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SWEET LIKING AND FAMILY HISTORY OF ALCOHOLISM IN HOSPITALIZED ALCOHOLIC AND NON-ALCOHOLIC PATIENTS

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Abstract — The present study was designed to test the hypothesis that preference for stronger sweet solutions may be associated with the genetic risk for alcoholism. Thirty-two male patients with alcohol dependence admitted for alcoholism in-patient treatment and 25 non-alcoholic control subjects were used in the study. Hedonic response to sweets was evaluated using the sweet preference test. Family history of alcoholism was evaluated using a Russian version of the Michigan Alcoholism Screening Test modified for the assessment of the alcohol-related behaviour of the subject's biological father. Similar to our previous findings, alcoholics were far more likely to prefer the highest offered sucrose concentration (0.83 M), compared to non-alcoholic controls. Such preference was determined by two factors: positive family history of alcoholism and alcoholic status. Statistically, these factors contributed to the likelihood of preferring sweet solutions independently. Therefore, the effects of these factors may enhance each other. These findings support the hypothesis that preference for a stronger sweet solution is associated with a paternal history of alcohol dependence and may reflect a genetic predisposition to alcoholism.

INTRODUCTION

There is strong evidence that genetic influences are important in the aetiology of alcoholism. Twin and adoption studies have generally found evidence of moderate to strong genetic influences (heritability estimates of 40–60%) on alcoholism (Goodwin *et al*., 1973; Cloninger *et al*., 1981; Hrubec and Omenn, 1981; Cadoret *et al*., 1985, 1987; Allgulander *et al*., 1991, Pickens *et al*., 1991; Romanov *et al*., 1991; McGue *et al*., 1992; Heath *et al*., 1997; Kendler *et al*., 1997; Prescott *et al*., 1999). The search for phenotypic markers of risk for alcoholism has led to the identification of several biological variables, including reduced behavioural responses to alcohol (Schuckit and Gold, 1988), a reduced P3 component of event-related brain potential (for review see: Begleiter and Porjesz, 1999) and lowered activity of the enzyme monoamine oxidase type B (MAOB) in platelets (Devor *et al*., 1994). However, despite the existence of intensive investigation in this field, health professionals do not have a test gauging the risk of developing alcoholism, indicating that further research in this area is needed.

A variety of studies performed in different mouse and rat strains/lines showed a close association between the consumption of sweet solutions and alcohol intake and there is evidence suggesting a genetic linkage between sweet solution consumption and subsequent alcohol intake (for review see: Kampov-Polevoy *et al*., 1999). In addition to a high intake of sweet solutions, alcohol-preferring rats were shown to prefer stronger concentrations of sweets compared to alcohol-avoiding rats (Sinclair *et al*., 1992). Human studies have also found an association between a preference for stronger sweet solutions and alcohol dependence (Kampov-Polevoy *et al*., 1997). Furthermore, sweet-liking [i.e. preferring the strongest offered sucrose concentration (0.83 M)] alcoholics seem to have a personality profile similar to that described by Yoshino *et al*. (1994) in alcoholics with the familial subtype of alcoholism (Kampov-Polevoy *et al*., 1998). The hypothesis has been made that preference to stronger sweet solutions may be associated with a genetic vulnerability to alcoholism. To test this hypothesis, the hedonic response to sweets and the family history for alcoholism were evaluated in patients with alcohol dependence and control non-alcoholic subjects.

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SUBJECTS AND METHODS

Subjects

The study group consisted of 32 male subjects who met the DSM-III-R (American Psychiatric Association, 1987) criteria for alcohol dependence [age 37.6 ± 1.4 years (mean ± SEM)] admitted for treatment to Psychiatric Hospital #6 at St Petersburg, Russia and 25 control male subjects (age 32.0 ± 1.8 years; difference from alcoholic group was statistically significant, $P = 0.02$) recruited among the patients undergoing treatment or rehabilitation in the general hospital at St Petersburg, Russia [departments of ophthalmology and neurosurgery (patients with a peripheral nerve damage)]. The patients did not receive any medications for at least 24 h prior to testing.

