

Genetic Influences on Relapses in Alcohol Consumption

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Abstract

Attempts at quitting drinking for an alcoholic can be a substantial and lifelong hurdle, with relapse rates as high as 80-95% in the year following an intervention (Hendershot, Witkiewitz, George, & Marlatt, 2011). There are three known cues that lead to relapse: consumption of a small amount of alcohol, cues that are associated with prior availability of alcohol, and stress (Hansson et al., 2006). A look at genes implicated in relapse can be an important step in creating efficacious individualized intervention treatment programs. In this review, two types of genes are inspected regarding their effects on alcohol relapse; those that involve the dopamine reward system as well as CRHR1, a gene that has been linked to stressful drinking of alcohol.

Genetic Influences on Relapses in Alcohol Consumption

Alcoholism has attracted a lot of research attention; perhaps attributable to the dramatic toll it has on the lives of those afflicted, as well as on their loved ones. Increasing the efficacy of interventions would be a significant boon to the health of the nation, especially considering the year long relapse rate following interventions resides around 80-95% (Hendershot, Witkiewitz, George, & Marlatt, 2011). Of course, in order to relapse, a person must first have sought or received treatment for alcohol problems. As such, there are obvious linkages between addiction propensity and relapse, though the differences in underlying reasons for drinking and addiction in the first place will undoubtedly lead to differences in the propensity of an individual to relapse.

One proposed behavioral pathway to relapse involves the course of action taken when facing a “risk situation”, a circumstance where the recovering addict is tempted to reuse. If the recovering addict successfully copes with the situation, their self efficacy is increased and their probability of future relapse is decreased. If, on the other hand, the coping response is ineffective, self-efficacy decreases and the perception of the alcohol making the addict feel better increases. This, in turn, increases the probability of a relapse event in the future (Hendershot, Witkiewitz, George, & Marlatt, 2011). While this pathway explains what is at stake during potential relapse situations, a closer look at the environmental cues that trigger them will aid in understanding the process of relapse.

Three categories have been implicated as triggers to relapse; consumption of a small amount of alcohol, cues that are associated with prior availability of alcohol, and stress (Hansson et al., 2006). While the behavioral phenotype of relapsing is the same across the three triggers,

the focus of this paper will be on genotypic differences which drive the varied relapse triggers, in particular focusing on the difference between the first two triggers in comparison to the third.

Why Look at Genes?

When looking through the literature concerning the genetic influence on propensity to relapse, a good place to start is considering why genetic influence has been implicated in relapse in the first place. For starters, there has been ample evidence supporting a genetic link to alcoholism in general. One early study provided evidence that adopted children with biological parents who were alcoholics had a much higher risk of being an alcoholic themselves, when compared to adopted children without alcoholic biological parents (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973). In addition, this group had higher divorce rates, and had higher incidence of receiving treatment for alcohol related offenses, though what the treatment consisted of was not known, as well as the results of the treatment and propensity for relapse (1973).

Another study looked into the possibility of alcohol relapse following liver transplants (Jauhar, Talwalkar, Schneekloth, Jowsey, Wiesner, & Menon, 2004). Of 111 transplant recipients with alcohol liver disease in their sample, 17 relapsed. 12 of these 17 had a family history of alcohol use. In other terms, 71% of those that relapsed had a family history of alcoholism, while making up only 38% of the entire sample size. What is not clear from this study is how much this relapse is attributable to genetic influence, and how much is due to environmental factors. Further, no specific genetic markers were presented in this relapse study.

Two genetic systems of interest have been implicated in the literature concerning relapse, which we will look into in this paper. The dopaminergic system is the brains reward system, and may plays considerable role in addiction (Markianos, Lykouras, Moussas, & Hatzimanolis,

2001). Due to its role in addiction and rewards, polymorphisms among the genes within the circuit may affect the propensity for relapse. Another circuit of interest involves stress system, and in particular the CRHR1 (corticotropin-releasing hormone receptor 1) gene polymorphism, which has been implicated in increasing alcohol consumption, lowering the initial age of drinking, and increasing relapse following stressful events (Hansson et al., 2006) (Schmid et al., 2010).

