Psychopharmacology (2001) 157:20–30
DOI 10.1007/s002130100741

ORIGINAL INVESTIGATION

Patricia J. Conrod · Jordan B. Peterson
Robert O. Pihl

Reliability and validity of alcohol-induced heart rate increase as a measure of sensitivity to the stimulant properties of alcohol

Received: 12 June 2000 / Accepted: 11 February 2001 / Published online: 7 June 2001

Abstract *Rationale:* Alcohol-induced heart rate (HR) stimulation during the rising limb of the blood alcohol curve reliably discriminates between individuals at differential risk for alcoholism, and appears to be a potential psychophysiological index of psychomotor stimulation from alcohol. *Objectives:* Three studies are presented which explore the reliability and convergent and discriminant validity of this alcohol response index. *Methods:* Young men with and without a multigenerational family history of alcoholism were administered a 1.0 ml/kg dose of 95% USP alcohol. Resting baseline cardiac and subjective measures were assessed before and after alcohol consumption. *Results:* Study 1 demonstrated that alcohol-induced HR stimulation was significantly and positively related to alcohol-induced changes in mood. Study 2 demonstrated that alcohol-induced HR stimulation was reliable across two alcohol administration sessions (r=0.33–0.66, P<0.01). Study 3 explored the relationship between the proposed index and measures of sensitivity to alcohol previously linked to genetic predisposition to alcoholism. Multiple regression analysis indicated that alcohol-induced HR increase and reduced subjective intoxication (measured using the Subjective High Assessment Scale) were both positively associated with alcohol-induced changes in mood states that have previously been shown to be sensitive to the effects of stimulant drugs and the reinforcing effects of alcohol. *Conclusions:* Sensitivity to alcohol-induced heart-rate stimulation during the ascending limb of the blood alcohol curve may be a useful and informative marker for understanding susceptibility to alcoholism.

P.J. Conrod (✉)
Department of Psychology, University of British Columbia,
2136 West Mall, Vancouver, BC, Canada V6T 1Z4
e-mail: pconrod@cortex.psych.ubc.ca

J.B. Peterson
Department of Psychology, University of Toronto,
Toronto, ON, Canada

R.O. Pihl
Departments of Psychology and Psychiatry, McGill University,
Montreal, QC, Canada

Keywords Alcohol sensitivity · Human responses · Reinforcement · Psychostimulation · Heart rate · Genetic predisposition to alcoholism

Introduction

The psychomotor stimulant theory of addiction suggests that the incentive properties of primary psychostimulants, such as cocaine and amphetamines, can be indexed by their ability to induce a motivational state which involves forward locomotion and activation of a dopamine reward circuitry in the medial forebrain bundle (Wise 1988; Wise and Bozarth 1987). Drugs of abuse with central nervous system depressant properties such as alcohol, opiates and barbiturates also have psychostimulant properties (DiChiara et al. 1992). Alcohol has dose-dependent and biphasic effects on locomotor activity (Pohorecky 1977; Friedman et al. 1980), and the locomotor-stimulant effects of alcohol also appear mediated (possibly indirectly through opiate mechanisms; DiChiara et al. 1992) by dopaminergic mechanisms (Dudek et al. 1984). Furthermore, research indicates that the anxiolytic effects of alcohol are mediated by separate brain structures (Wise and Bozarth 1987).

Activation of the mesolimbic dopamine system not only results in increased motoric behavior; autonomic arousal and changes in heart rate (HR) activity also result from such activation (Fowles 1983; Fowles et al. 1987; Wise and Bozarth 1987; Di Chiara et al. 1992). Increases in resting HR have been shown to be directly proportional to changes in the reinforcing properties of a stimulus, an effect that is also independent of the effects of anxiety responses and general motoric activity on HR (Fowles 1983). It has further been suggested that positive affective states result from activation of the mesolimbic reward system to facilitate learning of approach behavior toward the reward stimulus itself (Di Chiara et al. 1992), but that such states do not always result from activation of this system (Newlin 2000). Stress-induced behavioral activation, behavioral reinforcement, and drug-self administration all appear to be mediated by this system (Sorg 1992; Hemby et al. 1997) and have been shown to occur in the absence of positive subjective effects. Accordingly, current theories of addiction propose that the addictive liability of a drug is dependent upon its ability to produce “psychomotor stimulation,” but not necessarily “euphoria” (Newlin 2000), where “psychomotor stimulation” refers to the stimulating effects of a drug on mesolimbic dopamine activity (Wise and Bozarth 1987) and related patterns of behavioral (motoric) and autonomic (cardiac) activity (Reed et al. 1999).

A rather consistent finding resulting from research on alcoholic and young non-alcoholic individuals with a genetic predisposition to alcoholism is that they are characterized by a sensitivity to the stimulating effects of alcohol on resting HR (Finn et al. 1990; Conrod et al. 1995; Peterson et al. 1996; Newlin and Thomson 1999). We have proposed that alcohol-induced HR increase reflects a specific sensitivity to the psychomotor stimulant properties of alcohol and that genetic predisposition to alcoholism is partially mediated by a specific sensitivity to this very addictive property of alcohol (Peterson et al. 1996; Conrod et al. 1997b). A number of recent studies support this claim. Alcohol-induced increase in resting HR has been shown to co-vary with motoric reactivity to alcohol (Conrod et al. 1995), is alcohol-dose dependent (Stewart et al. 1992), mediated by opiate mechanisms (J.B. Peterson, P.J. Conrod, J. Vassileva, C. Gianoulakis, R.O. Pihl, unpublished data), specific to the ascending limb of the blood alcohol curve, enhanced with faster rate of alcohol ingestion (Conrod et al. 1997b), and correlated with a number of different drinking behavior measures (Conrod et al. 1997a), features that characterize stimulant drugs (Wise and Bozarth 1987; Sellers et al. 1991). However, the validity of alcohol induced HR increase as a measure of the psychomotor stimulant properties of alcohol is challenged by its apparent incongruity with the results of animal and human studies demonstrating an inverse relationship between alcohol-sensitivity and alcohol-preference or alcoholism vulnerability (e.g., Schuckit 1980, 1984; Krimmer and Schechter 1992; Schechter and Krimmer 1992; Rodrigez et al. 1993; see review by Newlin and Thomson 1990). For example, with regard to the human literature, sons of alcoholics have been shown to self-report decreased sensitivity to the subjective effects of alcohol relative to sons of non-alcoholics (Schuckit 1984), when subjective responses are measured using The Subjective High Assessment Scale (SHAS; developed by Judd et al. 1977).

The SHAS is a self-report scale that assesses the extent to which individuals experience various intoxicating effects of alcohol (e.g., clumsy, tired, nausea, high). Low responses to alcohol assessed by this scale have been shown to be predictive of the eventual development of alcohol dependence 8 years later (Schuckit and Smith 1996). However, despite its demonstrated discriminative and predictive validity, this measure of subjective intoxication is also greatly lacking in construct validity, in that it is unclear what the instrument actually measures. Integration of these two literatures is therefore difficult. Item analysis of the SHAS indicates that the scale reflects both positive (feel high) and negative (feel drowsy) alcohol effects, but appears weighted towards negative effects. A recent multivariate analysis indicated that a factor comprised mostly of negative items measured at 60–100 min post-alcohol consumption (descending limb) most optimally identified individuals at risk for the development of alcohol dependence (Schuckit and Smith 1996). Therefore, it is possible that the SHAS measures the negative or sedative effects of alcohol, rather than the euphoric or stimulant effects of alcohol.