During the first 3 days after admission, alcoholic patients were detoxified using a standard protocol of detoxification (for procedure description, see Westermeyer, 1986). On the fifth day after admission, the diagnosis of alcohol dependence was re-assessed using the DSM-III-R-based criteria by the trained interviewer (M.T.). Control subjects were also screened for alcohol-related problems and those who met the DSM-III-R criteria for alcohol misuse and/or alcohol dependence were excluded from the study. A complete description of the study was offered to all subjects, and written informed consent was obtained. The protocol was approved by the Ethical Committee of Pavlov Medical University, St Petersburg, Russia. No subjects had any evidence of significant or serious medical illness, including liver cirrhosis or endocrinopathy. At the time of testing, several alcoholic subjects exhibited mild elevations in serum alanine aminotransferase or aspartate aminotransferase,

compatible with a history of recent heavy drinking. Bilirubin levels were normal in all cases. None of the subjects received any medication during the study. All subjects in both the alcoholic and control groups were smokers (i.e. they smoked at least one pack of cigarettes every day for at least a year).

Tests

Sweet preference test. The sweet preference test was conducted in the morning at least 1 h 30 min after breakfast (8:30–9:00), and 1 h after smoking and teeth cleaning. Five concentrations of sucrose solution (0.05, 0.10, 0.21, 0.42 and 0.83 M) were each 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, swish 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 analogue scale, with one extreme labelled 'Not sweet at all,' and the other labelled 'Extremely sweet.' Each subject was then asked to rate each solution's pleasurableness, answering the question: 'How much do you like the taste?' with the two poles of this analogue scale being 'Disliked very much' and 'Liked very much' (for details see: Kampov-Polevoy *et al*., 1997, 1998). Sweet liking was defined as preferring the highest offered sucrose concentration, 0.83 M, and sweet disliking was defined as preferring one of the lower sucrose concentrations (0.05, 0.10, 0.21 or 0.42 M).

Family history of alcoholism. This was evaluated using a Russian version of the Michigan Alcoholism Screening Test (MAST) (Selzer, 1971) modified for the assessment of the alcohol-related behaviour of the subject's biological father (Levenson *et al*., 1987). In order to increase the semantic equivalence of the instrument, the back-translation method was used. For this purpose, a bilingual person translated the MAST from English to Russian, and another bilingual person translated the material from Russian back to English in order to assure accuracy of the original translation. Because the designation of risk for alcoholism was based on a subject's report of his father's drinking problems, the conservatively strict cut-off (≥9) was used to minimize false positives as suggested by Levenson *et al*. (1987). According to this study, there was a strong correlation [$r(75) = 0.85$] between the MAST scores completed by the subjects and by their biological fathers.

Procedures

Alcoholic subjects. Diagnostic interviews were completed on the fifth day after admission, and sweet preference tests were performed on the fifth and 14th days after admission.

Control subjects. In control subjects, the data regarding the family history of alcoholism and sweet preference test were collected between days 10 and 15 after admission; however, each subject completed the tests on the same day.

Statistical analysis. The rates of sweet liking were compared between control subjects and alcoholics using the χ^2-test. Between-group comparisons were based on the analysis of variance, with Fisher's LSD post-hoc comparisons.

Stability of the results of the sweet preference test in an individual was tested by assessing the agreement between the results using a weighted kappa measure. There were two sweet preference tests administered for the alcoholic subjects. The closeness of agreement between these tests was described by the kappa measure. Cohen's kappa has been widely used in categorical data analysis to determine the agreement between two ratings of the same event. Using measures of association (correlation), instead of agreement, is not appropriate in such a case, because the Pearson correlation coefficient, which is used to measure the strength of the linear relationship between two numerical variables, does not show agreement. For example, if the subjects always chose a sucrose concentration one level higher for the second, than for the first, test the association would be high (e.g. $r = 1$) whereas the agreement would be poor. Cohen's kappa shows how much more observations are on the main diagonal than would be expected if the variables were independent. The weighted kappa measure considers how far the observations are from the main diagonal.

