ALCOHOL-RELATED EXPECTANCIES ARE ASSOCIATED WITH THE D_2 DOPAMINE RECEPTOR AND $GABA_A$ RECEPTOR β3 SUBUNIT GENES.

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ABSTRACT

Molecular genetic research has identified promising markers of alcohol dependence, including alleles of the D_2 dopamine receptor (DRD2) and the $GABA_A$ receptor β3 subunit (GABRB3) genes. Whether such genetic risk manifests itself in stronger alcohol-related outcome expectancies, or in difficulty resisting alcohol, is unknown. In the present study, A1+ (A1A1 and A1A2 genotypes) and A1- (A2A2 genotype) alleles of the DRD2 and G1+ (G1G1 and G1 non-G1 genotypes) and G1- (non-G1 non-G1 genotype) alleles of the GABRB3 were determined in a group of 56 medically-ill patients diagnosed with alcohol dependence. Mood-related Alcohol Expectancy (AE) and Drinking Refusal Self-Efficacy (DRSE) were assessed using the Drinking Expectancy Profile (Young and Oei, 1996). Patients with the DRD2 A1+ allele, compared to those with the DRD2 A1- allele, reported lower DRSE in situations of social pressure (p=. 009). Similarly, lower DRSE was reported under social pressure by patients with the GABRB3 G1+ allele when compared to those with the GABRB3 G1- allele (p=.027). Patients with the GABRB3 G1+ allele also revealed reduced DRSE in situations characterized by negative affect than patients with the GABRB3 G1- alleles (p=. 037). Patients carrying the GABRB3 G1+ allele showed stronger AE relating to negative affective change (for example, increased depression) than their GABRB3 G1- counterparts (p=. 006). Biological influence in the development of some classes of cognitions is hypothesized. The clinical implications, particularly with regard to patient-treatment matching and the development of an integrated psychological and pharmacogenetic approach are discussed.

Keywords: Alcohol Expectancy, Self-Efficacy, Genetics, DRD2, GABRB3

INTRODUCTION

Addictive behavior research has tended to emphasize either biological or psychosocial factors. However, integration of these two factors is rare. Social cognitive theory (Bandura, 1986, 1997) is a comprehensive framework to guide research examining the relationship between genetic risk and cognitive expectancies about alcohol consumption. This theory emphasizes that addictive behavior is ultimately learned and is a product of individual cognitions about substance use. These cognitions are influenced by physiological and genetic processes as well as by personal and vicarious experience (Wilson, 1987; Young & Oei, 1993). Two key cognitive constructs, Alcohol Expectancy (AE) and Drinking Refusal Self-Efficacy (DRSE) are robust predictors of both the acquisition and maintenance of drinking behavior (Young, 1994; Connor et al., 2000).

AE has been defined as "if-then" contingencies representing the nature of alcohol-related reward, or motivation to drink (Goldman, 1999). There are several major domains of AE including mood change, assertive social behavior, sexual disinhibition, altered cognitive processes and reduced anxiety (Young & Oei, 1996). AE scores predict alcohol use over time in both clinical (Young, 1994) and non-clinical (Christiansen et al., 1989; Young & Oei, 2000) populations.

DRSE is confidence in resisting alcohol when exposed to specific cues (Bandura, 1986; Young et al., 1991). Three broad domains of DRSE have been identified. They are confidence in resisting alcohol when experiencing negative affect, when under social pressure to drink and when alcohol is readily available (Young & Oei, 1996). DRSE scores also have strong predictive power as regards drinking behavior and treatment prognosis (Young, 1994; Greenfield et al., 2000). Both AE and DRSE constructs add unique variance as indicators of drinking behavior (Young, 1994; Connor et al., 2000) and alcohol misuse is associated with high AE and low DRSE (Young & Oei, 1996). The strongest AE factors that discriminate between alcoholics and control subjects are those relating to mood, namely Affective Change and Tension Reduction (Young & Oei, 1996). All three DRSE factors significantly discriminate between these groups.