A recent attempt to integrate the discrepant findings on sensitivity to alcohol in sons of alcoholics (Newlin and Thomson 1990) concluded that sons of alcoholics are more sensitive to the positive effects of alcohol that are specific the ascending limb of the blood alcohol concentration (BAC) curve, and less sensitive to the negative, potentially sedative, properties of alcohol which occur as alcohol is being eliminate from the body. However, there is some evidence to suggest that sons of alcoholics demonstrate reduced sensitivity to the subjective effects of alcohol along the rising and falling limbs of the BAC curve (Schuckit et al. 1996). It appears that insufficient information on the construct validity of both alcohol-induced HR increase and subjective intoxication limits our ability to integrate these findings and incorporate them into current theories of drug abuse vulnerability. To address this problem, the current series of studies will explore the validity of alcohol-induced HR increase as a measure of sensitivity to the stimulant properties of alcohol and its relationship to other subjective measures of alcohol sensitivity, including subjective intoxication.

Another approach to the assessment of subjective sensitivity to the effects of alcohol has been to observe individual differences in alcohol-induced changes in natural mood states. The Profile of Mood States (POMS; McNair et al. 1971) is one of the most widely used scales for assessing self-reported mood states and has also been shown to be sensitive to different drug effects (Johanson and Uhlenhuth 1980; Johanson and de Wit 1989). Various subscales of the POMS have been shown reliably to reflect individual differences in alcohol responses (Nagoshi et al. 1991) and to be differentially sensitive to the effects of drugs with various reinforcing properties (e.g., amphetamines and diazepam; Johanson and Uhlenhuth 1980; Johanson and de Wit 1989). One advantage to using this instrument is that various subscales have been shown to be sensitive to individual differences in alcohol-self administration (de Wit et al. 1987, 1989), thus indicating sensitivity to the reinforcing effects of alcohol, rather than just the subjective effects. Therefore, despite the recent development of new scales to assess the stimulant and sedative effects of alcohol (e.g., Martin et al. 1993), the validity of the POMS subscales remain unparalleled with respect to reflecting subjective sensitivity to the stimulant and reinforcing properties of alcohol. The POMs also possesses good face validity regarding alcohol-induced “psychomotor stimulation” as it differentiates drug-induced feelings of energy (lively, active, vigorous) from feelings of euphoria (joyful, cheerful, elated) or anxiety reduction (composed, serene, calm). These drug effects are not differentiated in other subjective measures of alcohol effects (e.g., Martin et al. 1993).

When subjective sensitivity to alcohol is assessed using self-report measures that have been shown to be sensitive to the stimulant and sedative properties of alcohol, vulnerability to heavier patterns of drinking behavior appear to be associated with a enhanced subjective sensitivity, rather than reduced subjective sensitivity. For example, research comparing heavy and light drinking subjects suggests that enhanced subjective sensitivity to the stimulating effects of alcohol and reduced subjective sensitivity to the sedative and intoxicating effects of alcohol characterize individuals who are prone to heavier drinking (Gabrielli et al. 1991; Holdstock et al. 2000). Another study demonstrated that participants who chose alcohol over placebo across seven beverage-choice sessions were initially shown to self-report more alcohol-induced elation and vigor and less fatigue and confusion on the POMS during an initial alcohol sampling session relative to individuals who subsequently chose placebo over alcohol (de Wit et al. 1987). Finally, individuals who are prone to more alcohol consumption in the laboratory also report greater sensitivity to the stimulating effects of alcohol, reduced sensitivity to the sedative effects (de Wit et al. 1989), and interestingly, also demonstrate greater alcohol-induced increases in resting HR (Conrod et al. 1997a). These findings suggest that alcohol-induced HR increase should correlate with subjective sensitivity to the stimulating effects of alcohol and reduced subjective sensitivity to alcohol-sedation and intoxication. The current investigation will, therefore, explore the validity of alcohol-induced HR increase as reflecting sensitivity to the stimulant properties alcohol by examining how change in HR differentially co-varies with changes in subjective stimulation, sedation and intoxication.

Another factor that challenges the validity of alcohol-induced HR as a measure of sensitivity to the stimulant effects of alcohol is that it has yet to be demonstrated as a stable trait that can be measured across a number of alcohol-administration sessions. Few studies have investigated the stability of responses to alcohol intoxication, and those that have indicated that repeatability of such measures, particularly HR responses, were generally very low and close to zero (e.g., Wilson and Nagoshi 1987; Nagoshi and Wilson 1989). However, conclusions from the Nagoshi and Wilson (1989) study are somewhat limited by the fact they the study involved highly variable test-retest intervals (ranging from 3 to 39 months) and alcohol response measures were tested at different points along the blood alcohol curve across the test-retest periods. Heritable influences on alcohol-induced HR increase have been shown to be robust as BACs are rising, prior to the BAC peak (Conrod et al. 1997b). Therefore, the second study of this series of studies will examine the reliability of alcohol-induced HR across a 2-week test-retest period within an experimental design that will allow for assessment of HR at specific points of intoxication.

Study 1

Study 1 was designed to investigate the correspondence between alcohol-induced HR increase and alcohol-induced changes in mood states previously shown to be differentially sensitive to the effects of stimulant drugs. Data for this study were collected as part of two previously published studies investigating the effects of familial history of alcoholism on psychophysiological responses to alcohol (Conrod et al. 1997a, 1998). In these two studies, subjects were administered the POMS-bipolar (Lorr 1982) before and at various points after consumption of a 1.0 ml/kg dose of alcohol, which provided an occasion to examine the validity of HR as a measure of sensitivity to the stimulant properties of alcohol. The present results were not previously reported.

Materials and methods

Subjects

Sample 1. Fifty men between the ages of 18 and 25 years were contacted by telephone following responding to newspaper advertisements, and were briefly screened for personal and familial alcoholic history using the brief Michigan Alcoholism Screening Test (brief Mast; Pokorny et al. 1972). Non-alcoholic men with multigenerational alcoholic family histories (MFH) and no history of familial alcoholism (FH–) were matched for drinking practices based on the frequency at which they consume alcohol to the point of legal intoxication (0.08% BAC), or above. Subjects were excluded from participation if they were currently suffering from a medical condition for which alcohol consumption was contra-indicated. A more detailed description of the subject selection procedure was reported previously (Conrod et al. 1997b). Sample 1 subjects participated in two drinking sessions, one fast rate (alcohol consumed in 5 min) and one slow rate (alcohol consumed in 20 min). The slow rate data (comparable to those obtained in sample 2) are presented here. One subject vomited following alcohol consumption; therefore, data for 49 subjects are available for this analysis.