The relationship between sweet preference, alcoholism (alcohol dependence), and family history of alcoholism was studied using the proportional odds logistic regression models. The model for the *J*-category response is described by Agresti (1990) as:

$$L_j(\mathbf{x}) = \alpha_j + \beta'\mathbf{x}$$

$$J = 1 \ldots J - 1$$

where L_j are cumulative logits defined as

$$Lj(\mathbf{x}) = \ln \left\{ \frac{\pi_1(\mathbf{x}) + \ldots + \pi_j(\mathbf{x})}{\pi_{j+1}(\mathbf{x}) + \ldots + \pi_j(\mathbf{x})} \right\}$$

with $\{\pi_1(\mathbf{x}), \ldots, \pi_j(\mathbf{x})\}$ denoting the response probabilities as the value $\mathbf{x}$ for the set of explanatory variables. This model utilizes the presence of a latent continuous response variable. The model assumes that there is the same effect of an explanatory variable on the odds below category *j* for any *j*. The set of the response categories does not have to be unique. The invariance to the choice of the response categories property of the model allows one to use different response categories without producing a significant effect on the model.

Comparisons of the nested models showed that the main effects model:

$$L_j(\mathbf{x}) = \alpha_j + \beta_1 x_1 + \beta_2 x_2$$

is the most appropriate for describing the data.

RESULTS

Sweet preference test

Both alcoholics and control subjects were able to effectively discriminate between the different concentrations of sucrose, generating appropriate concentration–response curves. Sweet preference seems to be a stable trait: there was high agreement: weighted kappa = 0.65 [95% confidence interval (CI): 0.43–0.87] between the results of the two sweet tests in alcoholics. The proportion of individuals preferring different sucrose concentrations is presented in Fig. 1 (for alcoholics,

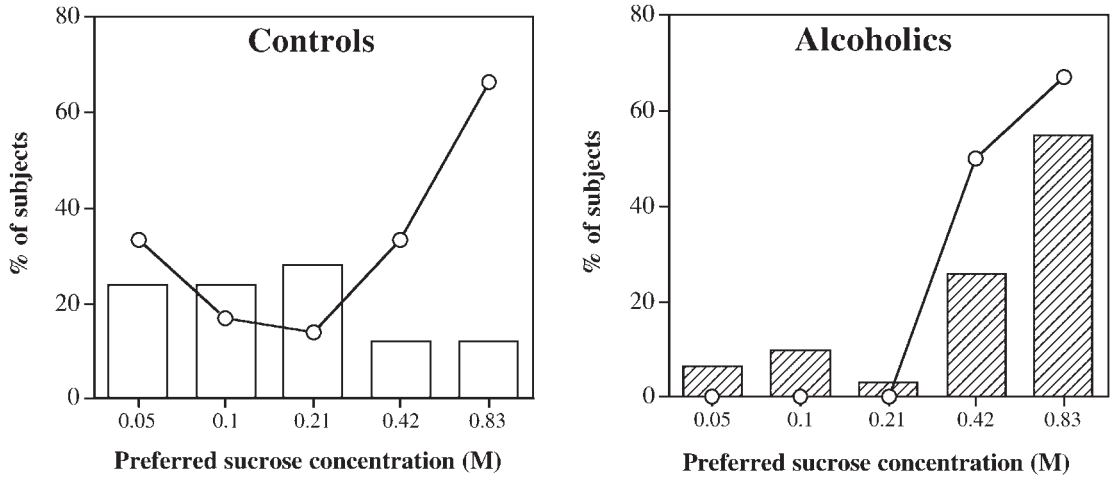

Fig. 1. Preference for different sucrose concentrations (bar graph) and prevalence of positive family of alcoholism (line graph) among non-alcoholic subjects and detoxified alcoholic subjects.
Bar graph represents percentage of subjects preferring given sucrose concentration in a subject group. Line graph represents percentage of subjects with positive family history of alcoholism among subjects preferring each particular sucrose concentration.

the data presented for the second sweet preference test on the 14th day after admission).