Genetic factors are likely to influence expectancies about alcohol. Tension-reduction expectancies are stronger in those with a family history of alcohol problems (Young, 1994). Twin studies indicate that alcohol expectancies regarding mood alteration and activation have significant genetic variance (Vernon et al., 1996). Advances in molecular biological techniques over the last two decades have made it possible to investigate specific genetic influences on psychological parameters related to drinking. For example, the ALDH2*2 allele, which is related to an aversive response to alcohol is associated with lower positive expectancies in a questionnaire study (McCarthy et al., 2000) and in the laboratory (McCarthy et al., 2001). ALDH*2 status may confer protection against alcohol problems. However, genes associated with severe substance misuse have not been investigated.

A variety of drugs of abuse, including alcohol, nicotine, stimulants and opiates, increase brain dopamine levels in the ventral tegmental area and the nucleus accumbens (DiChiara and Imperato, 1988). This mesolimbic dopaminergic response, mediated via D_2 dopamine receptors, is a primary substrate of drug reward (Wise, 1996; Maldonado et al., 1997). The reported association of the DRD2 A1+ allele with alcoholism suggests a genetic dopaminergic influence on drug-related behavior (Blum et al., 1990). Some individual studies have not supported this finding (for example, Blomqvist, Gelernter & Kranzler, 2000) and have suggested that positive effects may be attributable to population stratification in some groups studied. Indeed the frequency of the A1 allele varies amongst ethnic groups (Kidd et al., 1998) and to avoid stratification effects a recent meta analysis analyzed the frequency of the A1allele in 1037 alcoholics and 1492 Caucasian controls finding a significantly higher A1 allele frequency in the alcoholics ($P=2.14 \times 10^{-7}$)(Noble, 2003). The Noble et al 2003 review included three studies where the A1+ frequency was lower in alcoholics than in controls. A number of other meta-analyses have shown the association between A1+ and alcoholism to be robust (Uhl et al., 1993; Lawford et al., 1997; Pastorelli et al 2001). An earlier meta-analysis (Gelernter, Goldman & Risch, 1993) did not find an association but a reanalysis of these data has confirmed an association (Noble & Blum, 1993). Importantly the DRD2 A1+ allele has also been associated with other substance use disorders including, nicotine (Noble et al., 1994; Comings et al., 1996; Spitz et al., 1998), stimulant (Noble et al., 1993; Persico et al., 1996) and opiate (Lawford et al., 2000) dependence indicating that it is not a specific risk factor for alcoholism.

The A1 allele of the D2 dopamine receptor is associated with low CNS D2 receptor density. An *in-vitro* study using the D2 dopamine receptor ligand (^{3}H) spiperone (Noble, 1991) found a significant decrease in the number of D2 dopamine receptors in the brains of A1+ (A1/A1 and A1/A2 genotypes) compared to A1- allelic individuals (A2/A2 genotypes). An *in vivo* Positron Emission Tomography (PET) study using (^{11}C) raclopride found a significant reduction in brain D2 receptor density in the brains of healthy A1+ allelic subjects (Pohjalainen et al 1998). Other *in vitro* (Thompson et al., 1997) and *in vivo* (Jonsson et al., 1999) studies, using (^{11}C) raclopride, found significant associations of the A1 allele with low D2 dopamine receptor density. However, another study (Laruelle et al.,1998) reported no difference between A1+ and A1- allelic subjects in D2 dopamine receptor binding in a mixed group of subjects with and without schizophrenia. When those without mental illness and those with schizophrenia were separately examined a trend for lower binding was found in A1+ allelic subjects without schizophrenia. In contrast, a trend for higher binding potential was noted in A1+ allelic individuals with schizophrenia. Since two of the above studies (Pohjalainen et al, 1998; Laruelle et al, 1998) appeared in the same journal issue, an editorial (Hitzemann, 1998) reviewed their merits. It suggested that the study using (^{123} I) IBZM (Laruelle et al, 1998) had insufficient power to detect a significant difference between A1+ and A1- allelic individuals. Moreover, since those with schizophrenia showed a trend in the opposite direction the results on D2 dopamine receptor binding potential and allelic association in these subjects may have been confounded by prior neuroleptic treatment. In a subsequent PET study using (^{11} C) raclopride (Silvestri et al, 2000), increased D2 dopamine receptor binding was demonstrated in patients with schizophrenia who had received neuroleptic treatment, supporting this contention. Further, low striatal D2 dopamine receptor density predicts enhanced subjective reinforcement related to intravenous methylphenidate, a D2 dopamine transporter inhibitor (Volkow et al 1999, 2002). Moreover, animal studies have shown that over expression of D2 dopamine receptors is associated with reduced alcohol self-administration (Thanos et al 2001). The association of the DRD2 A1+ allele with both substance use disorders and reduced brain D_2 dopamine receptors has led to the hypothesis that the DRD2 is a reward or reinforcement gene (Noble, 1996, 2000).