Sample 2. Similar to the recruitment procedure for sample 1 (detailed above), subjects responded by telephone to the newspaper advertisements, and were briefly screened for familial risk and alcoholism status. Nonalcoholic MFH and FH– men between the ages of 18 and 30 years were included in the present study. Therefore, subjects were slightly older than those in sample 1 and were not matched for drinking history as they were in the previous sample. For a more detailed description of the screening proce-dure and measures used, refer to Conrod et al. (1997a). In total, 30 MFH men and 29 FH– men were included in this sample.

General procedure

All subjects were asked to refrain from consuming alcohol for 72 h before the study, and to avoid consuming breakfast on the day of the study. All subjects were instructed to present at the laboratory at 9:00 a.m. During their first session, they were asked to complete a number of questionnaires detailing their drinking history and personality characteristics. They were then seated in a comfortable chair, and attached to the polygraph. Following a 5-min resting baseline recording session for HR and mood they participated in a video game task. Subjects were randomly presented with one of three video games to play for 2 min, three times (with 1 min inter-game intervals). Each subject was assigned a performance criterion and instructed to attempt to reach that criterion within the 2-min game playing period. Subjects in sample 1 were not rewarded or punished for their performance, but were instructed to try as hard as possible to achieve the specified performance criterion. Subjects in sample 2 were randomly assigned to either receive monetary reward ($2.00) for good performance on each trial, or punishment (electrical shock) for poor performance on each trial.

All subjects in samples 1 and 2 consumed 1.0 ml/kg of 95% USP alcohol in 20 min. However, the details of alcohol administration differed somewhat across the two samples. In sample 1, alcohol was administered following the game play in the form of five “shots” of 40% vodka (equivalent to 1.0 ml/kg body weight of 95% USP alcohol in total), frozen to reduce taste intensity. Subjects received a shot at 0, 5, 10, 15 and 20 min. Shots were consumed in one swallow. Subjects in sample 2 participated in a sham alcohol taste-test (Schacter et al. 1968; adapted by Marlatt et al. 1973), described previously by Conrod et al. (1997a) immediately following the completion of the first video game, and were then administered a “topping-up” dose of orange juice and 95% USP alcohol, so that their total alcohol consumption within twenty minutes reached the required 1.0 ml/kg dose. Following alcohol consumption, all subjects (sample 1 and sample 2) relaxed for 10 min to allow time for alcohol absorption. Five minutes of resting measures of baseline HR and mood were then recorded. All subjects were paid $5.00/h of lab time, and were allowed to leave once their BACs reached 0.04 or less.

Measures and apparatus

Alcohol-induced changes in mood. Mood was assessed using the Profile of Mood States – Bipolar (POMS: Lorr 1982). This scale was designed and has been well validated as an inventory of mood states in normal and psychiatric populations, and is sensitive to changes in mood states along several dimensions of mood (Lorr 1982). Six bipolar dimensions of mood were assessed using the subscales outlined by Lorr (1982). They were: composed-anxious (C-A); elated-depressed (E-D); energetic-tired (E-T); agreeable-hostile (A-H); clearheaded-confused (C-C); and confident-unsure (C-U). Each dimension of mood was measured twice in the experiment: (1) following a sober resting baseline period, and (2) 30 min post-offset of alcohol consumption (50 min post-onset of consumption), following an alcohol-intoxicated resting baseline period. Arithmetic change scores were derived for each of the six POMS dimensions representing the change from sober resting state to alcohol-intoxicated resting state. Means for alcohol-induced changes in mood ratings for each sample appear in Table 1.

Alcohol-induced HR stimulation. A Grass Model 7d polygraph with a model 7P4 EKG tachograph preamplifier was attached to Medi-Trace pellet electrodes placed bilaterally on the lower chest of the subject for the measurement of HR. Within the 5-min resting baseline period, the most artifact-free 60-s period was selected and HR samples were scored every 2.5 s for the entire minute. An average HR was then obtained to reflect sober resting HR. Resting HR was measured in a similar manner 30 min following onset of alcohol consumption. Alcohol-induced change in resting heart rate was calculated by subtracting mean sober heart rate from mean alcohol-intoxicated heart-rate. The mean of the change scores for each sample appears in Table 1.

Table 1 Means and standard deviations for mood and cardiac responses to alcohol for samples 1 and 2

	Sample 1		Sample 2	
	Mean	SD	Mean	SD
Profile of Mood States scales				
Composed-anxious	0.4	4.5	1.1	7.3
Agreeable-hostile	0.8	4.6	0.6	3.8
Elated-depressed	1.6	5.7	0.7	4.8
Energetic-tired	0.7	9.6	–1.3	6.8
Confident-unsure	0.3	5.9	0.3	6.2
Clearheaded-confused	–4.2	6.8	–4.3	5.5
Cardiac measure				
Alcohol-induced HR stimulation	1.2	5.9	12.3	9.5

Table 2 Correlations between alcohol-induced increase in resting HR (HR) and mood

	Alcohol-induced HR stimulation	
	Study 1	Study 2
Profile of Mood States scales		
Composed-anxious	0.28*	0.22
Elated-depressed	0.18	0.41**
Energetic-tired	0.26*	0.28*
Agreeable-hostile	0.13	0.22
Confident-unsure	0.40**	0.38**
Clearheaded-confused	0.00	0.11
	(*n*=49)	(*n*=59)

Results

Correlation between alcohol-induced HR increase and alcohol-induced changes in mood

Estimates of the correspondence (r) between alcohol-induced HR stimulation and mood are presented in Table 2. It is indicated that alcohol-induced HR stimulation was correlated with positive change in mood, and was significantly related to feeling more composed, energetic and confident ($P<0.05$) in sample 1 and more elated, energetic, and confident in sample 2.

Evaluation of the repeatability of results across two samples

To assess the repeatability of the correlations between alcohol-induced changes in HR and mood yielded across samples 1 and 2, each correlation was then transformed into a Fisher’s Z-score for a meta-analysis across the two samples. Non-significant effects sizes for the difference between the correlations for each dimension of mood were yielded indicating that the correspondence between alcohol-induced change in HR and each dimension of mood yielded for sample 1 were not significantly different from those yielded for sample 2.

Discussion

This first study explored the validity of alcohol-induced HR stimulation as an index of psychomotor stimulation from alcohol. It was postulated that it should correlate positively with mood changes, to the extent that the stimulant effects of alcohol on mood are detectable. The proposed index was correlated with positive changes in mood. More importantly, HR responses were shown to correlate strongly and repeatedly with changes on mood scales that have been shown to be particularly sensitive to the effects of stimulant drugs (i.e., energetic-tired).

