PHARMACOLOGY AND CELL METABOLISM

Sweet Liking and High Novelty Seeking: Independent Phenotypes Associated with Alcohol-related Problems†

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Abstract — Aim: We tested the hypothesis that high novelty seeking (NS; a trait that promotes experimentation) and hedonic response to sweet taste (a trait that may reflect processing of hedonic stimuli) act independently to increase the risk for having alcohol-related problems in young adults. Methods: The study was conducted in 158 healthy subjects (age 20–25 years) with no lifetime history of alcohol and/or drug abuse/dependence. NS was evaluated using the Tridimensional Personality Questionnaire. Pleasurable response to sweet taste was tested, using a sweet taste test to identify sweet likers (SL; those preferring the strongest offered sucrose solution) and sweet dislikers (SDL; those preferring weaker sucrose solutions). Results: NS score, but not SL/SDL status, was positively correlated with drinks per month (P = 0.0054) and drinks per drinking day (P = 0.021). When tested individually, both NS and SL/SDL status predict having alcohol-related problems (NS: odds ratio [OR] = 5.3, P = 0.0016 and SL/SDL: OR = 5.8, P = 0.0001) with an OR similar to positive family history of alcoholism status (OR = 5.7, P = 0.0007). The combination of SL status and high NS score (greater than gender-specific 70th percentile) greatly increased the estimated odds of having alcohol-related problems (OR 27.5, P < 0.0001). Conclusions: These results support the hypothesis that high NS and SL phenotypes are independently associated with risk of alcohol-related problems. The combination of both phenotypes greatly increases the likelihood of alcohol-related problems. Although confirmation is necessary, this suggests that these phenotypes could contribute to improved methods to assess risk for alcohol-related problems and provide additional insight into processes underlying progression to alcohol-related problems.

INTRODUCTION

Identifying the traits associated with risk for developing alcohol use disorders (AUDs) is critical for understanding, predicting and intervening in the early phases of progression of this disease. Several phenotypes representing various neurobehavioral domains, e.g. neurocognitive disinhibition (Kamarajan et al., 2006), externalizing behavior (Krueger et al., 2007), insensitivity to the impairing effects of alcohol (Schuckit and Smith, 2006a,b), have been identified as risk factors for alcoholism. However, at present, the variety of factors that lead to AUDs and their interaction is not clear and the ability to predict AUDs in individuals is limited.

We and others have presented evidence that the hedonic response to sweet taste, a heritable trait (heritability ~50% [Keskitalo et al., 2007]) that probably indexes aspects of hedonic processing of rewarding stimuli, is significantly and positively associated with excessive alcohol intake in animals and with the risk of alcoholism in humans evaluated on the basis of a positive family history of alcoholism (FH+), with individuals preferring stronger sweet taste (sweet likers [SL]) having higher risk for alcoholism compared with individuals preferring a weaker sweet taste (sweet dislikers [SDL]; Kampov-Polevoy et al., 1999, 2001, 2003a,b; Krahn et al., 2006; Pepino and Mennella, 2007; Wronski et al., 2007). However, despite the association of SL with familial risk for alcoholism, this trait by itself may be insufficient to predict alcoholic status in clinical samples. For example, we have reported that alcoholic status can be predicted only when SL/SDL status is combined with the personality trait of novelty seeking (NS; Kampov-Polevoy et al., 1998, 2004). More recently, Grucza et al. (2006) showed that high NS increases the risk of AUDs in FH+ individuals, whereas low NS appeared to be a protective factor in this group. On the other hand, NS seemed to have a limited effect on prediction of the risk for AUDs in FH– individuals, which led the authors to the conclusion that NS primarily modulates the risk of AUDs only in individuals with genetic predisposition to this disease.

On the basis of the above evidence, we hypothesized that high NS would increase the risk of having alcohol-related problems to a greater extent in SL individuals compared with SDL individuals. We tested this hypothesis in a sample of 158 healthy young adults. The current study represents a secondary analysis of data previously reported (Kampov-Polevoy et al., 2003a).