Other neurotransmitters are implicated in substance use disorders (Wise, 1998). For example drugs such as alcohol, alter brain GABA activity (Dudek and Phillips, 1990). Dopaminergic and GABA-ergic systems are functionally inter-related, as the release of dopamine in the mesolimbic drug reward pathway is regulated by GABA interneurons (Maldonado et al., 1997). Further, GABA-ergic efferents to the mesolimbic dopamine neurons and the mesolimbic dopamine neurons themselves are primary components of drug reward circuitry (Wise, 1998). The importance of both dopamine and GABA in substance use disorders is underscored by a study examining the impact of genes related to both these neurotransmitter systems (Noble et al., 1998). In that study, the risk for severe alcohol dependence was best predicted by accounting for either the DRD2 A1+ allele or the $GABA_A$ receptor β3 subunit (GABRB3) G1- allele, with the risk for alcohol dependence being further increased when these two alleles were combined.

Genetic and psychological factors are important in the genesis and maintenance of addictive behavior. Treatment outcomes of combined pharmacological and psychological approaches remain modest. For example, 62 % of alcoholics treated with acamprosate and manualized cognitive behavior therapy relapsed over a 12- week period (Feeney et al, 2002). DRD2 A1+ allelic status, GABRB3 G1- allelic status, positive alcohol expectancy and low drinking refusal self-efficacy are all associated with severe alcohol problems but the relationship between them remains unexplored. The current study determined both expectancies and allelic status in a clinical sample of medically-ill subjects diagnosed with alcohol dependence. This study investigated the association of the DRD2 and GABRB3 genes with mood related AE and DRSE given that these factors are the strongest discriminators between alcoholic and control subjects (Young, 1994; Young & Oei, 1996). It was predicted that higher risk allelic status of both genes would be associated with more positive AE and reduced DRSE.

METHOD

Subjects

Of the 59 Caucasian subjects initially enrolled, three were excluded because of liver disease due to etiologies other than alcohol (Wilson's disease, hemochromatosis and Hepatitis C). The remaining 56 subjects, (44 men, 12 women) had a mean age of 50.0 years (s.d. = 8.1) and were alcohol dependent

according to DSM IV criteria and by the Michigan Alcoholism Test Screening (Selzer, 1971). The mean daily amount of alcohol consumed was 164 grams (s.d. = 95). When broken down by gender, the males consumed a mean daily amount of alcohol of 180 grams (s.d = 100 grams) and the females consumed 103 grams (s.d. = 33 grams).

The sample was composed of inpatients admitted to hospital because of severe medical consequences of persistent alcohol consumption. All patients were being investigated for liver disease and underwent biopsy. A mental state examination was undertaken of all patients. Those recruited were cognitively intact and recruitment was delayed if patients showed signs of hepatic encephalopathy so that informed consent could be obtained. The results are thus free of confounds due to confusion or the inability to understand instructional set. This confirmed that 39 had cirrhosis, 12 had alcoholic hepatitis, and 5 had fatty liver infiltration. Of the total sample, 30 had liver failure and 15 were being assessed for liver transplantation with 28 having peripheral edema, and 22 having clinical ascites. Other drug history included 18 patients who were currently smoking cigarettes while 7 patients reported a past history of opioid abuse, 6 a past history of stimulant abuse, 2 a past history of benzodiazepine abuse, 2 a past history of cannabis abuse and 1 a past history of hallucinogen abuse. No patients were abusing illicit or prescription substances at the time of the study.