Alcoholics were far more likely to prefer the highest offered sucrose concentration (0.83 M), compared with non-alcoholic controls (46 vs 12% respectively, $P = 0.048$ on the fifth day after admission, and 55 vs 12%, respectively, $P = 0.001$ for the χ^2-test for a two-way contingency table) on the 14th day after admission.

Family history of alcoholism

The data regarding family history of alcoholism was collected for 29 subjects with alcohol dependence (alcoholics) and 25 control subjects (total $n = 54$). Some 50% of alcoholic patients and 26% of control subjects were shown to have alcoholic fathers (Fisher's exact test $P = 0.1$). The proportion of individuals with a positive family history of alcoholism (FH+) (when the biological father had alcoholism) preferring different sucrose solutions among alcoholics and controls is presented in Fig. 1 (for alcoholics, the data are presented for the second sweet test).

The data ($n = 54$) were analysed by fitting the proportional odds logistic regression models with the two binary explanatory variables, alcoholics vs controls and FH+ vs FH–. The response variable was represented with five categories corresponding to 0.05, 0.1, 0.21, 0.42 and 0.83 M concentrations of sucrose solution.

Both of the main effects (i.e. being an alcoholic and having positive family history of alcoholism) produced significant increase in the model fit. For example, in both the FH+ and FH– groups, alcoholic subjects had the odds of preferring stronger sweet solutions 5.8 times greater than control subjects (95% CV: 2.0–18.2). Furthermore, in both alcoholic and control groups, the odds for FH+ subjects preferring stronger sweet solutions were 3.1 times higher than for FH– subjects (95% CV: 1.0–9.5). However, the interaction of these effects was shown to be statistically non-significant.

Therefore, it can be concluded that the chances of preferring stronger sweet solutions seem to increase in alcoholics and in subjects with a genetic predisposition to alcoholism, estimated by a positive family history of alcoholism.

DISCUSSION

This study extends previous research exploring the relationship between preference for sweet solutions and excessive alcohol intake. Since Ramirez and Sprott (1978) and Forgie *et al*. (1988) demonstrated a relationship between sweet intake and alcohol intake (by noting that alcohol-preferring C57BL mice consume more saccharin solution than alcohol non-preferring DBA/2J mice), several studies have confirmed these findings in mice (Belknap *et al*., 1993; Bachmanov *et al*., 1996) and rats (Kampov-Polevoy *et al*., 1990, 1994, 1995; Gosnell and Krahn, 1992; Sinclair *et al*., 1992; Overstreet *et al*., 1993, 1997; Bell *et al*., 1994; Gahtan *et al*., 1996; Dess *et al*., 1998; Koros *et al*., 1998). Several reports suggest a genetic link between the consumption of sweets and alcohol intake (Belknap *et al*., 1993; Overstreet *et al*., 1993; Bachmanov *et al*., 1996; Stewart *et al*., 1997; Bice *et al*., 2000; Foroud *et al*., 2000).

In addition to a high intake of sweet solutions, rats genetically selected for high alcohol intake were shown to prefer stronger concentrations of sweets compared to alcohol-avoiding rats. For example, alcohol-preferring AA rats showed an increasing preference for increasing saccharin concentrations in the range from 1 to 2048 mg/l concentrations, whereas alcohol non-preferring ANA rats showed a relatively high preference for lower saccharin concentrations (from 1 to 64 mg/l) with a decreasing preference for stronger saccharin solutions (Sinclair *et al*., 1992). Similar patterns of sweet preference were described in human subjects. For example, Thompson *et al*. (1976) showed that most individuals can be classified into one of two categories: sweet likers reporting increasing pleasurable response to increasing concentrations of sucrose across the range of 0.0 to 2.0 M, and sweet dislikers, who may show an increasing pleasurable response only up to a 0.2 M