METHODS

Subjects
Subjects were recruited via e-mail announcement from the office of Vice Chancellor of Student Affairs to students of the University of North Carolina at Chapel Hill (~22,000 messages), containing a description of the study. Six thousand responses were received. Approximately 800 candidates were screened to recruit 158 subjects that met the inclusion/exclusion criteria: age 18–25 years to target individuals before development of alcohol dependence, no lifetime history of alcohol and/or drug abuse/dependence, no current medical problems, 50% with a paternal history of alcoholism [FH+] and 50% without a paternal history of alcoholism [FH–].
The study was approved by the Committee for the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. After complete description of the study to subjects, written informed consent was obtained.

Assessments

Evaluation of personal psychiatric and substance abuse/dependence history was conducted using the structured clinical interview for diagnostic and statistical manual third edition, revised (DSM-III-R) (SCID-NP; Spitzer et al., 1990) using a trained rater.

Quantitative assessment of subject’s alcohol drinking during 30 days before the interview was done using the Timeline Followback technique (Sobell et al., 1988).

The Tridimensional Personality Questionnaire (a 100-item, self-administered, paper-and-pencil, true/false instrument) was used to assess the personality dimensions of NS, harm avoidance and reward dependence (Cloninger, 1987).

Subjects completed the Michigan Alcoholism Screening Test (MAST) modified for the assessment of the alcohol-related behavior of the subject’s biological father (FMAST). Because the designation of risk for alcoholism is based on the subject’s report of his or her father’s drinking, the conservatively strict cutoff (FMAST score >9) was used to minimize the false positives (Levenson et al., 1987).

The presence of alcohol-related problems were evaluated using the SCID-NP (Spitzer et al., 1990). Subjects who reached DSM-III-R criteria for alcohol and/or drug abuse/dependence were excluded from the study based on the original study criteria (Kampov-Polevoy et al., 2003a). Subjects who did not reach the full criteria for an AUD but still met at least one criterion were categorized as subjects with alcohol-related problems (n = 29; 18.4%). Subjects who did not meet a single DSM-III-R criterion for alcohol abuse or alcohol dependence were categorized as control subjects (n = 129; 81.6%).

Sweet taste test

To assess hedonic response to sweet taste, we used a standard sweet taste test (Kampov-Polevoy et al., 1997) that was conducted at the end of the visit, and at least 90 min after the last meal. Subjects had not chewed gum, drunk a flavored beverage or smoked for at least 1 h before the sweet taste test. During the test, 2 ml each of five concentrations of sucrose solution (0.05, 0.10, 0.21, 0.42 and 0.83 M) were presented five times in random order, for a total of 25 samples. For comparison, Coca-Cola Classic™ is a 0.33 M sugar solution. Subjects were instructed to sip the solution, swirl it around in their mouths and spit it out. They were then asked to rate the solution, rinse their mouth with distilled water and proceed to the next solution. To rate the sucrose solution sweet intensity, each subject was asked to rate: ‘how sweet was the taste?’ on a 200-mm analog scale. Each subject was then asked to rate each solution’s pleasurableness, answering the question: ‘how much do you like the taste?’, with the same analog scale. The two poles of this analog scale were ‘dislike it very much’ (scored as −100) and ‘like it very much’ (scored as +100). Average rating of pleasurableness of each sucrose solution was calculated. SL was defined as giving the highest pleasantness rating to one of the lower sucrose concentrations (0.05, 0.10, 0.21 or 0.42 M).