Procedure

Consecutive patients undergoing liver biopsy for suspected alcohol-induced liver disease, at a gastroenterology ward at the Princess Alexandra Hospital, were referred for assessment. Patients were medically examined and psychologically assessed. Demographic information and drug history were obtained, along with the Drinking Expectancy Profile (DEP, Young & Oei, 1996). The DEP has 43 AE items and 31 DRSE items and has a normative sample of several thousand (Young & Oei, 1996). The measure was produced through a rigorous psychometric development process to address deficiencies in previously developed expectancy measures (Young & Oei, 1993). The alpha coefficients of the DEP factors employed in this study ranged from 0.70-0.93 with two week test-retest reliabilities in the range of 0.72-0.89. There are consistent differences in expectancy between alcoholics and controls on DEP factor scores with alcoholics showing more reinforcing AE and diminished DRSE than community samples of drinkers (Young, 1994; Young & Oei, 1996).

The interviews were conducted with patients individually at the bedside and lasted on average 50 minutes. Consistent with our hypothesis and prior discriminant analysis only AE factors related to mood were examined. Additionally data on all three DRSE factors were obtained. The DEP was developed for use in Australasia and has is consistently related to drinking parameters (Knight and Godfrey, 1993; Vik et al., 1999; Williams et al, 1998). Sample items from the AE factor measuring Affective Change include “Drinking makes me bad tempered” and “Drinking makes me feel like a failure” and the Tension Reduction factor contains items such as “I drink to relieve tension” and “I do not drink alcohol to help me unwind after a hard day or week’s work” (reversed item). DRSE items include estimates of ability to resist alcohol in situations such as “When someone offers me a drink” (Social Pressure), “When I am uptight” (Emotional Relief) and “When I am waiting for someone” (Opportunisitc). The scale has sound reliability and validity (Young & Oei, 1996). Ten ml. of blood was drawn from each subject for molecular genetic analysis. Approval to conduct the study was obtained from the Ethics Committee of the Princess Alexandra Hospital.

Genotyping

Genomic DNA was extracted from blood of subjects using standard methods. The PCR method for determining Taq1A DRD2 alleles has been previously described (Grandy et al, 1993). Two alleles were found: A_1 (310 b.p.) and A_2 (180 b.p. and 130 b.p.) alleles.

CA repeat alleles of the GABRB3 were determined by a slight modification (Noble et al., 1998) of the procedure of Mutirangura et al (1992). Twelve CA repeat alleles were found, were designated as G_1 (181b.p.), G_2 (183 b.p.), G_3 (185 b.p.), G_4 (187 b.p.), G_5 (189 b.p.), G_6 (191 b.p.), G_7 (193 b.p.), G_8 (195 b.p.), G_9 (197 b.p.), G_{10} (199 b.p.), G_{11} (201 b.p.), G_{12} (203 b.p.).

Data analysis

The medical examination and psychological data collection were conducted blind to the patient’s genotype status. Similarly, the genotype data were analyzed blind to the patient’s medical and psychological data. The genotype, medical and psychological data were combined and analyzed after data collection was complete.

DRD2 allelic status was analyzed on the basis of the A1+ allele (A1A1 or A1A2 genotype) or the A1- allele (A2A2 genotype). GABRB3 allelic status was analyzed on the basis of the G1+ allele (G1G1 or G1 non-G1 genotype) or the G1- allele (non-G1 non-G1 genotype).

Multivariate analysis of variance (MANOVA) and post-hoc analysis of variance (ANOVA) were used to compare differences in expectancies amongst the various molecular genetic groups. A $p \leq .05$ was considered as significant and a $p > .05 < .10$ was considered as approaching significance.