Cardiac response to alcohol was also show to correspond with changes on the confidence-unsure dimension of the POMS-bipolar, which has received less attention with respect to exploring the effects of drugs of abuse on mood. This scale includes items such as feeling strong, forceful, bold and confident. Newlin (2000) recently postulated that the reinforcing properties of alcohol that are mediated by the cortico-mesolimbic dopamine system not only produce forward locomotion and reward, but a motivational state that is associated with basic survival and reproductive fitness. This latest theory would predict that activation of the cortico-mesolimbic dopamine system is associated with sympathetic arousal and HR increases, as it is associated with activation of brain system implicated in the activation of goal-directed behavior (e.g., foraging, feeding, sexual behavior, and approach behavior). However, it is further suggested that such activation not necessarily result in the subjective experience of euphoria (i.e., positive mood), but, more specifically, vigor/energy and an enhanced sense of empowerment (i.e., survival ability and reproductive fitness). The current findings of relationships between alcohol-induced HR increase and selective mood states are consistent with traditional psychomotor stimulant theory of addiction (Wise and Bozarth 1987), as well as, more recent theories of drug abuse that offer more elaborate hypotheses regarding human subjective experiences with drugs of abuse (Newlin 2000).

It seems important also to discuss the fact that mean alcohol-induced change in HR differed substantially across the two samples, despite the fact that the samples were administered equivalent doses of alcohol. Examination of potential order or drinking status effects on HR measures rules out the possibility that multiple drinking sessions and heavier drinking status of sample 1 could account for such differences (because such effects did not emerge). Rather, it appears that the most significant difference in methodology between the two samples is the type of stressor that preceded alcohol consumption. Subjects in sample 1 were asked to play a video game on which performance was not rewarded or punished, whereas, subjects in sample 2 engaged in the same video game, but performance was motivated either through monetary reward or avoidance of punishment. It is conceivable that this latter task resulted in activation of the cortico-mesolimbic dopamine system and thus caused a priming effect to enhance the subsequent effects of alcohol on that same brain system. In fact, analysis of HR increases to these different pre-alcohol stressors indicated that the reinforced game play of sample 2 resulted in a significantly greater cardiac reactivity than the non-reinforced game play of sample 1. Moreover, measures of HR reactivity to reinforced game play, receipt of reward, and receipt of punishment were correlated with alcohol-induced increases in resting HR (r=0.30–0.57, P<0.05). Several lines of evidence suggest that alcohol-induced dopamine activity and related psychomotor stimulation should interact, possibly cross-sensitize, with the effects of aversive stimulation, even when the two types of stimuli produce opposite hedonic/subjective effects (Sorg 1992; Prasad et al. 1998). Stress and psychostimulants are known to cross sensitize with respect to effects on locomotor behavior (Kalivas and Stewart 1991), drug self-administration (Piazza and Le Moal 1996) and drug-induced activity in the mesolimbic dopamine system (Kalivas and Stewart 1991). Whether the HR measure is more susceptible to the effects of pre-drinking stress is a question that warrants further investigation and that will have further implications for the validity of this measure as an indice of psychostimulation from alcohol. Such a finding would further support our claim that, more than subjective measures, this measure taps into the *reinforcing* properties of alcohol. However, additional investigation using drug-choice paradigms (deWit and Griffiths 1991) will be required to determine the extent to which this variable reflects sensitivity to alcohol reinforcement.

Study 2

Study 2 was designed to investigate the reliability of alcohol-induced HR stimulation. As mentioned in study 1, subjects in sample 1 participated in two alcohol administration sessions. As the alcohol dose remained constant across the two drinking sessions there was an occasion to examine the repeatability of alcohol-induced increases in HR. The data for this second study were collected as part of a previously published study investigating the effects of familial history of alcoholism on psychophysiological responses to alcohol (Conrod et al. 1997b). The following analyses were not previously reported.

Materials and methods

General procedure

Participants of this study involved sample 1 participants from study 1. Subjects participated in two counter-balanced drinking sessions that were separated by a 1-week period in which they were asked to remain abstinent from alcohol and other drugs (but not nicotine). For each drinking session, participants arrived in the laboratory at 9:00 a.m. Subjects were then seated in a reclining chair, attached to the cardiovascular recording device. They were then asked to sit quietly and relax for 10 min; during this period a 5-min resting (sober) baseline heart-rate measure was obtained and mood states were assessed using the POMS. Subjects were then randomly presented with one of three video games to play for 2 min three times (with 1 min inter-game intervals). Each subject was assigned a performance criterion and instructed to attempt to reach that criterion within the 2-min game playing period. He was assigned a more lenient or more difficult criterion depending on his performance in previous trials, but was not rewarded or punished for his performance.

Following game play, alcohol was administered in the form of five "shots" of 40% vodka (equivalent to 1.0 ml/kg body weight of 95% USP alcohol in total), frozen to reduce taste intensity. In the "fast-drinking" condition, subjects received a shot at 0, 1, 2, 3, and 4 min. In the "slow-drinking" condition, subjects received a shot at 0, 5, 10, 15 and 20 min. Shots were consumed in one swallow. Order of drinking session was counter-balanced. Resting HR was recorded every 10 min following consumption of alcohol. Mood was assessed every 30 min. When subjects' BACs reduced to a 0.06 level, they were disconnected from the polygraph, fed and presented a movie until their BACs further reduced to a 0.04 level. Subjects were paid $5.00/h for their participation. Although rate of alcohol ingestion has previously been shown to enhance post-ethanol HR (Conrod et al. 1997b), this variable was expected to increase the mean HR response to alcohol and not degree of individual variability in HR response. Therefore, it was postulated that reliability estimates across the two testing sessions would not be influenced by the rate of consumption variable.

Measures and apparatus

Cardiac measures. HR was recorded using a Grass Model 7D polygraph. Two Model 7P4 EKG Tachograph preamplifiers recorded HR from Medi-Trace pallet electrodes placed on both sides of the chest. Polygraph data were scored manually by two people. Cardiovascular response measures were derived for sober and alcohol-intoxicated resting periods at 10-minute intervals following alcohol consumption until BAC reduced to 0.06%. Alcohol-induced HR stimulation was calculated as the change from sober baseline HR to alcohol-intoxicated resting baseline HR.

Blood alcohol concentrations (BACs). These were determined using an Alco-Sensor III (Thomas Inst.) and were recorded only if the subject had not consumed alcohol within the previous 10 min. Subjects were asked to provide a strong breath that remained at a consistent intensity for 6 s. The Alco-Sensor III provides BAC estimates with an error of measurement of ±0.003. Mean BACs were calculated at 10-min intervals beginning at 10 min post-offset of alcohol consumption and following the HR recordings. The slow drinking procedure resulted in a mean peak BAC of 0.115±0.24 and the fast drinking condition resulted in a mean peak BAC of 0.110±0.24. Subjects achieved their peak BAC at approximately 60 min post-onset of drinking (60.43±19.8 for the slow drinking condition and 58.19±22.9 for the fast drinking condition). In our previous analysis of the data on BAC (Conrod et al. 1997b), the peak of the BAC curve was determined as the time at which the mean BAC for the sample peaked, which was at 50 min post-onset of alcohol consumption for each drinking session. Therefore, the rising limb of the BAC curve was considered to be from 0 to 50 post-onset of alcohol consumption and the descending limb began 60 min post-onset of drinking.

