AUTONOMIC REACTIVITY TO MENTAL STRESSORS AFTER SINGLE ADMINISTRATION
OF LORAZEPAM IN MALE ALCOHOLICS AND HEALTHY CONTROLS

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Abstract — Clinically unaffected sons of male alcoholics differ from controls without a family history of alcoholism in two respects: increased autonomic reactivity to aversive as well as non-aversive stimuli and increased attenuation of these responses by alcohol. This pattern of autonomic hyper-reactivity and alcohol-induced stress response dampening (SRD) might be a trait marker of genetic vulnerability and is often interpreted in terms of a diathesis stress model of alcohol dependence. Forty-five alcohol-dependent men (mean age: 39.20 years) and 37 healthy controls (mean age: 35.03 years) participated in a double-blind cross-over study in two experimental sessions each. The benzodiazepine lorazepam was selected as an alcohol substitute. Autonomic reactivity and lorazepam-induced SRD were assessed during incentive and non-incentive reaction time tasks as well as mental arithmetics. Alcohol-dependent men showed elevated resting heart rate levels and increased number of non-specific electrodermal responses. Evidence for autonomic hyper-reactivity was found for a subgroup of alcoholics with a family history of alcoholism.

INTRODUCTION

A family history of alcoholism is a major risk factor for the development of alcohol misuse and dependence. The first degree biological relatives of individuals with alcoholism have a risk for alcohol dependence that is three to five times higher than that of the general population (for a review see Hesselbrock, 1995). Twin and adoption studies indicate that genetic factors contribute to the increased lifetime prevalence that is reported for children of alcoholics (e.g. Kendler et al., 1994). Models of the transmission of this increased relative risk for children of alcoholics suggest an interaction of biological, social and psychological factors, e.g. decreased serotonergic functioning, prefrontal lesions, peer group influences and sensation seeking (e.g. Pihl and Peterson, 1992; Tarter et al., 1995). In a series of psychophysiological experiments, Finn and Pihl (1987, 1988) demonstrated that clinically unaffected sons of male alcoholics (SOMAs) differ from controls without a family history of alcoholism in two respects: increased autonomic reactivity to aversive as well as non-aversive stimuli and increased attenuation of these responses by alcohol. This pattern of autonomic hyper-reactivity and alcohol-induced stress response dampening (SRD) might be a trait marker of genetic vulnerability and is often interpreted in terms of a diathesis stress model of alcohol dependence (Pihl et al., 1990; Pihl and Peterson, 1992).

Besides an early study on pupillary reactivity (Rubin et al., 1980), no work has been done on the question whether alcoholics themselves show the same response pattern. Studies on this issue would be of both theoretical and clinical interest but are confronted with a great number of methodological and ethical problems. First, brain and tissue damage as well as other medical conditions caused by long-term alcohol misuse, medication, acute intoxication and withdrawal could produce changes in autonomic reactivity and substance sensitivity. It cannot be ignored that these alterations as well as other clinical manifestations and consequences of alcohol dependence confound the effects of premorbid subject characteristics. Therefore special attention must be paid to the selection of participants. Second, experimental design and procedure should be comparable to high-risk studies with respect to experimental manipulations, pharmacological challenge, dependent measures etc. as far as possible. However, ethical concerns limit the administration of alcohol in experimental studies (Lawson et al., 1980). Therefore a substance must be found that mimics the pharmacological and psychological effects of alcohol without challenging the abstinence of alcoholics in treatment. Benzodiazepines seem to be appropriate alcohol substitutes for several reasons (see Nichols and Martin, 1996), as the effects of alcohol and benzodiazepines on the central nervous system (CNS) are similar in many ways. Both drugs act on the γ-aminobutyric acid (GABA) receptor complex of the brain (Dildy-Mayfield and Harris, 1995; Paul, 1995; Tabakoff and Hoffman, 1996). In facilitating GABAergic transmission, alcohol and CNS depressants of the benzodiazepine type cause a reduced excitability of brain cells (Suzdak et al., 1986; Paul, 1995). The clinical effects of benzodiazepines resemble alcohol intoxication. Ingestion produces relief from anxiety and tension, mood alterations, sedation and cognitive impairment, e.g. increase of reaction time, impairment of recognition and free recall for material exceeding short-span memory (e.g. Ghoneim et al., 1981; Lister and Fite, 1984; Schuckit et al., 1991). Therefore, benzodiazepines should be given in small doses to avoid the sedation and cognitive impairment caused by large doses. Finally, it has been shown that alcohol and benzo diazepines produce approximately the same changes in event-related potentials (e.g. Martin et al., 1992).

