Massachusetts Academy of Mathematics and Science at WPI

Literature Review

The Effects of Ethanol Metabolism on the Reproductive System of D. melanogaster

Stuparu, Katy A.

12-22-2020

Table of Contents

Introduction 2

Ethanol – Health Risks 3

Ethanol – The Effect on Reproductive Organs in Rats 5

D. Melanogaster – The Physical Effects of Ethanol 7

D. Melanogaster – Ethanol and Behavior 8

Conclusion 8

References 9

Introduction

It is a well-known fact that the consumption of alcohol can do great damage to the human body. Many studies have been done to show that those who have a higher intake of alcohol are more susceptible to malfunctions throughout the body. Some of these effects are cancer, epilepsy, and heart disease. These risks may have other attributing factors but have an association with drinking (Rehm, 2011). In the last two decades, scientists have begun to look at the deeper causes of these diseases and have studied the way that ethanol affects the body at the molecular level. They discovered how the body reacts to small and large amounts of ethanol and understood why it can put the body at a health risk. While they found positive correlations between alcohol intake and the risk of many specific diseases, many of the causes remained unknown. What scientists did find, however, is understanding how ethanol is broken down in the body and how it can cause disease in a more general case.

By using the model organism, *Drosophila melanogaster* (a type of fruit fly commonly used for scientific research), scientists can grasp a better understanding for how the metabolism of ethanol represents the body. The choice for using this model organism lies within the facts that *D. melanogaster* and humans respond to disease similarly (with nearly 75 percent similarities in genes relating to disease) and have similar anatomical functions. This allows scientists to extend their main findings with *D. melanogaster* to humans and to understand how certain aspects of the body function in response to variables (Pandey & Nichols, 2011). In this literature review, the effects of ethanol and the usage of *D. melanogaster* with ethanol will be discussed.

Ethanol – Health Risks

When alcohol is taken into the body, it is absorbed into the bloodstream, mainly through the stomach and the small intestine. The ethanol in the blood gets delivered to many places around the body. In these places, primarily the liver, the enzymes alcohol dehydrogenase along with catalase and P4502E1 in minimal amounts work to break down the ethanol into acetaldehyde. Acetaldehyde is an extremely toxic substance that can cause many diseases or malfunctions of the body because it damages DNA when it reacts with it creating free radicals, discussed in the next paragraph. Next, a chemical reaction with aldehyde dehydrogenase in mitochondria eliminates the acetaldehyde and produces acetate. When a surplus of ethanol is in the body, the function of alcohol dehydrogenase increases to accommodate. However, the rate at which aldehyde dehydrogenase works stays the same, so the result is an excess amount of acetaldehyde which remains in the body for hours until it is broken down. When this occurs often, it becomes especially dangerous for the body as acetaldehyde is unsafe (NIAAA Publications, n.d.).

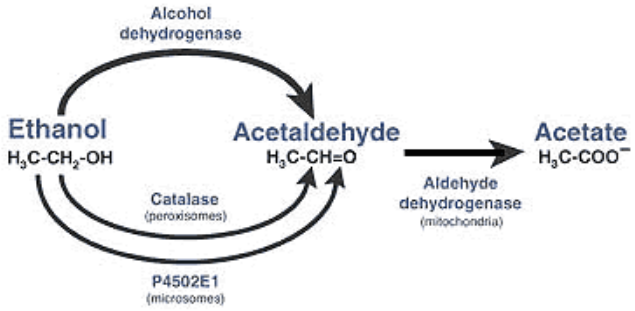

Figure 1: Ethanol Metabolism

This diagram gives a visual of the process of the metabolism of ethanol, as described in the paragraph above. It shows in the center the molecule before and after each process (ethanol to acetaldehyde to acetate) and on the sides the enzymes which are part of the processes (alcohol dehydrogenase, catalase, P4502E1, and aldehyde dehydrogenase) as well as includes the locations of some of the enzymes below.

NIAAA Publications. (n.d.). Retrieved October 13, 2020, from https://pubs.niaaa.nih.gov/publications/aa72/aa72.htm

Acetaldehyde and the function of alcohol dehydrogenase and aldehyde dehydrogenase produce free radicals such as 1-hydroxyethyl and hydroxyl (Comporti et al., 2010). Free radicals are a byproduct of a metabolic process and are chemically unstable molecules, meaning that they are very reactive. The body balances these toxins out with antioxidants, but when there are too many free radicals, the ratio of the toxins to antioxidants becomes too high. In this way, the reactive oxygen species can damage parts of cells. This situation, called oxidative stress, occurs when too much alcohol is consumed. When the body breaks down the large amounts of ethanol, it reaches a point where the free radical to antioxidant ratio becomes too high, increasing the risk for disease (Zima et al., 2001).