RESULTS

Of the 56 patients on whom DNA samples were collected, DRD2 allelic status was obtained on 53 patients (24 A1+, 29 A1-) and GABRB3 allelic status was obtained on 52 patients (31 G1+, 21 G1-). There were no differences in reported alcohol consumption according to allelic status of either the DRD2 or the GABRB3 gene. Thus subjects were well matched for alcohol consumption across allelic groups. All comparisons also took account of gender, given that significant differences in level of consumption in male and female drinkers are typically found. An ANOVA examining mean daily alcohol consumption related to DRD2 allelic status indicated no main effect for allele, $F(1,49) = 0.04$ (NS), or allele by gender interaction, $F(1,49) = 0.805$ (NS). However, there was a significant main effect for gender, $F(1,49) = 5.87$, ($p = .019$). An ANOVA examining mean daily alcohol consumption with participants grouped by GABRB3 allelic status showed a non-significant main effect for allele $F(1,48) = 0.017$ (NS) and a non-significant allele by gender interaction $F(1,48) = 0.628$ (NS). However, the main effect for gender was significant $F(1,48) = 4.118$ ($p = .049$).

Table 1 shows the correlations among the Drinking Expectancy and the Drinking Refusal Self-Efficacy profile scores. The correlation coefficient between Affective Change and Tension Reduction of the Alcohol Expectancy (AE) scores was 0.816. The correlations among Affective Change of the AE and the Drinking Refusal Self-Efficacy (DRSE) factors were low, ranging from 0.096 to 0.315. Similar correlations were evident among the Tension Reduction factor and the DRSE factors with a range of 0.203 to 0.399. However, the correlations among the DRSE factors themselves were relatively high and ranged from 0.716 to 0.829.

Mood-related AE scores (Affective Change, Tension Reduction) of the DRD2 A_1 + and A_1^- allelic subjects were compared using MANOVA and subsequent one-way ANOVA to examine specific pair-wise differences. The mean expectancy scores according to allelic status are presented in Table 2. Both the AE Affective Change and Tension Reduction scores were significantly skewed; thus a 1/x transformation was employed to normalize these data. The MANOVA for AE was not significant, $F(2,49) = 0.216$, $p = .807$; however, the MANOVA for DRSE showed a trend toward significance, $F(3,47) = 2.40$, $p = .080$. Given the trend toward significance the univariate differences between A_1 + and A_1^- allelic subjects in the DRSE factor scores were examined. There was a trend toward significance in DRD2 allelic status in Negative Affect DRSE $F(1, 49) = 2.842$, $p = .098$, as well as in Opportunistic Drinking DRSE, $F(1, 49) = 2.83$, $p = .099$. A significant effect of allelic status on the DRSE Social Pressure factor was also found, $F(1,46)=7.425$, $p= .009$, $\varepsilon^2 = 0.519$ indicating a medium to large effect size (Cohen, 1988). Specifically, those with A_1 + allelic status reported lower Social Pressure factor scores, i.e., A_1+ allelic individuals were significantly less confident in their ability to resist alcohol when subjected to social pressure, than A_1^- allelic subjects.

The mean expectancy scores according to GABRB3 allelic status are shown in Table 3. MANOVAs and post-hoc ANOVAs were conducted according to G1+ or G1- allelic status. The MANOVA for AE factors was significant, $F(2,48) = 4.60$, $p = .014$, and the MANOVA for DRSE factors showed a trend toward significance, $F(3,46) = 2.45$, $p = .076$. In an examination of univariate effects, a significant difference in AE scores emerged on the transformed Affective Change factor, $F(1, 49) = 8.353$, $p = .006$, $\varepsilon^2 = 0.582$ indicating a medium to large effect size (Cohen, 1988). G1+ allelic subjects reported significantly more negative mood change (i.e., increased agitation, anger, feelings of failure, embarrassment and depression) in response to alcohol than did G1- allelic subjects. No significant difference was found on the transformed AE factor of Tension Reduction, $F(1, 49) = 0.217$, $p = .643$. Regarding the DRSE factors, significant differences were found on the DRSE factors of Social Pressure and Negative Affect. Specifically, G1+ allelic subjects reported less confidence resisting alcohol when subjected to social pressure, $F(1, 46) = 5.174$, $p = .027$ $\varepsilon^2 = 0.349$ indicating a small to

medium effect size (Cohen, 1988) and when needing emotional relief if anxious or depressed, $F(1, 48) = 4.590$, $p = .037$ $\varepsilon^2 = 0.296$ indicating a small to medium effect size. The result for Opportunistic Drinking factor of the DRSE was not significant, $F(1,48) = 1.611$, $p = .210$.

