetaminophen, benzene, CCl 4, halogenated hydrocarbon at toxic levels and pro-carcinogens (nitrosamines, and azo compounds) [].

In an experiment sponsored by the University of Texas Southwerstern Medical Center, Immunocytochemical localization of animal brains administered EtOH discovered immunoglobulin antibodies, B-cells (InterLeukin-4), and T-cells (CD4-L) clustered in very high amounts (Kozlowski and Sterzl). The Researchers predicted that cytokine IL-4, recruited macromolecular immunoglobulin proteins into the brain that

rallied with CD4-L and caused neuronal endocytosis in brain's of the animals fed EtOH. Alcohol promotes inflammatory response in neuronal and glial cells by activating signalling pathways (MAPKs, IKK), increasing production of inflammatory mediators, cytokines, and transcription factors involved in apoptosis and injury response (AP-1, NF-kB) [Alcohol and Neuroinflammation: Involvement of Astroglial Cells and IL-1RI/TLR4 Receptors Vol. 25 Num. 3/ 2006]

Malnutrition

Chronic alcohol use can cause malabsorption of important nutrients. Health expert for Bright Hub magazine, Kimberly Roberts, offers insight into the unhealthy effect of alcohol in one's diet "Individuals that abuse alcohol also tend to fill their caloric needs with drinks, as opposed to food. When they do eat meals, they tend to be unhealthy. This is because alcohol is an addictive carbohydrate. Consuming large amounts of this type of carbohydrate increases cravings for more unhealthy carbohydrates, as well as salts and sugars."

Chronic alcoholic consumption can lead to a cycle of eating low nutrient foods. But long term alcohol malnutrition has a wide spread strain on many systemic organ functions. It inhibits secretions of digestive enzymes, neglects natural metabolic pathways (glycogenesis) and damages the cells lining the intestines and stomach impairing their ability to absorb nutrients into the bloodstream. Vitamin B 6 (pyridoxine), 2 (riboflavin), 1 (thiamin), and folate are some of the nutrients crucial to brain health (nutrient transport, cell growth, homeostasis, which are in lowest proportion within alcoholics (Leevy et al).

Alcohol is associated with cerebral deficiency of folate, a B vitamin soluble in water. Folate is involved in metabolic processes such as that produce neurotransmitters (glutamate) and aid in DNA synthesis. Deficiency of Folate and other B-vitamins contributes to accelerated neural degradation and initiation of disease (Molero-Luis M et al. 2015). For example Fetal Alcohol Syndrome (FAS) is prevalent disorder in which a pregnant woman (even at early stages in which she may not be aware of the pregnancy) consumes alcohol that suppresses nutritional flow (folate in particular) resulting in neuronal malformation (Shibley IA Jr, Pennington 1997).

Thiamin deficiency for example is related to Wernicke-Korsakoff syndrome of ophthalmoplegia, cerebellar dysfunction, and cerebral degeneration.

Morphological Changes in the Brain

Cerebral Cortex

Hippocampal Formation

-reduction in thickness

- reduction in the numerical density of granule cells

Prelimbic Cortex

-Degradation of Myelin sheaths

Cortical subcortical atrophy

Associated Neuropathies

-Multiple sclerosis like symptoms

Genetic Damage and Heritability of Alcoholic Symptoms

-Predisposition

-Fetal AS

-Lower iq unrelated to poor upbringing

Some Regeneration is possible with abstinence of alcohol and lifestyle changes

Decrease or reverse the decline of brain matter

References

1.Fall Semester-A Time for Parents To Discuss the Risks of College Drinking. (2019, December 24). Web Retrieved from https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/time-for-parents-discuss-risks-college-drinking

2. Heit, C., Dong, H., Chen, Y., Thompson, D. C., Deitrich, R. A., & Vasiliou, V. K. (2013). The Role of CYP2E1 in Alcohol Metabolism and Sensitivity in the Central Nervous System. In Subcellular Biochemistry (pp. 235–247). https://doi.org/10.1007/978-94-007-5881-0_8

3. McDonnell, PharmD, BCOP, A.M., & Dang PharmD, BCPS, C.H. (2013). Basic Review of the Cytochrom P405 System. Jouranl of the Advanced Practitioner in Oncology, 4(4). https://doi.org/10.6004/jadpro.2013.4.4.7

4.[1] Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

5. [2] Johnson, S. B., Blum, R. W., & Giedd, J. N. (2009). Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. The Journal of adolescent health : official publication of the Society for Adolescent Medicine, 45(3), 216–221. https://doi.org/10.1016/j.jadohealth.2009.05.016

6. Dynamic mapping of human cortical development during childhood through early adulthood. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM Proc Natl Acad Sci U S A. 2004 May 25; 101(21):8174-9.

7. (n.d.). Retrieved from https://www.usgs.gov/special-topic/water-science-school/science/water-you-water-and-human-body?qt-science_center_objects=0#qt-science_center_objects

8. Ehlers CL, Criado JR. Adolescent ethanol exposure: does it produce long-lasting electrophysiological ef

9. Allen CD, Lee S, Koob GF Rivier C . Immediate and prolonged effects of alcohol exposure on the activity of the hypothalamic-pituitaryadrenal axis in adult and adolescent rats. Brain Behav Immun. 2011 June;25(-Suppl 1):S50–S60

10. Silva, C. S., Portari, G. V., & Vannucchi, H. (2016). Antioxidant Treatment and Alcoholism. In Molecular Aspects of Alcohol and Nutrition (pp. 119–131). Elsevier. https://doi.org/10.1016/b978-0-12-800773-0.00010-0)

11. Dervaux A, Laqueille X. [Thiamine (vitamin B1) treatment in patients with alcohol dependence]. Presse Med. 2017;46(2 Pt 1):165-171. doi:10.1016/j.lpm.2016.07.025

12. Tardelli VS, Lago MPPD, Silveira DXD, Fidalgo TM. Vitamin D and alcohol: A review of the current literature. Psychiatry Res. 2017;248:83-86. doi:10.1016/j.psychres.2016.10.051

13. American Addiction Centers. The Effects of Alcohol on the Pancreas. October 2019.

13. Spector R, Johanson CE. 2007. Vitamin transport and homeostasis in mammalian brain: focus on vitamins B and E. J. Neurochem. 103(2): 425–38