Results

Test-retest reliability of alcohol-induced HR increase

Within the context of a two-way mixed ANOVA design, single measure inter-class correlations were calculated to estimate the test-retest reliability of alcohol-induced HR stimulation. Reliability estimates are illustrated in Fig. 1 for each 10-min period along the blood alcohol curve. Alcohol-induced HR stimulation appears to be a moderately stable measure across two alcohol administration sessions, particularly at earlier points of intoxication (r=0.33–0.61 along the ascending limb and r=0.11–0.42 along the descending limb).

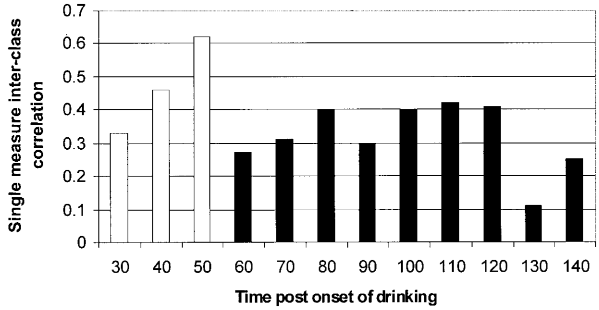

Fig. 1 Two-week test-retest reliability estimates for alcohol-induced HR stimulation. *Light colored bars* indicate that BACs are rising and *dark colored bars* indicated that BACs are falling. Mean time to peak for the slow drinking session=60.43±19.8 min, and mean time to peak for the fast drinking session=58.19±22.9 min. Time is indicated as number of minutes post onset of drinking

Discussion

The current findings stand in contrast to those of two studies reported by Nagoshi and Wilson (1989) and Wilson and Nagoshi (1987) which yielded very low test-retest reliability coefficients for heart rate responses to alcohol. These discrepant findings may be attributed to several methodological differences across the studies. First, it is likely that the reliability estimates yielded for alcohol-induced change in HR in the Wilson and Nagoshi (1987) study were influenced by the fact that their baseline HR measures were not reliably measured. Our protocol yielded much higher test-retest reliability estimates for both baseline and post-alcohol resting HR levels (inter-class r=0.65, P<0.01 and r=0.84, P<0.01, respectively), which most likely explains why our sensitivity scores were so much higher than those of this previous study. The greater reliability of the sensitivity measures yielded in the present study may also be due to the fact that HR measures were taken at each 10-min period post-offset of drinking. These previous studies involved the assessment of repeatability of alcohol response measures over longer and more variable test-retest intervals (ranging from 1 to 39 months) with a protocol for re-testing alcohol sensitivity that involved topping up doses and a shortened version of the initial test battery. Therefore, alcohol response measures were likely tested at various points along the blood alcohol curve across the test and retest sessions.

That this cardiac response was shown to be most reliable at early stages of intoxication, when blood alcohol levels are rising, further supports the validity of this index; psychostimulant properties of alcohol are similarly limited to the ascending limb of the BAC curve (Friedman et al. 1980; Mello 1983). It can be concluded from the current study that alcohol-induced HR increase can be reliably measured within a relatively short test-retest period and under experimental conditions that allow for HR recordings that are closely matched for time post-onset of alcohol consumption.

Study 3

The final study of this series explored the convergent and discriminant validity of alcohol-induced increase in HR. Specifically, study 3 examines the differential relationship between three alcohol response measures (HR increase, subjective intoxication and reduction of experimentally-induced anxiety) and alcohol-induced changes on two subscales of the POMS that have been shown to be sensitive to distinct drug effects. The Composed-anxious subscale will serve as an index of anxiety-reduction from alcohol and the Energetic-Tired subscale will serve as an index of psychostimulation from alcohol. The discriminative validity of the HR measure will be explored by demonstrating that it is related to the stimulant effects of alcohol and unrelated to the anxiety-reducing effects, but that other alcohol response measures (e.g., reduction in experimentally induced anxiety) do correlate with alcohol-induced changes in anxious mood. This study will also provide a preliminary examination of the construct validity of the Subjective High Assessment Scale (Judd et al. 1977).

Materials and methods

Subjects

Thirty-two non-alcoholic, Caucasian males between the ages of 18 and 25 years were contacted by telephone following responding to newspaper advertisements, and were briefly screened for personal and familial alcoholic history using the brief Mast (Pokorny et al. 1972). Subjects were included in the study if they met criteria for non-alcoholic status, multigenerational alcoholic family history (MFH) or no history of familial alcoholism (FH–), and if they were not currently suffering from a medical condition for which alcohol consumption was contra-indicated. The current sample comprised 12 MFH and 20 FH– male subjects.

General procedure

Upon their arrival, subjects were briefed as to the procedure of the study and were then presented with a consent form to sign. All subjects were aware that they could withdraw from participation at any time in the experiment, but once intoxicated could not leave the laboratory until their blood alcohol concentration had reduced to below a 0.04% level. A short semi-structured interview was conducted in order to collect demographic and personal drinking information. Subjects were then asked to remain seated, and relaxed for 10 min during which time 5-min baseline measures for HR were recorded.

A concentric shock electrode was then attached to the inside of the subject’s forearm and headphones were placed over his ears. The shock delivery procedure consisted of three signaled successive electric shocks. Subjective responses to the shock were subsequently recorded using the Shock Anticipation and Shock Rating Scales (see below). Following consumption of the alcohol dose, a second 5-min baseline measure was recorded, and the shock administration paradigm was repeated. The subject was then disconnected from the cardiovascular recording devices, was fed, debriefed regarding the experimental procedures, and allowed to leave the laboratory only once his BAC reduced to below 0.04%.

Measures and apparatus

Shock administration. Electric shocks were administered using a Farral Instrument Mark I at an intensity of 1.85 mA for 0.5 s using a concentric electrode attached to the inside of the elbow of the subject’s non-dominant arm. A tone was heard and then ten count-down numbers were visually presented to the subjects prior to the delivery of the shock. Shock anticipation and shock rating scales were administered following both sober and alcohol-intoxicated shock administration procedures.

Alcohol administration. Each participant was administered a dose of 1.0 ml/kg body weight of 95% USP alcohol mixed 5:1 parts orange juice. The beverage was presented to the subject in three separate glasses and subjects were instructed to consume each beverage within 5 min.

Alcohol-induced change in mood. Due to the relatively small sample size, we limited our assessment of alcohol-induced changes in mood to the two POMs dimensions that have been shown to be sensitive to different drug effects: the Energetic-tired and the Composed-anxious subscales. Change scores were calculated as the difference in mood ratings between resting (pre-shock) baseline to 30 min post-alcohol consumption resting (pre-shock) baseline.

Subjective intoxication. Subjective intoxication ratings were assessed using the Subjective High Assessment Scale (SHAS; Judd et al. 1977). A composite score was derived for the first 15 items of the SHAS which detail the subjective effects of the drug (e.g., dizzy, high, sleepy, clumsy, etc.). The last two items of the SHAS (i.e., “the best that I have ever felt” and “the worst that I have ever felt”) were not involved in the calculation of this composite score because they were postulated to be related to different dimensions of alcohol-effects.

