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Will mutations in the *nmr-1* Gene Modify Ethanol Responses in *C. elegans*

Alcoholism is a problem that affects over 140 million people worldwide. Alcohol misuse is associated with more than 100,000 deaths annually in the Unites States alone. It is associated with many social and legal problems, acts of violence, and accidents. Alcoholism is among the most common psychiatric disorders in the general population (htt). Susceptibility to alcoholism has a significant genetic component, which has been proven throughout multiple experiments (Schuckit). By analyzing the differences in people’s genes, we can find out why there is such a difference in the human population for ethanol sensitivity and alcoholism.

Ethanol is the main psychoactive constituent in alcoholic drinks and affects the body in many ways. The NMDA is a major target of alcohol (ethanol) in the brain and has been implicated in ethanol-associated phenotypes such as tolerance, dependence, withdrawal, craving, and relapse (Ron). Many experiments have been done that show that ethanol acutely inhibits NMDA activated ion currents. (Lovinger DM). It has already been tested that over time the sensitivity of NMDAR to ethanol decreases over time. (Grover CA). Due to the fact that everyone has variations in their genes and thus different alcohol tolerance levels; we can find that if someone has a mutated version of a gene whether or not they can be at a higher risk for alcoholism. Knowing if variation in the NMDAR gene can change ethanol sensitivity might enable you to know if someone is more at risk of developing alcoholism and thus we can take precautions to minimize this risk. Also if *nmr-1* does turn out to be important in the effects of ethanol then we can possibly start to better understand other effects of alcohol such as tolerance and withdrawal.

At the molecular level function is preserved and therefore we are able to conduct experiments in organisms other than humans to see how modifying certain genes will affect the body’s response to ethanol. The organism that we are using to better understand ethanol effects on humans is the worm *C.* *elegans*. The same concentrations of ethanol that produce intoxication in humans have the same neurodepresive effects on behavior in *C. elegans* (Davies et al., 2003).

The acute response to ethanol in *C.* *elegans* is what is going to be tested. The acute level of response is the response that occurs within thirty minutes of ethanol administration. It has been observed that if tissue alcohol concentration is kept constant then there are behavioral adaptations that are observed within that time period alone. The *C.* *elegans* is comparatively less drunk after thirty minutes even thought the tissue ethanol level is the same as it was twenty minutes prior. It is believed that this acute tolerance represents the plasticity of the nervous system that allows the nervous system to undergo an adaptation in the presence of ethanol. This shows how the nervous system compensated for the physiological effects of the ethanol. (Sci. STKE, 22 June 2004)

The experiment will be done using a strain of wild-type *C.* *elegans* as well as a mutated strain. The mutated *C.* *elegans* will have a mutation at the *nmr-1* gene. The mutation already occurs naturally, so there is no need to go in and change the gene. The mutants have already been created and can be ordered from the stock center. The mutations in these strains have already been characterized, however in order to make sure that you are in fact using the mutated version of the gene PCR can be run to make sure there is actually a mutation.

The *C. elegans* will first be observed and recorded using the software ImagePro, and their rate of movement will be recorded. Once this data is collected the *C.* *elegans* will be placed onto agar plates that have ethanol concentration values of 100,200,300,400,and. The *C.* *elegans* will be observed and data will be recorded for 50 minutes using the Imagepro software.

The data from the movement of the wild-type *C.* *elegans* will be compared to the data from the mutant strain to determine if the mutated gene has an effect on the acute tolerance of the *C.* *elegans*. In order to minimize the error in the experiment the environment that the experiment is going to be conducted in will be kept constant. Also the frequency of direction changes can be observed with the collected data. Which we predict may be important because *nmr-1* is known to affect direction changes. (Brockie et al, 2001).

Previous data suggests that humans that are less sensitive to alcohol or develop tolerance to ethanol faster are much more likely to become alcoholics (Schuckit). If the data shows that with the mutant gene the acute ethanol response is larger, then we can determine that those people with the mutant gene are at a higher risk of developing alcoholism. If there is no change with the mutant then it could mean that this gene does not have an effect on the acute tolerance of *C. elegans*.