Alcohol consumption over a period is associated with many physical and mental diseases, such as infections, cancer, diabetes, neuropsychiatric diseases, cardiovascular issues, liver diseases, and pancreatic illnesses. Some of these effects have been shown to be directly because of alcohol consumption. Other risks such as contracting HIV and mental disorders have other attributing factors but are correlated with drinking. This could mean that the alcohol could be related to why the diseases occur or why alcoholism could be a byproduct. Liver disease, however, is known to be caused by alcohol (Rehm, 2011). When ethanol is absorbed into the bloodstream, mainly through the stomach and the small intestine, about 90 to 98 percent of it ends up being metabolized by the liver. The process described earlier with alcohol dehydrogenase and aldehyde dehydrogenase occurs in the liver most often, causing it to be damaged the most. However, other areas of the body are capable of metabolizing ethanol as well, leading to the damage of these tissues based on the level of alcohol dehydrogenase expression. The function of alcohol dehydrogenase producing acetaldehyde and free radicals can create damage in those parts of the body too, not just in the liver as it is commonly known.

As explained earlier, the breaking down of ethanol can weaken cells where the metabolism occurs. Thus, many diseases and malfunctions of the body can arise. Ethanol is even known as a carcinogen (Jelski & Szmitkowski, 2008). For a long time, scientists were aware of a correlation between alcohol drinking and cancer. They were not sure if the cancer arose due to the metabolism of ethanol or the increase of estrogen with alcohol consumption. Scientists experimented with rats, altering the levels of acetaldehyde, free radicals, and estrogen. They discovered an increased functionality of alcohol dehydrogenase, meaning more acetaldehyde, in cancerous cells (Jelski & Szmitkowski, 2008). They also found that acetaldehyde, free radicals, and estrogen all ended up leading to oxidative stress, which increases the risk of cancer. The three carcinogens are all dangerous, but when combined, they can damage or weaken cells or cause cancer (Castro & Castro, 2014). This case shows that many of the diseases that are related to alcohol may have another contributing factor that is important to look at to understand the functionality of the organ or location of the body. However, it is notable that ethanol gets broken down in many places across the body and can do much damage, especially for high amounts.

Ethanol – The Effect on Reproductive Organs in Rats

Higher-end studies using rats as a model organism discovered the nature of the metabolism of ethanol in the reproductive organs of female and male rats. These studies analyzed the organs using tools in labs rather than looking at behavior, disease development, or death rates to show what was happening at a microscopic level without influence from other possible factors. The three studies described below were about the uterine horn, ovarian tissue, and testicular microsomes.

The uterine horns are located at the intersection of the uterus and the fallopian tubes in females. The health of this section of the reproductive system is important for the flow of eggs to occur. One group of researchers found that an increase of ethanol intake in rats leads to oxidative stress in the uterine horn. A small amount of ethanol is metabolized in situ and creates a higher ratio of acetaldehyde. This microsomal process requires oxygen to take place. In addition to this, an enzyme called xanthine oxidoreductase produces reactive oxygen species. Due to this information, the researchers concluded that an increase in the metabolism of ethanol increases the oxidative stress in the uterine horn and can lead to malfunctions of the reproductive system (Buthet et al., 2011).

A different study found that ethanol oxidation in the ovaries can cause them to malfunction. When they exposed the rats to ethanol multiple times, the activity of alcohol dehydrogenase increased, therefore increasing the amount of acetaldehyde and free radicals. The scientists also found differences in the structure of the ovary, particularly a dilation of the endoplasmic reticulum and mitochondria, as well as broken or absent cell processes because of the destructiveness of the increased oxidative stress. This could all explain why the ovary function was decreased with an increase of the metabolism of ethanol (Faut et al., 2009).