Alcohol-induced reduction in experimentally induced anxiety. The Shock Anticipation Scale, developed by Finn et al. (1990), consists of five items rated on a 10-point Likert scale concerning the degree of tension, anxiety, worry, fear and anger experienced in anticipation of shock administration with higher scores reflecting higher levels of subjective anticipatory emotional arousal. Alcohol-induced reduction in anxiety ratings was calculated by subtracting post-alcohol shock anticipation ratings from their corresponding sober ratings. This measure was selected to reflect anxiety reduction from alcohol over other measures previously used in the literature (e.g., dampening of HR reactivity) to reduce the potential shared measurement variance between two HR measures and because it more directly measures anxiety-reduction from alcohol. This scale has been shown to be sensitive to the effects of alcohol (Finn et al. 1990), as well as individual differences in sensitivity to the anxiety reducing effects of alcohol (Conrod et al. 1998).

Alcohol-induced HR stimulation. HR levels were recorded using a Contact Precision Instruments polygraph. Two medi-Trace pellet electrodes placed bilaterally on the lower chest were used to detect HR. Average HR levels for sober and alcohol-intoxicated resting periods were computed using Contact Precision Instruments software. Alcohol-induced HR stimulation was calculated according to the same procedure used in the previous two studies (alcohol intoxicated baseline HR–sober resting baseline HR).

Results

Means and standard deviation for the five alcohol-response measures (two mood measures and three non-

Table 3 Means and standard deviations for subjective and cardiac responses to alcohol and shock administration

Profile of Mood States scales (change scores)	Mean	SD
Composed-anxious	1.0	4.7
Energetic-tired	2.0	8.0
Reduction in anxiety to shock anticipation	4.3	10.1
SHAS total scores	130.2	79.3
Alcohol-induced HR stimulation	6.4	5.0

Table 4 Partial relationships between alcohol-induced changes in mood, subjective intoxication, shock anticipation ratings, and HR

Alcohol response	SE	B	*T*	*P*	*r*-partial
Composed-anxious					
(Constant)	1.94	0.35	0.18	0.86	
Subjective intoxication (SHAS)	0.01	0.01	0.80	0.43	0.15
Reduction in shock rating	0.08	0.15	1.81	0.08	0.32
Increase in resting HR	0.17	–0.18	–1.05	0.30	–0.20
Total model				0.08	0.39
Energetic-tired					
(Constant)	2.94	1.92	0.65	0.52	
Subjective intoxication (SHAS)	0.02	–0.03	–2.30	0.03	–0.40
Reduction in shock rating	0.13	–0.02	–0.16	0.87	–0.03
Increase in resting HR	0.26	0.72	2.78	0.01	0.47
Total model				0.00	0.58

mood measures) appear in Table 3. Correlational analyses indicated that the two measures reflecting alcohol-induced change in mood (Energetic-tired and Composed-anxious) were orthogonal (r=–0.16, P>0.1). Therefore, we were justified in performing two separate multiple regression analyses to explore the independent contribution of each of the alcohol-response measures to the independent effects of alcohol on these mood dimensions.

Multiple regression analyses were performed with the alcohol response measures as the independent variables and alcohol-induced change on the two mood scales as the dependent measures. Table 4 demonstrates that the anxiety-reduction variable was uniquely related to alcohol-induced changes on the Composed-anxious factor and accounted for 15% of the variance (r=0.39) on this measure. One-third of the variance (r=0.58) on the Energetic-tired scale was accounted for by a combination of low scores on the SHAS and alcohol-induced increases in resting HR.

Discussion

This study sought to explore the convergent and discriminant validity of alcohol-induced HR stimulation as a measure of sensitivity to the stimulant effects of alcohol. Multiple regression analyses indicate this cardiac measure is distinctly related to subjective feelings of energy and vigor from alcohol and unrelated to the anxiety-reducing effects of alcohol, when individual differences in anxiety reduction are considered. These findings are consistent with those of a recent study demonstrating that sensitivity to the subjective stimulant effects of alcohol (assessed using the ARCI-Amphetamine scale) is associated with increased ratings of energy and arousal and lower ratings of fatigue and confusion on the POMs, and unrelated to alcohol-induced changes in anxiety ratings (Holdstock and de Wit 1998).

The finding of a relationship between alcohol-induced change in anxiety scores on the POMs and alcohol-induced change in anxiety ratings in response to an aversive stimulus provides some support for the use of the Composed-anxious subscale of the POMs as a measure of the anxiety-reducing effects of alcohol. However, the fact that this relationship was only mild suggests that the effects of alcohol on experimentally manipulated anxiety states are only mildly related to the effects of alcohol on resting, or tonic, anxiety states. The resting POMs measures were taken approximately 10 min prior to administration of the shock paradigm when subjects were likely not yet anticipating the receipt of an electrical shock (although they were aware that it would happen eventually). It is possible that stronger relationships between the two measures would have been yielded if mood had been measured just before the presentation of the shock paradigm. Furthermore, it is possible that only modest alcohol-induced reductions in anxiety could be observed in the present study because the sample did not include anxious individuals. We previously demonstrated that individual differences in alcohol-induced reduction in anxiety are largely mediated by a personality factor that is associated with sensitivity to anxiety states (Conrod et al. 1998).

A rather novel finding of this final study was that indicating an inverse relationship between SHAS scores and subjective sensitivity to the stimulant effects of alcohol (i.e., feeling energetic). That is, lower scores on the SHAS were associated with lower subjective ratings of feeling tired from alcohol and higher subjective ratings of feeling energized from alcohol. Although the small number of subjects in this study limits the strength of conclusions that can be drawn about these findings, they do suggest that sensitivity to the effects of alcohol on HR and reduced sensitivity to the subjective effects of alcohol concurrently, yet independently, relate to the psychostimulant effects of alcohol. This finding is particularly important for the integration of two seemingly discrepant areas of research on the genetic predisposition to alcohol reinforcement and alcoholism (e.g., Finn and Pihl 1988; Newlin and Thomson 1990; Schuckit and Smith 1996). While one group of researchers has shown that children of alcoholics demonstrate a sensitivity to the stimulating effects of alcohol on certain psychophysiological and subjective measures (e.g., Finn and Pihl 1988; Peterson et al. 1996; Conrod et al. 1998), other research groups have demonstrated that young men from alcoholic pedigrees demonstrate reduced sensitivity to alcohol on subjective and objective measures of intoxication (e.g., Schuckit 1984; Schuckit et al. 1996). The present findings suggest that sensitivity to the positive effects of alcohol and reduced sensitivity to the negative effects co-occur and reflect a general sensitivity to psychostimulation from alcohol that is, in turn, distinct from anxiolysis from alcohol. Interestingly, correlational analysis indicated that alcohol-induced HR increase and subjective intoxication are discrete factors. These findings are also consistent with those reported by Holdstock and de Wit (1998) indicating no relationship between subjective measures of intoxication and psychostimulation from alcohol (as measured by the ARCI-A scale). The lack of relationship between these two alcohol response measures is consistent with research demonstrating a dissociation between reinforcing (i.e., wanting) and the subjective (i.e., liking) properties of rewarding stimuli (e.g., Nader et al. 1997), or the distinction between motivation for drug self-administration and subjective sensitivity to drug effects (Muntaner et al. 1989; Lamb et al. 1991). This study was not able to test whether alcohol-induced HR increase was associated with sensitivity to alcohol-reinforcement, per se. However, recent studies linking this alcohol-induced cardiac response to susceptibility to the effects of alcohol on the encoding of memory for positively valenced events (Bruce et al. 1999) and to drinking behavior (Conrod et al. 1997a) suggests that such a relationship may be revealed with further investigation.