Dopamine System

For an addict, attainment and usage of the addictive substance has the propensity to stimulate a reward response, via increased dopaminergic activity (Markianos, Lykouras, Moussas, & Hatzimanolis, 2001). This activity is not implicit on the substance containing dopamine, but rather stimulates the reward circuit via its mere presence, taste, or initial effects after usage. In this way, the dopamine system may hold greatest effect over the first two triggers of relapse: small priming doses, and cues associated with prior presence of alcohol. Polymorphisms among the genes within the reward system may change the strength of the reward response, therein increasing the chance of relapse.

One study looked at genes complicit in the serotonin and dopamine functioning, and their relation to alcohol relapse (Wojner et al., 2009). In particular, six polymorphisms were analyzed which have been associated with impulsiveness and suicidality, two traits linked with serotonin and dopamine system dysfunctions. The polymorphisms were among the TPH2, 5-HTT, HTR2A, HTR2B, COMT, and BDNF genes. Their sample consisted of 154 Polish alcoholics admitted to treatment programs. Participants with the Val allele of the BDNF Val66Met polymorphism and the Met allele of the COMT Val158Met polymorphism had a statistically higher chance of relapsing than those without the polymorphisms. Having two copies of the

BDNF Val polymorphism increased the speed to relapse, and this genotype in conjunction with one COMT Met allele created a behavioral phenotype with the highest propensity towards relapse.

Due to attrition, the sample size of 154 was decreased to 123. The authors discuss that a higher proportion of those without follow up data are generally more likely to have relapsed than those that continue in a study (Wojner et al., 2009). They reran the data, this time considering all that did not complete a follow up had relapsed. Their findings concerning the Val allele of the BDNF Val66Met polymorphism remained significant, though the authors did not mention the significance of the COMT Met allele under their new analysis.

Another study focused on the effects of a decrease in D2 receptor responsivity in the early stages of alcohol abstinence, which may predict relapse for the addict (Markianos, Lykouras, Moussas, & Hatzimanolis, 2001). This was assessed by administering haloperidol, a dopamine receptor blocker, and measuring prolactin plasma levels. Dopamine is an inhibitor of prolactin; while drinking, prolactin levels of those seeking treatment are reduced, below the average for healthy subjects. After detoxification, the prolactin levels of successful abstainers increased to normal, healthy levels.

A different pattern emerges for those that relapsed within the next year. Their average prolactin level was significantly lower than successful abstainers 7 to 17 days after refraining from drinking alcohol. It would appear from this study that those with less malleability in their dopaminergic reward system have more difficulty adjusting to life without alcohol, though this study did not assess if genetic differences were present for the two groups. While there might be no genetic difference between the two groups, the researchers found no significant difference in age, depression inventory scores, scores on the Brief Michigan Alcoholism Screening Test,

prolactin response upon entry into treatment, or quantity of alcohol consumed prior to treatment (Markianos, Lykouras, Moussas, & Hatzimanolis, 2001). A potential direction for future research would be to address if there is in fact a genetic difference between these groups, which may help in tailoring alcohol treatment plans at intake.

CRHR1

While the dopamine system may hold an impact on the first two triggers of relapse, one gene of interest, CRHR1, appears to hold great sway over the third trigger, stress. A polymorphism of the CRHR1 gene has been associated with heavy drinking, as well as earlier age of drinking, when coupled with stressful life events (Schmid et al., 2010). An experimental study has been designed utilizing rats bred for high alcohol preference, with up-regulated expression of the CRHR1 gene. The researchers confirmed a higher sensitivity to stress in this line, and confirmed a lower stress threshold for alcohol seeking behaviors in these rats (2009). Importantly, administration of a CRHR1 antagonist reduced alcohol searching behavior in this line of rats, while having no effect on this behavior for a different breed of rats.

To further assess the effects of CRHR1 on stressful drinking, another study bred two separate lines of mice; one with a global knockout of the CRHR1 gene, and another with CRHR1 knocked out of the central nervous system, but still present in the pituitary and adrenal glands of the HPA axis (Molander et al., 2011). This was due to an observation of delayed and reduced, but still present stress induced drinking in mice without a functional CRHR1 gene, which should mimic mice administered CRHR1 antagonist in complete reduction of stress induced drinking. There is potential that this difference was due to compensatory changes during development for mice without the functional CRHR1 gene, though the authors hypothesized that perhaps the CRH/CRHR1 circuit in the HPA axis acts in opposition to the CRH/CRHR1 circuit present in

the rest of the brain. In line with their hypothesis, the mice with CRHR1 global knockout showed increased alcohol consumption after stressful events, while the mice with CRHR1 present in the HPA, but absent elsewhere showed reduction in drinking behavior (Molander et al., 2011).