Another article about the reproductive system of male rats explained why testosterone production is lower when more alcohol is consumed. Scientists tested the amount of acetaldehyde and 1-hydroxyethyl in centrifuged rat testes. Enzymes such as CYP2E1 and P450 reductase (lipoxygenase- or peroxidase-like behavior) break down ethanol in testes, producing acetaldehyde and the free radical 1-hydroxyethyl, which is also formed in the mitochondrion with NADPH. This study suggests that the toxic compounds acetaldehyde and 1-hydroxyethyl cause the lower level of testosterone production. They also concluded that reactive oxygen

species can play a role in lowered fertility rates (Quintans et al., 2005). According to these studies, the metabolism of ethanol itself can affect the functionality of the reproductive system.

D. Melanogaster – The Physical Effects of Ethanol

Drosophila melanogaster can be used as a model to discover trends or to understand how processes in the body can be affected. The benefits of using this species lies in the fact that a larger sample size is made possible and the results may be extended to humans *(D. melanogaster* and humans have been shown to respond to diseases in similar manners). In general, this model organism can be used to better understand how many animals respond to specific conditions.

For example, scientists developed a model of fetal alcohol effects (FAE) or fetal alcohol spectrum disorder (FASD) using *D. melanogaster.* They had already found that developmental ethanol exposure leads to the inhibition of insulin-like peptides. In this study, they found that developmental ethanol exposure leads to the dysregulation of lipid metabolism. The unusual process of fatty acid metabolism then leads to oxidative stress, a cause of many developmental issues. They added

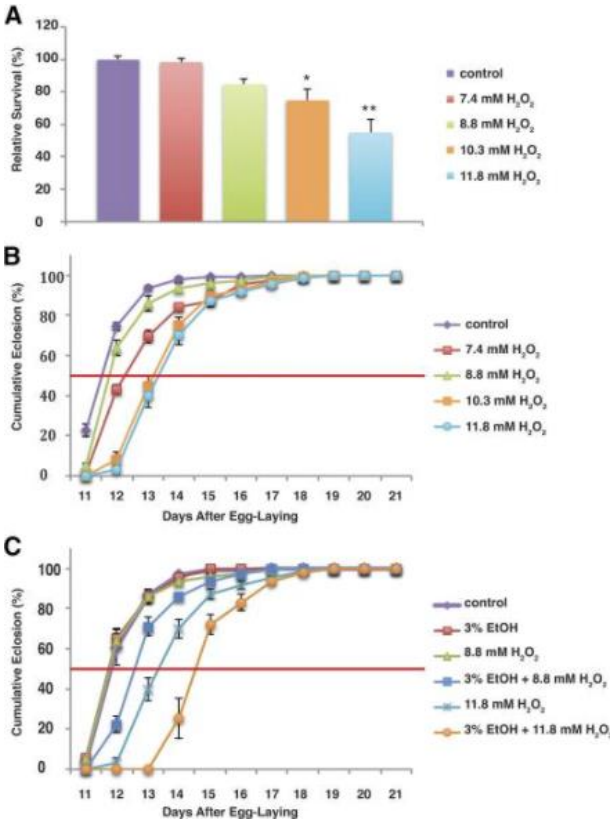

Figure 2: Ethanol and FAE and FASD

In graph A, it is shown that higher levels of H_2O_2 decrease the survival rate. Graphs B and C tell that increased levels of H_2O_2 and ethanol lead to a longer cumulative hatching time.

Logan-Garbisch, T., Bortolazzo, A., Luu, P., Ford, A., Do, D., Khodabakhshi, P., & French, R. L. (2014). Developmental Ethanol Exposure Leads to Dysregulation of Lipid Metabolism and Oxidative Stress in Drosophila. *G3: Genes|Genomes|Genetics*, *5*(1), 49–59. https://doi.org/10.1534/g3.114.015040

various levels of H_2O_2 to invoke oxidative stress, which reduced the survival rate and increased the hatching time (Logan-Garbisch et al., 2014). This study not only provides an effective example of using *D. melanogaster* as a model, but also shows how oxidative stress affects these flies. The scientists found that the offspring with oxidative stress were less likely to survive and took longer to hatch than the control group, as shown in the figures to the right.

D. Melanogaster – Ethanol and Behavior

Scientists have found that *Drosophila melanogaster* act differently, particularly with sexual behavior, if they consume or are dependent on ethanol. While doing research about the metabolism of ethanol in the reproductive system with *D. melanogaster,* it is important to use methodology or find dependent variables that are not affected by the behavioral effects of ethanol but instead the metabolism only. The behavior of the flies based on varying conditions can also change the flies' voluntary consumption of food, water, ethanol, and so on.