The final set of analyses examined the impact of the DRD2 and GABRB3 allelic status on the AE and DRSE factors that showed the strongest evidence of allelic association in prior analyses (Affective Change AE and Social Pressure DRSE). The scores on each factor were converted to Z scores and added. Although these constructs are theoretically distinct they were combined to give an index of "risky cognitions" regarding alcohol. The combined AE/DRSE composite was then compared across allelic groups using non-parametric statistics. The Mann-Whitney U test comparing A1+ and A1- allelic subjects on the composite expectancy measure was significant, $U=233.5$, $p= .0089$; however, the difference between G1+ and G1- allelic subjects did not reach significance. This indicates that across both expectancy domains, the DRD2 gene was more strongly associated with "at risk" expectancies than the GABRB3 gene. Further analysis examining the interaction of both genes was not possible given the small numbers of participants in these groups.

DISCUSSION

Two genes associated with drinking behavior were also related to self-reports of alcohol-related cognitions. The DRD2 A1+ allele was associated with lower confidence in resisting alcohol (DRSE), however there was no relationship between DRD2 allelic status and the reported outcomes of drinking (AE). GABRB3 G1+ allelic status was associated with a lessened negative affective response to alcohol (AE). In addition, GABRB3 G1+ allelic status was associated with lower DRSE under situations of social pressure and in situations characterized by emotions such as anxiety or depression. When social pressure DRSE and affective change AE were examined together as an index of risk there was a significant effect for DRD2 status only. The differential association of allelic status with self-efficacy domains indicates that both environment and genetic risk are important, or that these effects are due to other genetic influences that were not accounted for in the current study.

Both DRD2 A1+ and GABRB3 G1+ allelic status were associated with diminished self-efficacy. Self-efficacy is a robust psychosocial predictor of outcome following detoxification (Noone et al., 1999), in inpatient and outpatient cognitive-behavior therapy (Young, 1994; Long et al., 2000), in inpatient 12-step therapy (Greenfield et al., 2000) and in DUI education (Wells-Parker et al., 2000). Early relapse and premature termination of treatment are associated with the A1+ allelic status (Lawford, et al, 2000), which may indicate low self-efficacy amongst this group. The onset of problem drinking amongst A1+ allelic individuals is also significantly earlier than in A1- allelic subjects (Connor et al., 2002), which may reflect the development of low self-efficacy early in their drinking careers. Furthermore, A1+ allelic subjects reported more inpatient detoxification attempts than A1- allelic individuals (Connor et al., 2002).

The association of A1+ allelic status with diminished social pressure DRSE, rather than the level of reinforcement obtained (as indicated by AE), is consistent with models of substance dependence that separate the dimensions of "wanting" and "liking". "Wanting", or the desire to engage in an activity or use a drug, is thought to be primarily related to midbrain structures, whereas liking is related to the extent of subsequent reinforcement obtained and reflects orbitofrontal cortical activity (Berridge and Robinson, 1995; Robinson and Berridge, 2001). Similarly, DRSE and AE are statistically and conceptually distinct (Young, 1994, Young & Oei, 1996). DRSE reflects the cues that elicit the desire to drink and may represent classical conditioning processes. Our results indicate that A1+ allelic status may confer such a risk in social situations. Further, acute risk may be related to the response of A1+ allelic individuals to drinking environments as their attentional capacity to alcohol related cues further limits the frontal cognitive resources which are required to generate the flexible problem-solving necessary for adaptive coping (Dimitrov et al., 1996). A1+ allelic individuals are susceptible to stress resulting in acute neuropsychological impairment (Berman & Noble, 1997) and increased alcohol consumption (Bau, Almeida & Hutz, 2000; Madrid et al., 2001).

Expectation of reward is reflected in distinct neuronal responses (Hollerman et al., 1998; DiChiara et al., 1993) and MRI studies indicate involvement of midbrain activity (Depue & Collins, 1999).