The present study differs from the initial investigations of Finn and Pihl (1987, 1988) not only with respect to pharmacological challenge, but also regarding the experimental stressors. Finn and Pihl (1987, 1988) delivered unavoidable electric shocks to induce stress. According to Young et al. (1990) shock threat situations have limited validity in inducing tension or anxiety similar to that which alcohol is expected to alleviate. Therefore, a reaction time (RT) task and mental arithmetic (MA) were chosen for the present investigation. In particular, cardiovascular reactivity during MA has been found to be predictive of stress
SUBJECTS AND METHODS

Subjects

Forty-five alcohol-dependent men and 37 apparently healthy controls participated in a double-blind cross-over study in two experimental sessions each. The experimental group was a subsample of a larger group of alcohol-dependent patients that participated in a study concerning prediction of treatment outcome. The study was approved by the Medical Ethical Committee of the University of Heidelberg. All subjects gave written informed consent. The alcoholics were in-patients at the Central Institute of Mental Health in Mannheim (Germany). Some patients underwent detoxification in a general hospital or another in-patient treatment unit before admission to the Central Institute of Mental Health. The treatment programme included group therapy, relapse prevention training, education and individual counselling. Attendance at meetings of different self-help groups was also required. The mean length of in-patient stay was 19.5 days (median = 20.0; SD = 3.4). Patients were selected from successive admissions for participation in the study if they met the following criteria: (1) alcohol dependence according to ICD-10 (German version by Dilling et al., 1993); (2) no other psychiatric diagnosis than alcohol dependence; (3) no serious physical disorder (e.g. cirrhosis, hepatitis, cardiovascular disease); (4) no neurological disorder (e.g. alcohol-induced dementia); (5) no medication that could influence autonomic reactivity or substance sensitivity; (6) no acute alcohol withdrawal; (7) maximum age of 50 years. Lifetime histories of drug and alcohol use were obtained from all patients using a structured clinical interview recommended by the German Council on Addiction Research and Treatment (Deutsche Gesellschaft für Suchtforschung und Suchttherapie e. V., 1992). A number of questionnaires were also completed by the alcohol-dependent subjects as part of the assessment, including a German version of the Alcohol Use Inventory (Funke et al., 1987).

The 37 controls were recruited through advertisements and screened for mental illness and family history of alcoholism using a short, standardized interview. The controls were paid for their time. Table 1 summarizes the general demographic characteristics of both groups.

Table 1. General demographic characteristics of alcoholics and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alcoholics (n = 45)</th>
<th>Controls (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean (SD)]</td>
<td>39.20 (6.69)</td>
<td>35.03 (6.04)</td>
</tr>
<tr>
<td>Marital status [n, (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>12 (27)</td>
<td>23 (62)</td>
</tr>
<tr>
<td>Married</td>
<td>24 (53)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Divorced</td>
<td>9 (20)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>School-leaving qualification [n, (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Secondary school</td>
<td>34 (76)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Higher qualification</td>
<td>10 (22)</td>
<td>31 (84)</td>
</tr>
<tr>
<td>Smoker [n, (%)]</td>
<td>35 (78)</td>
<td>17 (46)</td>
</tr>
</tbody>
</table>

Most alcoholics (89%) reported previous out-patient treatments because of alcohol dependence or misuse (physician, self-help group or counsellor). First contact to an out-patient treatment unit had been 4.8 (median = 2.0, SD = 6.1) years earlier. The average duration of regular drinking reported was 20.0 years (median = 22.0, SD = 8.2). Loss of control first appeared 6.8 years (median = 4.8, SD = 5.9) ago. During the 6 months preceding the study, the patients had consumed 218.08 g (SD = 94.44) of absolute alcohol on an average drinking day. The recruited alcoholic subjects did not differ from other samples drawn from in-patient treatment programmes in Germany with respect to demographic characteristics, drinking history and pretreatment (see Küfner and Feuerlein, 1989).