concentration and then show decreasing pleasurable responses as sucrose concentrations rise above 0.6 M. These two patterns of the hedonic response to sweets were described in humans in a number of studies (Pangborn, 1970; Thompson *et al*., 1976; Cabanac, 1979; Looy and Weingarten, 1991; Looy *et al*., 1992). These patterns were shown to reflect qualitative differences in taste perception, rather than in a cognitive reaction based on the associations between the taste and attitudes toward, or social acceptability of, liking sweet foods (Looy and Weingarten, 1991). In adults, sweet preference appears to be resistant to different metabolic manipulations such as lunch, dinner, dieting or overnight fasting (Drewnowski and Greenwood, 1983) and relatively stable over time (Thompson *et al*., 1976; Looy and Weingarten, 1991). However, it should be noted that there is evidence indicating a downward shift in the most preferred sucrose concentration after puberty (Desor *et al*., 1975; Desor and Beauchamp, 1987) that should be taken into consideration when planning longitudinal studies.

Similar to the animal data (Sinclair *et al*., 1992), there are indications that, in humans, preference for stronger sweet solutions may be associated with alcoholism. Our own study showed that the prevalence of sweet-liking individuals (preferring the highest offered 0.83 M sucrose solution) was found to be higher (65%) among alcoholics than among non-alcoholic control subjects (16%; $P = 0.0003$, Fisher's exact test) (Kampov-Polevoy *et al*., 1997).

In this study the sweet preference test was administered to alcohol-dependent individuals twice: on the fifth and 14th days after admission. The high agreement (weighted kappa = 0.65) between the results of these two tests supports the previous suggestion that sweet preference is relatively stable over time (Thompson *et al*., 1976; Looy and Weingarten, 1991). The majority of alcohol-dependent individuals (55%) preferred the 0.83 M sucrose solution, compared to 12% in the non-alcohol-dependent subjects, which is similar to the results obtained in a different patient population (Kampov-Polevoy *et al*., 1997, 1998).

Our previous study (Kampov-Polevoy *et al*., 1998) suggested that the personality profile of sweet-liking alcoholics is similar to that described in male alcoholics with a highly heritable Type B clinical subtype of the disease (Yoshino *et al*., 1994). This finding led us to postulate that sweet liking may be associated with a genetic vulnerability to alcoholism. To test this hypothesis, we evaluated in the present sample the family history of alcoholism among biological fathers of alcoholics as well as among biological fathers of control non-alcoholic subjects. It was shown that, in both the alcoholic and control groups, the odds for FH+ subjects to prefer stronger sweet solutions were approximately three times higher than for the FH– subjects, which is consistent with the hypothesis that the preference for stronger sweet solutions is associated with the genetic risk of alcoholism. However, it is important to keep in mind that positive family history of alcoholism may contribute to higher sweet preference through non-genetic mechanisms as well (e.g. families of alcoholics tend to have lower family income and, therefore, are more likely to have poorer diet and unhealthy food habits; children of alcoholics may start drinking alcohol at an earlier age and consume more alcohol on social occasions, etc.). These environmental factors have not been controlled in the present study. The fact that not all FH+ subjects preferred the strongest offered sucrose solutions and, conversely, some FH– individuals did prefer this solution, agrees with the view that alcoholism risk may relate either to the effect of multiple genes (a polygenic inheritance), or the expression of a dominant factor may be modified by a number of other important variables (i.e. incomplete expression) (for discussion, see Schuckit, 1991).

The results of this study seem to be at odds with the recent report by Kranzler *et al*. (2000) indicating that both FH+ and FH– individuals with no individual history of alcohol-related problems are sweet dislikers (i.e., prefer 0.05, 0.10, 0.18 and 0.42 M sucrose concentrations). These results led these authors to the conclusion that there is no association between the preference for stronger sweet solutions and a genetic risk of alcoholism. However, the thorough analysis of this report suggests an alternative explanation of the results. The literature suggests that individuals with a familial form of alcoholism have an early onset of alcohol-related problems ['before the age of 25' according to Cloninger *et al*. (1988) or 'at the age of 21' according to Babor *et al*. (1992)]. Considering that the average age of subjects in the study by Kranzler *et al*. (2000) was 25 years and that individuals with alcohol-related problems had been excluded from the study, it is reasonable to suggest that subjects at high risk for alcoholism were excluded from the study. In this case, the FH+ group was represented by individuals who did not inherit the risk for alcoholism from their fathers and would be expected to show high prevalence of sweet dislikers, thus supporting our hypothesis. However, more studies are needed to resolve this issue.