Statistical analysis

Summary statistics (mean ± standard deviation for continuous measures; counts and percents for categorical measures) were first computed. We used logistic regression models to systematically test whether NS score and SL/SDL status are associated with having alcohol-related problems, and whether these associations are independent of FH+, and from one another. We examined models with alcohol problems as the outcome, and tested each predictor individually, as well as combinations of predictors to assess the effects of specific predictors with adjustment for others. The predictors we examined were: SL vs. SDL, continuous NS score, high vs. low NS (> vs. ≤ gender-specific 70th percentile for NS score), a four-category variable based on the combinations of SL/SDL status and high vs. low NS and FH+ vs. FH−. We also examined whether SL/SDL status and NS are associated with FH status. Finally, we used analysis of covariance models to test whether the predictors are associated with the number of drinks consumed in a month and number of drinks consumed per episode. Number of drinks consumed in a month preceding the study was first log-transformed, so that the residuals conformed approximately to model assumptions (i.e. normality and homoscedasticity). All analyses were adjusted for gender. All statistical tests were performed using SAS software (Version 9.0, SAS Institute, Cary, NC, USA).

RESULTS

Characteristic of the sample

The study sample consisted of 158 subjects (39% males). The sample included 128 Caucasians, 14 African American, 9 Asian, 4 Native Americans and 3 Hispanic subjects. A total of 29 subjects (18%) were categorized as having alcohol-related problems. As shown in Table 1, individuals with alcohol-related problems (both men and women) are more likely to have an FH+, to have higher NS scores and to have higher alcohol intake (both in terms of drinks per drinking episode and drinks during last month). Men with alcohol-related problems are more likely to be SL. In women, this trend did not reach statistical significance (P = 0.097). SL and SDL individuals were able to discriminate the concentrations of sucrose equally, so no further analyses of sweet intensity were conducted.

Relationship between SL/SDL status and NS score

We first tested whether NS (total NS score ranged from 4 to 33 with mean = 16.6 ± 5.83) and SL/SDL status are associated traits. There was no evidence for association between SL/SDL and NS (P > 0.05).

Relationship between SL/SDL status, NS score and FH+ status

SL status was associated with an increased odds of having FH+ status before (odds ratio [OR] = 2.7, P = 0.0030) and after (OR = 2.7, P = 0.0042) adjustment for NS. A one-unit
increase in NS score is associated with having FH+ status, with an estimated OR of 1.1 ($P < 0.01$) both before and after adjustment for SL/SDL status.

**Relationship between SL/SDL status, NS score and alcohol drinking behaviors**

We observed no statistically significant evidence for an association between SL/SDL status and alcohol drinking behavior neither in terms of drinks per month or drinks per drinking day ($P > 0.05$). NS score was positively associated with both drinks per month ($P = 0.0054$) and drinks per drinking day ($P = 0.021$).

**Relationship between SL/SDL status, NS score and alcohol-related problems**

SL/SDL status and NS were significantly associated with alcohol problems both before and after (i.e., independently) adjustment for each other. SL (vs. SDL) is associated with having an alcohol-related problem, with an OR of 5.3 (95% CI 1.9–15.1; $P = 0.0016$) before adjustment for NS and an OR of 5.8 ($P = 0.0021$) after adjustment for NS (Fig. 1). A one-unit increase in NS score is associated with having an alcohol-related problem, with an OR of 1.2 ($P < 0.0001$) and no attenuation after adjustment for SL/SDL status. Having an NS score above the gender-specific 70th percentile is associated with having an alcohol-related problem, with an OR of 5.8 (95% CI 2.4–13.9; $P = 0.0001$) before adjustment for SL/SDL status and 6.4 ($P = 0.0001$) after adjustment for SL/SDL status (Fig. 1). Because some cell sample sizes were modest, we confirmed these finding with Fisher’s exact test, and the results were very similar (data not shown).