Stimuli and apparatus

Presentation of stimuli and measurement of reaction times were controlled using the software package Experimental Run Time System (Version 3.0) developed by Jörger Beringer (Frankfurt am Main, Germany) installed on an IBM-compatible personal computer. All instructions and visual stimuli (white figures on blue ground) were displayed on a computer monitor (Sony, CPD-15SF1) placed 120 cm in front of the subjects. Each experimental session comprised four baseline measurements of autonomic activity (duration of baseline measurements: 100 s), two RT tasks and MA. There were no differences between the two RT tasks besides feedback about hits and misses and reward for hits. Both tasks consisted of 12 trials of 5000 ms duration each (inter-trial interval: 19 000 ms). At the beginning of the task, a fixation cross appeared in the centre of the screen. After 6000 ms, two arrows were presented at the left and right margin of the monitor (1770 ms) signalling the beginning of a trial. Then the arrows started to move towards the centre of the screen. Subjects had to press the key of a PC mouse after collision of the fast-moving arrows in the centre of the screen (time window for reaction: 55 ms). Each trial was terminated by a feedback about hits and misses presented on the computer screen in front of the subjects (duration of feedback: 2000 ms). In one of the two RT tasks, subjects had the opportunity to earn a monetary gain of 1 DM for each hit (incentive reaction time task). In the other RT task, each miss was followed by a signal tone [1 kHz, 85 dB(A), 1 750 ms] presented binaurally through Uhren W766A stereo headphones (non-incentive reaction time task). Order of conditions (incentive vs non-incentive) was counterbalanced between subjects, but remained constant for each individual across days. The MA task involved six trials of continuous subtraction of three beginning at a three-digit number (448, 559, 637, 701, 894, 980, 593). Subjects were requested to perform the subtractions silently as quickly and accurately as possible and were prompted after 20 s to report their results aloud.

Signal recording

Electrocardiogram (ECG), digital blood volume amplitude (DBVA), dermoptical activity (EDA) and electroencephalogram (EEG) were continuously recorded using a second IBM-compatible computer system that was connected with a polygraph (Nihon Kohden, EEG-4414G) and an additional amplifier for EDA (ZAK-Medizinteznik, Modulares Biosystem). The analysis of electroencephalographic activity is beyond the scope of the present paper. All signals were digitized...
online with a sampling rate of 100 Hz using the software package ASYST (Version 3.10). ECG was recorded using Ag/AgCl electrodes (In Vivo Metric, IVM E 224; surface area ~0.5 m²) filled with a commercial electrode paste (Med-Tek Corporation). DBVA was obtained from a photoplethysmograph (S&W Medico Teknik A/S, Pulse Pick-Up 8070.01) attached to the nail of the ring-finger of the left hand. A black cloth was draped over the finger to block artefacts from ambient light sources. Bipolar recording of skin conductance was done using Ag/AgCl over the finger to block artefacts from ambient light sources. Signals (Version 1.92) by J. Kaiser and H.-J. Trosiener (Berlin, Germany) were attached to the hand. A black cloth was draped over the finger to block artefacts from ambient light sources.

**Procedure**

During the second week of treatment patients were informed about the experiment and signed informed consent. To familiarize subjects with the experimental setting and to avoid nonspecific effects of stress produced by novelty, all participants attended a pre-experimental session (Newlin and Pretorius, 1991; Maltzman and Marinkovic, 1996) lasting about 30 min. During this session, the experimental regime was explained to the subjects and they completed the Freiburg Personality Inventory (Fahrenberg et al., 1994). The first experimental session occurred 6–39 days after admission to the Central Institute of Mental Health (mean = 12.7, SD = 4.7). Autonomic reactivity and lorazepam-induced SRD were assessed in two 1.5 h sessions beginning at 9.00 a.m. each. Following an initial mood rating, either 0.5 mg lorazepam or inactive placebo was given to subjects of both groups. The order of administration was randomized. Both lorazepam and the inactive placebo were identical in appearance and were taken orally. Experimenter and subject were blind to order of substance administration (lorazepam/placebo vs placebo/oralzepam). After ingestion of the tablet, subjects were seated in a comfortable chair and electrodes for the recording of ECG, DBVA, EDA and EEG were attached. Then a second mood rating was completed and subjects were requested to relax during the succeeding resting baseline measurement. Mood ratings and measurement of resting baseline activity were repeated following each task. After further instructions and some practice, the first RT task started followed by MA and the second RT task.