The reason for the close association between preference for concentrated sweet solutions and positive family history of alcoholism is not known. The literature provides some evidence that the neurobiological mechanisms underlying the hedonic response to alcohol and sweets may be mediated, at least partially, by similar brain systems. Though a review of this area is beyond the scope of this paper, we would like to refer to a number of reports demonstrating the parallel neurochemical actions of sweets and alcohol. For example, there is evidence that both sweet substances and alcohol enhance the activity of putative dopaminergic reward systems (Smith and Schneider, 1988; Weiss *et al*., 1993; Panocka *et al*., 1995; Di Chiara *et al*., 1996) and endogenous opioid systems (Brown and Holtzman, 1979; Dum *et al*., 1983; Dum and Hertz, 1984; Gatto *et al*., 1984; Fantino *et al*., 1986; Acquas *et al*., 1993; Froehlich and Li, 1994). Furthermore, there are reports indicating differences in functioning of the brain opioid system of FH+ and FH– individuals. For example, the beta-endorphin response to alcohol which seems to be under strict genetic control (Froehlich *et al*., 2000) has been found to be different in FH+ versus FH– subjects (Gianoulakis *et al*., 1989, 1996) and was suggested as a potential biomarker that can be used to identify individuals who are at an elevated genetic risk for developing alcoholism (Froehlich *et al*., 2000).

Our study also showed that the odds of liking stronger sweet solutions are approximately six times higher for alcoholics than for control subjects regardless of their FH status. This finding indicates that preference for stronger concentrations in alcoholics may be determined not only by genetic factors, but may be influenced by environmental factors that are not associated with an alcoholic father. This finding is in agreement with a recent report indicating that chronic (31 weeks) alcohol consumption results in preference for stronger sucrose

solutions and higher sucrose intake in alcohol-preferring female rats (Stewart *et al*., 2000). The mechanism of this effect is not completely understood. However, it was suggested that the shift of sweet preference towards the stronger concentrations may result from a chemosensory adjustment of the olfactory system to excessive alcohol intake (Hirsch, 1997). Chronic alcohol intoxication is known to impair an olfactory ability (Mair *et al*., 1986) which, in turn, results in suppression of taste perception (for discussion, see Hirsch, 1997). It should also be noted that poor diet and unhealthy eating habits may contribute to the changes in perception of sweetness in alcoholic patients. To minimize the effect of dietary factors, for the main statistical analysis, we used the results of the second sweet preference test that was conducted on the 14th day after admission, i.e. when patients were stabilized on a standard hospital diet.

It is important to keep in mind that the positive family history of alcoholism and alcoholic status contribute to the likelihood of preferring sweet solutions independently. Therefore, one would predict that the effects of these factors will enhance each other.

In summary, the results of the present study are consistent with the animal (Sinclair *et al*., 1992) and human (Kampov-Polevoy *et al*., 1997, 1998) data indicating an association between preference for stronger sweet solutions and excessive alcohol intake. The fact that the present sample was significantly different from the sample used in previous clinical studies (Kampov-Polevoy *et al*., 1997, 1998) in terms of ethnic background and drinking culture suggests the generalizability of this finding. Preference for stronger sweet solutions seemed to be a relatively stable trait that did not significantly change during 14 days of in-patient treatment. We also found that positive family history of alcoholism, believed to indicate the involvement of genetic mechanisms (Schuckit, 1991), can be three times as frequent among sweet-liking, compared with sweet-disliking, individuals. This finding supports the hypothesis that sweet-liking may be associated with an elevated genetic risk for alcoholism. It was also found that alcoholic status may itself contribute to preference for stronger sweet solutions, which probably reflects the changes in sensory perception of sweetness as a result of excessive alcohol drinking.

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