**Associations of FH+ status with alcohol-related problems**

We also evaluated the association of FH+ status, which to date is considered to be one of the best predictors of alcoholism risk (Merikangas, 1990), and alcohol-related problems. In our sample, having an FH+ status is significantly and positively associated with alcohol-related problems (OR = 5.7, $P = 0.0007$) before adjustment for SL/SDL status and NS. The positive association remains statistically significant after adjustment for SL/SDL status (OR = 4.8, $P = 0.0031$) and NS score (OR = 3.6, $P = 0.018$), individually, but loses statistical significance after adjustment for both (OR = 2.9, $P = 0.063$). Conversely, both SL/SDL status (OR = 4.4, $P = 0.0071$) and NS (OR = 1.2, $P = 0.0002$ for continuous; OR = 4.8, $P = 0.0009$ for dichotomous) remain statistically significant after adjusting for family history.

**Interaction between SL/SDL status and NS score and its association with alcohol-related problems**

Further analysis indicates that the combination of SL status and an NS score greater than the gender-specific 70th percentile ($n = 15$ with alcohol-related problems; $n = 11$ without alcohol-related problems) is associated with an OR of 27.5 (95% CI 6.4–118.0) for having an alcohol-related problem, vs. SDL and NS score less than or equal to the gender-specific 70th percentile ($n = 3$ with alcohol-related problems; $n = 49$ without alcohol-related problems; Fig. 1). The estimated ORs for having one risk factor but not the other were substantially smaller (OR = 3.1 for SL; OR = 2.2 for high NS). This analysis indicates that a combination of SL/SDL status and NS has a high predictive value regarding alcohol-related problems in young adults.

**Table 1. Sample descriptives by gender and presence/absence of alcohol-related problems**

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No alcohol-related problems ($n = 84$)</td>
<td>With alcohol-related problems ($n = 13$)</td>
<td>$P$ for diff.</td>
<td>No alcohol-related problems ($n = 45$)</td>
</tr>
<tr>
<td>Age</td>
<td>22.1 (3.4)</td>
<td>20.2 (2.2)</td>
<td>0.035</td>
<td>22.7 (2.6)</td>
</tr>
<tr>
<td>Paternal history of alcoholism</td>
<td>42 (50%)</td>
<td>12 (92%)</td>
<td>0.0043</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>NS score</td>
<td>14.8 (5.5)</td>
<td>21.9 (6.8)</td>
<td>0.0006</td>
<td>16.7 (5.1)</td>
</tr>
<tr>
<td>SL</td>
<td>44 (52%)</td>
<td>10 (77%)</td>
<td>0.097</td>
<td>19 (42%)</td>
</tr>
<tr>
<td>Drinks last month</td>
<td>8.8 (10.7)</td>
<td>28.0 (26.6)</td>
<td>0.0049</td>
<td>15.4 (16.5)</td>
</tr>
<tr>
<td>Drinks per episode</td>
<td>2.7 (1.6)</td>
<td>4.0 (2.3)</td>
<td>0.043</td>
<td>3.5 (2.4)</td>
</tr>
</tbody>
</table>

*χ² tests were used for dichotomous traits, and Wilcoxon non-parametric tests were used for continuous traits.

**Fig. 1.** Comparison of individual predictors for alcohol-related problems ($n = 158$).
Gender-specific analysis of the results

Finally, we conducted gender-specific analysis of the data. In gender-stratified analysis, SL status was not significantly associated with alcohol-related problems ($P = 0.11$) in females, whereas it was associated in males ($P = 0.0055$). NS (dichotomized at the gender-specific 70th percentile NS score in males $= 21$ and in females $= 18$) was significantly associated with alcohol-related problems in both females ($P = 0.0025$) and males ($P = 0.0055$). As in the gender-combined analysis, $P$-values and coefficients did not appreciably change for either SL status or NS in models adjusting for the other term, indicating that the effects of the two measures are independent. The sample size was too small to test for the effects of the combination of SL and NS on alcohol-related problems by gender.