Self-ratings of actual mood were completed five times each session using six unipolar 11-point rating scales (elated, irritated, even, depressed, dull, aroused).

**Data analysis**

All physiological data were analysed using the software package Event Detection and Analysis for Physiological Signals (Version 1.92) by J. Kaiser and H.-J. Trosiener (Berlin, Germany). Heart rate (HR) was derived from the ECG by defining the peak of the R-Wave and converting R-R intervals into beats per minute (bpm). These scores were subtracted from resting heart rate during the preceding baseline phase (100 s). DBVA was calculated second by second as the change in mean amplitude from preceding resting baseline (100 s). For statistical analysis, HR and DBVA were averaged across trials of five (RT tasks) respectively 20 s (MA). Since DBVA obtained using photoplethysmography is an arbitrary measure, absolute resting values cannot be compared between subjects. Therefore only DBVA reactivity is reported as percentage of change from preceding baseline. To assess electrodermal activity the number of non-specific responses (NSRs) greater than 0.05 µS was calculated for each resting baseline. To make the description of results more vivid, the numbers of NSRs per minute are presented (see Hugdahl, 1995, p. 105). The number of hits and correct subtractions were calculated as measures of performance.

All statistical analyses were performed with the BMDP (Version 7.0) software package. Greenhouse–Geisser corrections were used to adjust degrees of freedom for violations of the homogeneity of variance–covariance assumption for repeated measures factors. P < 0.05 was considered statistically significant.

**RESULTS**

**Mood ratings**

The self-report data of four subjects were excluded because of extreme bias, e.g. stereotype or inconsistent responses. Six separate analyses of variance (ANOVA) were performed with diagnosis (alcoholics vs controls) and drug order (lorazepam/placebo vs placebo/oralzepam) as between factors and drug (lorazepam vs placebo) and time (rating 1–5) as within factors. The ANOVAs revealed main effects of time for the rating scales elated [F(4,296) = 2.83; P < 0.05], irritated [F(4,296) = 6.68; P < 0.001] and even [F(4,292) = 11.38; P < 0.001]. Concerning the subscale score dull, main effects of diagnosis [F(1,74) = 16.69; P < 0.001] and time [F(4,296) = 9.84; P < 0.001] and an interaction of both factors [F(4,296) = 4.74; P < 0.01] emerged. With regard to the self-ratings of arousal, ANOVA yielded also main effects of diagnosis [F(1,74) = 6.76; P < 0.05] and time [F(4,296) = 9.09; P < 0.001] and an interaction among them [F(4,296) = 3.67; P < 0.05].

Generally, alcoholics described themselves as more aroused (mean = 7.14 vs 6.04) and less dull (mean = 1.21 vs 2.65). ANOVAs for contrasts indicated that only controls reported an increase of arousal [F(1,74) = 8.06; P < 0.001] and a decrease of dullness [F(1,74) = 14.93; P < 0.001] following the second rating. The groups did not differ in their final ratings of arousal at the end of the experiment (mean = 7.12 vs 6.56).

**Task performance**

Because of technical failure the data of two and three subjects respectively from the experimental and control groups were lost. The reported analyses involved a sample of 44 alcoholics (RT and MA), the RT data from 36 controls and the MA data from 35 controls.

ANOVA were performed with diagnosis (alcoholics vs controls) and drug order (lorazepam/placebo vs placebo/oralzepam) as between factors and drug (lorazepam vs placebo) as within factor. Additionally, the factor condition (incentive vs non-incentive) was included in the ANOVA concerning the number of hits in the RT tasks. This ANOVA revealed a drug × drug order interaction [F(1,76) = 7.77; P < 0.01]. Simple effects testing indicated that lorazepam slightly enhanced performance if placebo was administered first [F(1,76) = 4.09;
Physiological measures