A study which shows an example of male behavior found that the lack of sexual activity of males increased the voluntary intake of ethanol. The sexual deprivation was found to inhibit the neuropeptide F (NPF) system. This increased the intake of alcohol for the male flies and can be generalized to find a connection between physical activity, sexual experience, and the NPF system activity (Shohat-Ophir et al., 2012). While doing testing with *D. melanogaster*, the possible behavioral causes and effects should be considered when creating the methodology and analyzing the results.

Conclusion

This literature review discussed the general metabolism of ethanol as well as its effects on the human body, the studies done with rats as a model organism for the effects of ethanol on

the reproductive system, and information about how *D. melanogaster* are affected physically and behaviorally when there is ethanol involved. The topics discussed in this paper should be considered while studying the metabolism of ethanol and testing with *D. melanogaster* to obtain more accurate and informative results.

References

Buthet, L. R., Bietto, F. M., Castro, J. A., & Castro, G. D. (2011). Metabolism of ethanol to acetaldehyde by rat uterine horn subcellular fractions. *Human & Experimental Toxicology*, *30*(11), 1785–1794. https://doi.org/10.1177/0960327110396537

Castro, G. D., & Castro, J. A. (2014). Alcohol drinking and mammary cancer: Pathogenesis and potential dietary preventive alternatives. *World Journal of Clinical Oncology*, *5*(4), 713–729. https://doi.org/10.5306/wjco.v5.i4.713

Comporti, M., Signorini, C., Leoncini, S., Gardi, C., Ciccoli, L., Giardini, A., Vecchio, D., & Arezzini, B. (2010). Ethanol-induced oxidative stress: Basic knowledge. *Genes & Nutrition*, *5*(2), 101–109. https://doi.org/10.1007/s12263-009-0159-9

Faut, M., Rodríguez de Castro, C., Bietto, F. M., Castro, J. A., & Castro, G. D. (2009). Metabolism of ethanol to acetaldehyde and increased susceptibility to oxidative stress could play a role in the ovarian tissue cell injury promoted by alcohol drinking. *Toxicology and Industrial Health*, *25*(8), 525–538. https://doi.org/10.1177/0748233709345937

Jelski, W., & Szmitkowski, M. (2008). Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the cancer diseases. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *395*(1–2), 1–5. https://doi.org/10.1016/j.cca.2008.05.001

Logan-Garbisch, T., Bortolazzo, A., Luu, P., Ford, A., Do, D., Khodabakhshi, P., & French, R. L. (2014). Developmental Ethanol Exposure Leads to Dysregulation of Lipid Metabolism and Oxidative Stress in Drosophila. *G3: Genes|Genomes|Genetics*, *5*(1), 49–59. https://doi.org/10.1534/g3.114.015040

NIAAA Publications. (n.d.). Retrieved October 13, 2020, from https://pubs.niaaa.nih.gov/publications/aa72/aa72.htm

Pandey, U. B., & Nichols, C. D. (2011). Human Disease Models in Drosophila melanogaster and the Role of the Fly in Therapeutic Drug Discovery. *Pharmacological Reviews*, *63*(2), 411–436. https://doi.org/10.1124/pr.110.003293

Quintans, L. N., Castro, G. D., & Castro, J. A. (2005). Oxidation of ethanol to acetaldehyde and free radicals by rat testicular microsomes. *Archives of Toxicology*, *79*(1), 25–30. https://doi.org/10.1007/s00204-004-0609-5

Rehm, J. (2011). The Risks Associated With Alcohol Use and Alcoholism. *Alcohol Research & Health*, *34*(2), 135–143.

Shohat-Ophir, G., Kaun, K. R., Azanchi, R., Mohammed, H., & Heberlein, U. (2012). Sexual Deprivation Increases Ethanol Intake in Drosophila. *Science*, *335*(6074), 1351–1355. https://doi.org/10.1126/science.1215932

Zima, T., Fialová, L., Mestek, O., Janebová, M., Crkovská, J., Malbohan, I., Stípek, S., Mikulíková, L., & Popov, P. (2001). Oxidative stress, metabolism of ethanol and alcohol-related diseases. *Journal of Biomedical Science*, *8*(1), 59–70. https://doi.org/10.1007/BF02255972