DISCUSSION

This study extends previous research exploring the relationship between the hedonic response to sweet taste and alcohol use, problems and disorders. Hedonic response to sweet taste is a stable heritable trait (Keskitalo et al., 2007; Mennella et al., 2005) with phenotypic differences noted in infancy (Steiner et al., 2001) that persist as children become young adults (Desor and Beauchamp, 1987). Two major types of hedonic response to sweet taste have been noted in humans (Thompson et al., 1976): the SL pattern is characterized by increased liking as the concentration of sucrose increases, though this levels off in the 0.8–1.0 M range, and the SDL pattern is characterized by an increase in the liking for sucrose (or other sweet tastes) up to 0.2–0.4 M, followed by a breakpoint after which preference decreases as concentrations increase. In adults, hedonic response to sweet taste is stable over time (Kampov-Polevoy et al., 2003b).

Hedonic response to sweet taste, like all pleasurable experiences with both natural and drug-related rewards, is associated with an increased dopamine release in the nucleus accumbens. Sweet-tasting substances (both caloric and non-caloric sweeteners) stimulate the sweet taste receptors on the gustatory neurons on the surface of the tongue that polysynaptically leads to activation of μ-opioid receptors on γ-aminobutyric acid interneurons in the ventral tegmental area that are thought to cause a disinhibition of dopamine cell firing in the nucleus accumbens (Lemon et al., 2004). Microdialysis studies show a robust rise in extracellular accumbens dopamine levels following exposure to sweet tastes (DiChiara et al., 1999). Recently, Pecina and Berridge (2005) have shown that the perception of pleasantness of sweet taste in rats is strongly influenced by μ-opioid receptor activation in a single cubic millimeter site localized in the rostrodorsal quarter of the medial shell of the nucleus accumbens indicating very tight neuroanatomical localization of the hedonic response to sweet taste.

Animal studies indicate that stimulation of the endogenous opioid system shifts the sweet preference/aversion curve left toward preference for a weaker sweet taste (Calcagnetti and Reid, 1983), and its blockade with opiate receptor antagonists shifts the curve toward preference for more concentrated sweet solutions (i.e. SL: Leventhal et al., 1995). Therefore, sweet preference may serve as an index of activity of the brain opioid system with preference to stronger sweet taste, indicating a lower level of its basal activity. It is of interest, therefore, that the SL phenotype may provide information regarding the response to the opioid antagonist naltrexone in alcohol dependence (Garbutt et al., 2009).

Hedonic response to sweet taste has been associated with alcohol intake in animals and with AUDs in humans. Initially, this phenomenon was demonstrated in rodents by showing a high correlation between consumption of saccharin solution and alcohol intake. For example, Belknap et al. (1993) showed a high genetic correlation ($r = 0.77$) between consumption of saccharin and alcohol solutions in 15 inbred strains of mice. Later, Sinclair et al. (1992) showed that rats genetically selected for high-alcohol intake prefer stronger sweet taste than rats selected to avoid alcohol.

In humans, hedonic response to the sweet taste is associated with familial alcoholism. Several groups have independently shown that the preference for stronger sweet taste is more prevalent among children of alcoholics regardless of their drinking status (Kampov-Polevoy et al., 2001, 2003a,b; Krahn et al., 2006; Pepino and Mennella, 2007; for conflicting evidence, Kranzler et al., 2001). However, despite the association of the SL phenotype with an FH+, the SL/SDL status by itself is a weak predictor for a diagnosis of alcohol dependence in clinical samples (Kampov-Polevoy et al., 1999, 2001, 2003b; Wronska et al., 2007). These findings led us to the hypothesis that for prediction of risk for developing alcohol-related problems and alcoholism, SL/SDL status may need to be combined with other risk factors. Our previous studies (Kampov-Polevoy et al., 1998, 2004) conducted in two separate clinical samples showed that a combination of SL/SDL status with the personality trait of NS greatly enhanced the identification of patients with alcohol dependence.