Resting heart rate. An ANOVA including the factors diagnosis (alcoholics vs controls) and drug order (lorazepam/placebo vs placebo/orazepam) as between factors and drug (lorazepam vs placebo) and baseline period (period 1–4) as within factors revealed significant main effects of diagnosis \( [F(1,75) = 26.01; P < 0.001] \) and baseline period \( [F(3,234) = 1.63; P < 0.001] \) as well as two-way interactions of diagnosis and drug order \( [F(1,75) = 5.79; P < 0.05] \), diagnosis and baseline period \( [F(3,234) = 5.05; P < 0.01] \) and drug and baseline period \( [F(3,234) = 3.16; P < 0.05] \). Generally, resting HR was higher in alcoholics (mean = 84.54 vs 73.49 bpm). Simple effects testing indicated that order of substance administration changed resting HR in controls, but not in alcoholics \( [F(1,75) = 4.50; P < 0.05] \). Mean resting HR was lower in controls if lorazepam was administered first (lorazepam/placebo: mean = 70.08 bpm; placebo/orazepam: mean = 76.89 bpm). Moreover, resting HR increased throughout the session in controls \( [F(3,234) = 12.46; P < 0.001] \) but decreased in alcoholics \( [F(3,234) = 10.55; P < 0.001] \). ANOVAs for contrasts revealed that lorazepam induced an elevation of resting HR in baseline period 2 \( [F(1,80) = 4.86; P < 0.05] \) and baseline period 3 \( [F(1,80) = 6.95; P < 0.05] \) compared to initial resting HR (placebo: mean = 78.64 vs 79.69 vs 79.10 vs 78.68 bpm; lorazepam: mean = 78.01 vs 80.15 vs 79.46 vs 78.37 bpm).

Heart rate reactivity. Two separate ANOVAs were employed including the factors diagnosis (alcoholics vs controls) and drug order (lorazepam/placebo vs placebo/orazepam) as between factors and drug (lorazepam vs placebo), second (s 1–5 for the RT task respectively s 1–20 for the MA task) and the additional factor condition (incentive vs non-incentive) for the RT task as within factors. With regard to RT task, ANOVA revealed main effects of second \( [F(4,312) = 65.07; P < 0.001] \) and condition \( [F(1,75) = 9.96; P < 0.01] \), an interaction between drug and drug order \( [F(1,75) = 9.38; P < 0.01] \) and a drug × drug order × second interaction \( [F(4,312) = 8.01; P < 0.001] \). Acceleration of HR increased throughout single trials (see Fig. 1) and was larger when subjects had the opportunity to earn a monetary gain (mean = 1.04 vs 0.69 bpm). Simple effects testing indicated that the two-way interaction between drug and drug order was due to a larger HR acceleration during the first session (see Fig. 1). The drug × drug order × second interaction was due to a steeper increase of acceleration on the first day (see Fig. 1).

With respect to the MA task, main effects of second \( [F(19,1482) = 39.52; P < 0.001] \) and drug \( [F(1,78) = 4.10; P < 0.05] \) emerged. Furthermore, two-way interactions between drug and drug order \( [F(1,78) = 8.96; P < 0.01] \) as well as between diagnosis and second \( [F(19,1482) = 8.06; P < 0.001] \) were revealed. Simple effects testing indicated that the two-way interaction between drug and drug order was due to a slower mean HR acceleration after administration of lorazepam in the group that received placebo first \( [F(1,78) = 19.06; P < 0.001] \). Furthermore, only controls showed a marked initial HR acceleration at trial onset (see Fig. 2).

Digital blood volume amplitude

Two separate ANOVAs were performed as described above for HR reactivity. Regarding the RT task a main effect of second \( [F(4,312) = 30.31; P < 0.001] \) and a drug × drug order interaction \( [F(1,75) = 15.03; P < 0.001] \) emerged. DBV A decreased during a single trial (mean = 90.07 vs 90.70 vs 89.36 vs 87.19 vs 83.31 percentage of change from resting baseline level). This result is in accordance with elevation of HR acceleration, as a decrease of DBV A indicates an increase of sympathetic activation. Simple effects testing indicated that the two-way interaction of drug and drug order was due to a larger decrease of DBV A on the first day which is also in accordance with reported HR changes. With respect to the MA task, only a main effect of second \( [F(19,1482) = 3.97; P < 0.05] \) emerged. DBV A fluctuated in an unsystematic way during the course of a single trial.