General discussion

This series of studies demonstrated that alcohol-induced HR stimulation has adequate reliability and validity as an index of the stimulant properties of alcohol. This index correlates with increases in mood states that are sensitive to the effects of stimulant drugs (e.g., feeling energized, vigorous and less sedated), and with other subjective measures that are heuristically linked to alcohol-reinforcement sensitivity (e.g., feeling confident, and reduced subjective intoxication). The heart-rate index also appeared to assess something distinct from the anxiolytic effects of alcohol. These findings are consistent with a number of recent studies demonstrating that alcohol causes more stimulation and less sedation for subjects who self report heavier drinking (Holdstock et al. 2000), for normal social drinkers who chose alcohol over placebo in a drug-choice paradigm (de Wit et al. 1987, 1989) and for normal social drinkers who self report amphetamine-like effects from alcohol (Holdstock and de Wit 1998). The evidence appears to be accumulating linking sensitivity to alcohol-induced psychomotor stimulation and reduced sensitivity to alcohol-induced sedation to alcoholism vulnerability (Schuckit 1980, 1984; Schuckit and Smith 1996 Peterson et al. 1996; Conrod et al. 1997a; Holdstock et al. 2000). The advantage of using HR as a measure of alcohol-induced psychostimulation is that it now appears to be well validated and that the CNS pathways involved in the mediation of alcohol-induced changes in HR are better delineated (e.g., Reed et al. 1999). This measure may prove to be a very useful tool when exploring brain mechanisms involved the genetic predisposition to alcohol sensitivity and alcoholism.

There are, nevertheless, important limitations to the current series of studies. First, all subjects were male, and considering that at least two studies suggest that men and women are differentially sensitive to the anticipated and subjective effects of alcohol (Gabrielli et al. 1991; Rodriguez et al. 1993), there are limitations to the extent to which the current findings can be applied to females. Second, the current studies only examined the reliability of alcohol-induced HR increase at one alcohol dose (1.0 ml/kg), which is considered quite high for most alcohol-administration studies. However, a number of previous studies suggest that the stimulant effects of alcohol on mood (Holdstock and de Wit 1998) and resting HR (Stewart et al. 1992) only occur following ingestion of a high dose of alcohol in humans. The dose-dependent nature of the HR measure is in keeping with the literature on the stimulant properties of alcohol which suggests that alcohol's stimulating effects are most evident at moderate to high doses (Pohorecky and Brick 1977). Furthermore, the fact that HR response to alcohol was shown to be less reliable as blood alcohol concentrations were decreasing (study 2) suggests that this measure is only valid when assessed as blood alcohol levels are rising.

The most important finding of this series of studies is potentially that linking reduced subjective sensitivity to alcohol (i.e., SHAS scores) to alcohol-induced changes in positive mood, when mood is measured along a bipolar dimension. Some researchers have claimed that genetic risk for alcoholism is mediated by reduced sensitivity to the subjective effects of alcohol (e.g., Schuckit 1984). However, such a claim has been criticized as being inconsistent with most theories of drug addiction and human motivation. Why would an individual be more motivated to consume alcohol just because they are less sensitive to its effects? The literature on the psychomotor theory of addiction suggests that the addictive properties of drugs are determined by their ability to produce incentive rewarding states. The current findings suggest that reduced scores on the SHAS not only reflect reduced sensitivity to the sedative effects of alcohol, but more specifically reflect a sensitivity to the energizing effects of alcohol. The current findings provide a missing link between two areas of research on the genetic predisposition to alcoholism that previously were considered contradictory.

Acknowledgements This research was supported by the Medical Research Council of Canada.

References

Bruce KR, Shestowsky JS, Mayerovitch JI, Pihl RO (1999) Motivational effects of alcohol on memory consolidation and heart rate in social drinkers. Alcohol Clin Exp Res 23:693–701

Conrod PJ, Pihl RO, Ditto B (1995) Autonomic reactivity and alcohol-induced dampening in men at risk for alcoholism and men at risk for hypertension. Alcohol Clin Exp Res 19: 482–489

Conrod PJ, Peterson JB, Pihl RO (1997a) Disinhibited personality and sensitivity to alcohol reinforcement as predictors of drinking behaviour. Alcohol Clin Exp Res 21:1320–1332

Conrod PJ, Peterson JB, Pihl RO, Mankowski S (1997b) The biphasic effects of alcohol on heart rate are influenced by alcoholic family history and rate of alcohol ingestion. Alcohol Clin Exp Res 21:140–149

Conrod PJ, Pihl RO, Vassileva J (1998) Differential sensitivity to alcohol reinforcement in groups of men at risk for distinct alcoholism syndromes. Alcohol Clin Exp Res 22:585–597

Di Chiara G, Acquas E, Carboni E (1992) Drug motivation and abuse: a neurobiological perspective. In: Kalivas PW, Samson HH (eds) Annals of the New York Academy of Sciences, pp 207–219

Dudek BC, Abbott ME, Garg A, Phillips TJ (1984) Apomorphine effects on behavioural response to ethanol in mice selectively bred for differential sensitivity to ethanol. Pharmacol Biochem Behav 20:91–94

Finn PR, Pihl RO (1988) Risk for alcoholism: a comparison between two different groups of sons of alcoholics on cardiovascular reactivity and sensitivity to alcohol. Alcohol Clin Exp Res 12:742–747

Finn PR, Zeitouni NC, Pihl RO (1990) Effects of alcohol on psychophysiological hyperreactivity to nonaversive aversive stimuli in men at high risk for alcoholism. J Abnorm Psychol 99:79–85

Fowles DC (1983) Appetitive motivational influences on heart rate. Person Indiv Diff 4:393–401

Fowles DC, Fisher AE, Tranel DT (1987) The heart beats to reward. The effect of monetary incentive on HR. Psychopysiology 19:506–513

Friedman HJ, Carpenter JA, Lester D, Randall CL (1980) Effect of alpha-methyl-*p*-tyrosine on dose dependent mouse strain differences in locomotor activity after ethanol. J Stud Alcohol 41:1–7

Gabrielli WF, Nagoshi CT, Rhea SA, Wilson JR (1991) Anticipated and subjective sensitivities to alcohol. J Stud Alcohol 52:206–214

Hemby SE, Co C, Koves TR, Smith JE, Dworkin SI (1997) Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rate. Psychopharmacology 133:7–16

Holdstock L, de Wit H (1998) Individual differences in the biphasic effects of ethanol. Alcohol Clin Exp Res 22:1903–1911