NS is a trait contained within the broader concept of the externalizing spectrum (Krueger et al., 2007). Numerous longitudinal studies have shown that NS and related externalizing spectrum traits, such as behavioral disinhibition, behavioral under control and deviance proneness, can be antecedents of substance use, abuse and dependence (Masse and Tremblay, 1997) facilitating experimentation and abuse of a wide range of substances and, as a result, lead to early onset of alcohol-related problems (Finn et al., 2000; Masse and Tremblay, 1997; Wills et al., 1994). However, although alcoholics consistently have higher NS score than nonalcoholics, most studies failed to establish an association between NS and genetic risk of alcoholism (for review, see Howard et al., 1997). Recently, Grucza et al. (2006) showed that NS modulates the level of the alcoholism risk in high-risk families with high NS magnifying this risk and low NS acting as a protective factor. At the same time, there was no effect of NS on the level of alcoholism risk in the low-risk families. Similar results have been reported by Schuckit and Smith (2006a,b), who showed that the low level of response to alcohol interacts with externalizing symptoms to mediate the relationship between an FH+ and alcohol outcomes. As was mentioned earlier, our own studies (Kampov-Polevoy et al., 1998, 2004) showed that NS strongly enhances the predictive value of SL regarding the AUDs in a clinical sample. For example, the estimated odds of being an alcoholic, on average, increase by 11% as the NS score increases by one point in SL but not SDL subjects (Kampov-Polevoy et al., 2004). A combination of NS and the hedonic response to the sweet taste was able to predict alcoholic vs. nonalcoholic group status at 65% sensitivity and
94% specificity and correctly classified 85% of subjects (Kampov-Polevoy et al., 1998). The results of these studies led us to hypothesize that high NS, a trait that promotes experimentation with alcohol and excessive drinking, when combined with SL, a trait that may identify sensitivity to hedonic stimuli such as alcohol, will increase the risk for having alcohol-related problems.

The results of the present study provide initial support to this hypothesis. It was shown that NS and SL/SDL status are independent phenotypes associated with FH+. As expected, NS (but not SL/SDL status) is associated with the level of alcohol drinking both in terms of a number of drinks per drinking episode and a total number of drinks during the month preceding the study. This finding provides support to our hypothesis that SL/SDL status does not facilitate alcohol drinking per se. On the other hand, NS does facilitate such behavior. Both SL status and high NS score significantly increased the individual risk of having alcohol-related problems—similar to that predicted by FH+ status. The combination of SL status and high NS significantly increased the likelihood of having alcohol-related problems yielding an OR of 27. One interpretation of these results is that high NS facilitates experimentation and use of alcohol and when this occurs in the context of possible increased susceptibility to the rewarding effects of alcohol as seen in the SL phenotype, the development of alcohol-related problems is much more likely.

The present findings should also be viewed in the context of efforts to identify the genetic and phenotypic underpinnings of AUDs. Currently, on the order of 50 or more genes have been associated with alcohol dependence and many more are likely to be identified. Furthermore, a number of endophenotypes related to alcohol dependence have been characterized, and the genetic basis of these endophenotypes is being elaborated. To understand the diversity and pathophysiology of AUDs, it will be necessary to understand how these various risk factors interact with one another to lead to particular forms of alcoholism that may vary in both clinical course and response to treatment. On the basis of the present study and previously reported work, high NS and the SL phenotype need to be considered in the overall effort to develop a more complete description of the pathophysiology of the alcoholisms.

Study limitations
The current study has several limitations that need to be noted: (a) the reported findings were derived from post hoc analyses rather than from an a priori hypothesis, (b) groups were not balanced by gender or presence/absence of alcohol-related problems, (c) the subsample of subjects with alcohol-related problems was relatively small and (d) individuals with AUDs were excluded from the sample. These limitations will need to be addressed in future work.

In summary, we have found that the SL phenotype and high NS are independent factors that contribute to an increased likelihood of having alcohol-related problems. Furthermore, the combination of the two factors greatly increases the odds for alcohol-related problems. If confirmed, these findings will expand our understanding of the processes that lead to AUDs and may offer clues to assist with diagnosis, prognosis and treatment.

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