Dopamine release results in the labeling of environmental stimuli with appetitive value and is the basis of incentive learning (DiChiara et al., 1992). On the basis of conditioned association, the release of dopamine occurs when exposed to cues that have been associated with past reward (Shultz et al., 1997). This mechanism may contribute to diminished DRSE given that short pulses of dopamine stimulate approach behavior (Schultz et al., 1997), resulting in enhanced motivation (Ikemoto & Pansepp, 1999), conditioned place preference (Di Chiara et al., 1992) and anticipation of reward (Schultz, 1998). While this process is initially similar for "natural" (for example, food, sex, water) and drug-related rewards, "natural" rewards are much more likely to habituate than those related to substance use (DiChiara et al., 1993). Drug addiction may be a disorder of associative learning where addictive substances continue to activate dopamine release producing powerful cue conditioning (DiChiara, 1997). A1+ allelic individuals with, on average, 30-40 % fewer mesolimbic D2 receptors (Noble, et al, 1991; Thompson et al., 1997; Pohjalainen et al., 1998; Jonsson et al., 1999) may experience a more powerful priming effect of these dopamine pulses, than do A1- allelic individuals. This may be reflected in more impulsive risk taking; for example, A1+ allelic heroin users are more likely to be infected with Hepatitis C due to needle sharing (Lawford et al 1999). Diminished DRSE supports the conceptualization of the A1 allele of the DRD2 as a reward gene.

G1- status is found more frequently in severe alcoholics (Noble et al., 1998). Within this group of severe alcoholics studied G1+ allelic status was associated with diminished DRSE, presenting an apparent paradox. However, DRSE and AE do not operate independently and drinking behavior is more accurately predicted by both constructs together (Young, 1994). The association between the G1+ allele and affective change AE represents an expected response to alcohol that involves increased disinhibition, depression, anger, aggression and "avoidance of people or situations" associated with alcohol "for fear of embarrassment" (Young & Oei, 1996). These expectancies may act to limit consumption in many drinkers once acute use of alcohol is initiated and may be associated with anticipatory anxiety. This might also explain why G1+ status has not been associated with severe alcoholism despite the association with diminished DRSE. In G1- individuals, despite having higher DRSE, the lack of aversive consequences may result in increased alcohol consumption and the development of more significant alcohol problems over time. Speculatively, affective change AE is consistent with the G1+ allele of the GABRB3 being associated with greater activation of GABAergic CNS inhibitory neurons in the presence of alcohol. This is consistent with a broad array of research confirming the role of GABA-A receptors as the primary receptors involved in CNS neuronal inhibition induced by alcohol (Davies, 2003). The phenotypic characteristics of GABA-A β 3 variants are unknown, but the relative composition of the five GABA-A subunits within a given receptor dictates receptor sensitivity (Luddens & Korpi, 1995). The association of various subunit alleles with response to alcohol requires further investigation.

G1- allelic alcoholics expect fewer of problems related to disinhibition as a consequence of their drinking. Under the circumstances of chronic and severe physical illness or psychosocial stress consequent to alcohol misuse, G1- allelic drinkers may be drinking to improve their affective state and the G1+ allelic drinkers may use alcohol due to reduced DRSE in the presence of negative affect. The association of the G1- alleles with reports of a lessened affective response to alcohol cannot be considered without reference to dopamine activity, as GABA-A interneurons transynaptically inhibit the mesolimbic dopamine system (David, Durkin & Cazala, 1997). The activity of the GABA-A system regulates the VTA dopaminergic response to addictive substances. The more reinforcing expectancies reported by G1- allelic individuals may represent a differing underlying physiological response to alcohol than their G1 + allelic counterparts. Phenotypic expression of subjects with G1- allele may result in GABA-A receptors that are less responsive to alcohol, producing less inhibition of dopamine response and subsequently greater drug reward. Conversely, phenotypic expression of subjects with the G1+ allele may result in a more responsive GABAergic system which inhibits alcohol induced dopamine release; this may result in negative affect, such as anxiety and depression.