Holdstock L, King AC, de Wit H (2000) Subjective and objective responses to ethanol in moderate/heavy and light social drinkers. Alcohol Clin Exp Res 24:789–792

Johanson CE, de Wit J (1989) The use of choice procedures for assessing the reinforcing properties of drugs in humans. Testing for abuse liability of drugs in humans. In: Fischman MW, Mello NK (eds) Testing for abuse liability of drugs in humans. NIDA Research Monograph No. 92, US Government Printing Office, Washington, D.C., pp 123-146

Johanson CE, Uhlenhuth EH (1980) Drug preference and mood in humans: *d*-amphetamine. Psychopharmacology 71:275–279

Judd LL, Hubbard B, Janowsky DS, Huey LY, Attewell PE (1977) The effect of lithium carbonate on affect, mood, and personality of normal subjects. Arch Gen Psychiatry 34:346–351

Kalivas PW, Stewart J (1991) Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Rev 16:223–244

Krimmer EC, Schechter MD (1992) HAD and LAD rats respond differently to stimulating effect but not discriminative effects of ethanol. Alcohol 9:71–74

Lamb RJ, Preston KL, Schindler CW, Meisch RA, Davis F, Katz JL, Henningfield JE, Goldberg SR (1991) The reinforcing and subjective effects of morphine in post-addicts: a dose-response study. J Pharmacol Exp Ther 259:1165–1173

Lorr M (1982) Profile of mood states: bi-polar form (manual). Educational and Industrial Testing Service, San Diego, Calif.

Martin C, Earleywine M, Musty RE, Perrine MW, Swift RM (1993) Development and validation of the Biphasic Alcohol Effects Scale. Alcohol Clin Exp Res 17:140–146

Martlatt GA, Demming B, Reid JB (1973) Loss of control drinking in alcoholics: an experimental analogue. J Abnorm Psychol 88:233–241

McNair DM, Lorr M, Droppleman LF (1971) Profile of mood states. Educational & Industrial Testing Service, San Diego, Calif.

Mello N (1983) A behavioural analysis of the reinforcing properties of alcohol and other drugs in man. In: Kissin B, Begleiter H (eds) The biology of alcoholism, vol 7. Plenum Press, New York

Muntaner C, Kumor KM, Nagoshi C, Jaffe JM (1989) Intravenous cocaine infusions in humans: dose responsivity and correlations of cardiovascular vs. subjective effects. Pharmacol Biochem Behav 34:697–703

Nader K, Bechara A, van der Kooy D (1997) Neurobiological constraints on behavioral models of motivation. Annu Rev Psychol 48:85–114

Nagoshi CT, Wilson JR (1989) Long-term repeatability of human alcohol metabolism, sensitivity and acute tolerance. J Stud Alcohol 50:162–169

Nagoshi CT, Wilson JR, Rodriguez LA (1991) Impulsivity, sensation seeking and behavioral and emotional responses to alcohol. Alcohol Clin Exp Res 15:661–667

Newlin D (2000) The self-perceived survival ability and reproductive fitness (SPFit) theory of substance use disorders. Paper presented at the Annual Meeting of the Research Society on Alcoholism, Denver, Colorado, June

Newlin DB, Thomson JB (1990) Alcohol challenge with sons of alcoholics: a critical review and analysis. Psychol Bull 108: 383–402

Newlin DB, Thomson JB (1999) Chronic tolerance and sensitization to alcohol in sons of alcoholics: II. Replication and reanalysis. Exp Clin Psychopharmacol 7:234–243

Peterson JB, Pihl RO, Gianoulakis C, Conrod PJ, Finn PR, Stewart SH, LeMarquand DG, Bruce KR (1996) Ethanol-induced change in cardiac and endogenous opiate function and risk for alcoholism. Alcohol Clin Exp Res 20:1542–1552

Piazza PV, Le Moal M (1996) Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopamine neurons. Annu Rev Pharmacol Toxicol 36:359–378

Pohorecky L (1977) Biphasic action of ethanol. Biobehav Rev 1:231–244

Pohorecky LA, Brick J (1988) Pharmacology of ethanol. Pharmacol Ther 36:335–427

Pokorny AD, Miller BA, Kaplan HB (1972) The Brief MAST: a shortened version of the Michigan Alcoholism Screening Test. Am J Psychiatry 129:342–345

Prasad BM, Ulibarri C, Sorg BA (1998) Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Am J Psychiatry 156:34–40

Reed SF, Porges SW, Newlin DB (1999) Effect of alcohol on vagal regulation of cardiovascular function: contributions to the polyvagal theory to the psychophysiology of alcohol. Exp Clin Psychopharmacol 7:484–492

Rodriguez LA, Wilson JR, Nagoshi CT (1993) Does psychomotor sensitivity to alcohol predict subsequent alcohol use? Alcohol Clin Exp Res 17:155–162

Schacter S, Goldman R, Gordon A (1968) Effects of fear, food deprication and obesity on eating. J Person Soc Psychol 10:91–97

Schechter MD, Krimmer EC (1992) Differences in response to the aversive properties and activity effects of low dose ethanol and LAS and HAS selectively bred rats. Psychopharmacology 107:564–568

Schuckit MA (1980) Self-rating of alcohol intoxication by young men with and without family histories of alcoholism. J Stud Alcohol 41:242–249

Schuckit MA (1984) Subjective responses to alcohol in sons of alcoholics and controls. Arch Gen Psychiatry 41:879–884

Schuckit MA, Smith TL (1996) An 8-year follow-up of 450 sons of alcoholic and control subjects. Arch Gen Psychiatry 53:202–211

Schuckit MA, Tsuang JW, Anthenelli RM, Tipp JE, Nurnberger JI (1996) Alcohol challenges in young men from alcoholic pedigrees and control families: a report from the COGA Project. J Stud Alcohol 57:368–377

Sellers EM, Otton SV, Busto UE (1991) Drug metabolism and interactions in abuse liability assessment. Br J Addict 86:1607–1614

Sorg BA (1992) Mesocorticolimbic dopamine systems: cross-sensitization between stress and cocaine. Ann NY Acad Sci 28:136–144

Stewart SH, Finn PR, Pihl RO (1992) The effects of alcohol on the cardiovascular stress response in men at high risk for alcoholism: a dose response study. J Stud Alcohol 53:499–506

Wilson JR, Nagoshi CT (1987) One-month repeatability of alcohol metabolism, sensitivity and acute tolerance. J Stud Alcohol 48:437–442

Wise RA (1988) The neurobiology of craving: implications for the understanding and treatment of addiction. J Abnorm Psychol 97:118–132

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94:469–492

Wit H de, Griffiths RR (1991) Abuse liability of anxiolytic and hypnotic drugs. Drug Alcohol Depend 28:83–11

Wit H de, Uhlenhuth EH, Pierri J, Johanson CE (1987) Individual differences in behavioral and subjective responses to alcohol. Alcohol Clin Exp Res 11:52–59

Wit H de, Pierri J, Johanson CE (1989) Assessing individual differences in ethanol preference using a cumulative dosing procedure. Psychopharmacology 98:113–119