While selective knockout versus complete knockout of the CRHR1 gene affected stress induced alcohol consumption, there are two points of concern regarding the findings of this article. The first involves a lack of discussion on how administration of CRH antagonist has repeatedly shown elimination of stress induced drinking in animals with the CRHR1 polymorphism. CRH antagonist should equally impact the HPA axis when administered, so it is odd that they have found evidence that lack of the CRHR1 in the HPA axis would increase drinking. The authors also did not explicitly state that the CRHR1 present in the HPA of the selective knockout mice contained the polymorphism associated with stress induced alcohol consumption. Further research should include these parameters to better assess if the CRHR1 polymorphism has a differential effect in the HPA axis than in the central nervous system.

Regardless, the CRHR1 polymorphism appears to hold an effect on drinking due to stressful situations. If the CRHR1 gene presence in the HPA axis reduces drinking due to stress, while its presence in the central nervous system increases drinking due to stress, it would appear based on the literature that overall, the polymorphism has a net positive effect on stress induced drinking. The fact that CRH1 antagonists reduce stressful drinking in mice holds obvious implications for alcohol treatment programs, though further research must still be conducted concerning the side effects of its administration.

Similarities and Differences

Looking at CRHR1 and dopamine's association with relapse in alcoholism, we can see two separate systems that may goad on a similar behavioral outcome. While the phenotypes are

similar, they are spurred on by different environmental effects. To a certain degree, relapse due to dopaminergic polymorphisms relate most to pursuit of alcohol and the reward that comes along with it, while relapse due to the corticotrophin polymorphism might represent alcohol usage as a withdrawal from a stressful environment.

Earlier, three environmental stimuli were presented that have been implicated in relapse; small doses of alcohol, cues that have been associated with alcohol in the past, and stress (Hansson, 2009). It would appear that differences in the dopamine system might play mostly towards conditioned cues that have been associated with alcohol, as well as “priming” small doses of alcohol. Because the dopamine acts as a reward, perhaps the conditioned cues and taste acts as a primer toward the reward. The effects seen from the CRHR1 polymorphism are more obviously implicit in the stress trigger towards alcohol relapse. Two polymorphisms among the dopaminergic system and one in the stress response system have been implicated in higher incidence of relapse, which may be due to increased relapse trigger proneness, though each system likely effects different triggers towards relapse.

Conclusion

It is important to note the definition of relapse may vary depending on the researcher, which may impact their findings. For example, one study in this review considered relapse as those that successfully completed two to six months of alcohol abstinence, and then relapsed within the next four months (Bauer, Covault, & Gelernter, 2012). When the BDNF polymorphism was assessed for relapse propensity, the results were not significant. Other studies have recruited participants during their treatment, and followed up within a set timeframe (Jakubczyk et al., 2013; Wojnar et al., 2009). Using this method, the BDNF polymorphism was a significant predictor of relapse, as well as a predictor of earlier relapse (Wojnar et al., 2009).

These varied methods of defining relapse may have a differential effect on the outcomes of the studies, creating potential for Type 1 errors.

Other genes have also been implicated in relapse, including genes associated with serotonin functioning (Jakubczyk et al., 2013), though for brevity this paper focused on two systems whose mechanisms can easily be associated with triggers toward relapse. Genotyping, as well as assessing D2 receptor responsivity following treatment, can predict higher proneness for relapse, information which can aid in targeting successful alcohol treatment for the individual. That stated, it is of genuine concern how research on the genetic components of relapse is utilized. For example, it would be worrisome if the decision concerning who receives a liver transplant is decided solely based on the patient's genomic propensity of relapse. A continued focus towards creating more targeted individual treatments should help to ameliorate the potential risk of this from occurring, through better treatment outcomes for current relapse risk profiles.

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