The overall influence of the GABA-A β 3 subunit alleles was not significant when both cognitive constructs were examined together and indeed their influence was complex given the G1- allelic status indicating a less aversive response to alcohol but higher self efficacy in resisting alcohol than their G1+ counterparts. The lack of an overall effect is not surprising given the G1- association with alcoholism is considerably less than the association of DRD2 A1+ allelic status (Noble, et al., 1998) and the relatively small and homogeneous sample of heavy drinkers.

In summary, there are three major findings in the current study, firstly that A1+ drinkers showed low self-efficacy under social pressure despite not expecting more significantly reinforcing outcomes related to drinking, secondly that G1+ individuals showed less self-efficacy in resisting alcohol when under social pressure and expected more aversive outcomes regarding affective change and finally that G1- allelic individuals showed comparatively greater self-efficacy than their G1+ counterparts but expected less aversive outcomes of drinking. These different profiles allow the possibility of developing targeted therapies, particularly important in a group facing liver transplantation who would need to abstain both pre- and post-operatively.

This study is limited by the relatively small sample size and the cross-sectional methodology employed. The patients studied all had severe problems and the generalizability to less severe samples has yet to be established. It is however, likely that the effects will be more marked in severe drinking subgroups whose drinking may be more strongly influenced by genetic factors. It is remarkable that the medium to strong effect sizes obtained were evident within a group with such restricted variance in alcohol related severity. Prospective data are also needed to more fully examine the impact of the DRD2 and the GABRB3 genes and expectancies on outcome.

Genetic-expectancy associations are potentially of great clinical value considering the high relapse rate from the current approaches to treatment. There is now sound research evidence regarding the relative effectiveness of treatments for alcoholism (Miller & Wilbourne, 2002). Rather than viewing those with those with alcohol dependence as a homogeneous group where similar treatments are applied to all patients, a “psychopharmacogenetic” approach is likely to be beneficial. Thus, specific psychological and pharmacological treatments could be employed in a strategic manner, taking account of specific genes. For example, an anticraving and anxiolytic response to bromocriptine, a D2 dopamine receptor agonist, occurs only in A1+ allelic alcoholics (Lawford et al 1995). However, other treatment approaches may also be matched on the basis of genetic-expectancy associations. Diminished ability to refuse alcohol is likely a product of classical conditioning processes. Given their lower DRSE in situations of social pressure, repeated non-reinforced exposure (that is, extinction of reinforcement) under situations of social pressure to drink may be more beneficial in A1+ or G1+ allelic individuals than those with A1- or G1- allelic status. Cue exposure treatments have shown promise for some but not all patients (for example, Monti et al 2001). Social skills training that assists alcoholics to assertively refuse alcohol may also be of particular benefit to A1+ and G1+ allelic individuals (Miller & Wilbourne, 2002). Failure to address the power of alcohol related cues in DRD2 A1+ allelic or GABRB3 G1+ allelic patients might result in early relapse and a poor response to treatment, reflected in diminished self-efficacy. Equally, the G1+ allelic individuals may require pharmacological or cognitive-behavioral treatment to diminish the likelihood that they will drink in the presence of negative affect and emphasize the learned associations present between alcohol and the expected aversive consequences of drinking via covert sensitization (Miller & Wilbourne, 2002). It would be anticipated that cognitive therapy that challenges beliefs about the positive consequences of drinking may be of most value in G1- allelic patients and reflect operant conditioning processes.

This study supports the principles of Social Cognitive Theory (Bandura, 1997). Influences on self-efficacy and outcome expectancies are both genetic and environmental. Our findings indicate that the DRD2 A1+ and GABRB3 G1+ allelic status is associated with lower confidence in resisting alcohol under social pressure. Furthermore, GABRB3 G1+ allelic status was associated with lower confidence in resisting alcohol when experiencing negative affect. Stronger expectancies of depression reported in this group may reflect higher comorbidity. In contrast G1- allelic status was associated with reports of a response to alcohol that was not characterized by worsened affect. Overall the DRD2 gene was most strongly associated with combined expectancy risk as defined by low DRSE and positive AE. Alcoholics who carry the A1+ have low self-efficacy and those with the G1- allele low expectancies of aversive consequences.This combination of A1+ and G1- status may place these individuals at high risk for prolonged high dose alcohol consumption with frequent relapse and require future evaluation.

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