Electrodermal activity

Because of technical failure the data of eight subjects were lost. The reported analyses thus involved a sample of 42 alcoholics and 32 controls.

An ANOVA including the factors diagnosis (alcoholics vs controls) and drug order (lorazepam/placebo vs placebo/orazepam) as between factors and drug (lorazepam vs placebo) and baseline period (period 1–4) as within factors revealed significant main effects of diagnosis \( [F(1,75) = 6.75; P < 0.05] \). Controls performed better on this task than alcoholics (mean = 51.37 vs 40.87 correct subtractions).
lorazepam) as between factors and drug (lorazepam vs placebo) and baseline period (1–4) as within factors revealed significant main effects of diagnosis \( [F(1,70) = 7.59; P < 0.01] \)
and baseline period \( [F(3,210) = 4.04; P < 0.05] \). Generally, the number of NSRs was higher in alcoholics (mean = 3.65 vs 1.97 NSRs). Contrasts indicated that the main effect of baseline period (mean = 3.19 vs 2.86 vs 3.09 vs 2.54 NSRs) was due to a smaller number of NSRs in baseline period 4 compared to baseline period 1 \( [F(1,70) = 7.74; P < 0.01] \) and baseline period 3 \( [F(1,70) = 9.45; P < 0.01] \).

**DISCUSSION**

The results of the present investigation do not conform with the assumption that alcoholics show a response pattern of autonomic hyper-reactivity and increased SRD. On the contrary, alcoholics showed a decreased acceleration of HR during MA, compared to healthy controls. Furthermore, no evidence for enhanced SRD was found. Before these unexpected results are discussed, possible interpretations of the differences in resting baseline levels will be considered.

**Resting baseline levels**

Resting HR was elevated and the number of NSRs heightened in alcohol-dependent subjects compared to healthy controls. Both corresponded with increased feelings of arousal in alcoholics. The differences in baseline HR are in accordance with the results of previous studies and clinical evidence. Acute alcohol intake as well as chronic alcohol misuse cause an increase in baseline HR (e.g. Dolinsky et al., 1987; Levenson et al., 1987; Bauer, 1994; Sheffield et al., 1997). The toxic effects of habitual alcohol misuse on the cardiovascular system is the main reason for the high prevalence of cardiovascular diseases in alcoholics (e.g. Matikainen et al., 1986; Malpas et al., 1991). Elevated resting HR level is not reported for high-risk subjects, e.g. sons of alcoholics or subjects scoring high on the MacAndrew Alcoholism Scale (e.g. Sher and Levenson, 1982; Levenson et al., 1987; Sayette et al., 1994). Therefore it can be assumed that high baseline levels are merely a consequence of alcohol dependence.

Evidence concerning tonic aspects of skin conductance in alcohol-dependent subjects is scant and heterogeneous. While some authors report negative findings (e.g. McCaul et al., 1989) others found both lower (Knott and Bulmer, 1985) and higher (Kaplan et al., 1985) SCLs in alcoholics. These mixed results may be due to divergent patient characteristics, e.g. different drinking histories.

Both the elevated resting HR and the great number of NSRs may be a consequence of sympatheticonita and increased noradrenaline activity during acute or protracted alcohol withdrawal (see Tabakoff and Hoffman, 1992). Despite the fact that the first experimental session was conducted 17.4 days after termination of alcohol intake, prolonged alcohol withdrawal cannot be ruled out as the cause of increased physiological arousal. Therefore correlations between baseline levels of autonomic activity and the daily consumption of alcohol during the 6 months prior to admission, time since last alcohol intake, as well as blood alcohol concentration (BAC) at time of admission were calculated. Data about BAC at the time of admission were available for 23 patients only. None of these correlations was significant, except that between number of NSRs and BAC \( (r = 0.52, P < 0.02) \). But this correlation failed to remain significant when the data of one outlier or zero BACs were excluded. Therefore it seems unlikely that the higher baseline activity in alcoholics is due to acute alcohol withdrawal.

Another interpretation of the increased number of NSRs in alcoholics is suggested by evidence concerning the evocation and habituation of the orienting response (OR) in non-alcoholic high-risk subjects (Finn et al., 1990). These latter authors found a larger amplitude of the skin conductance response (SCR) to non-aversive stimuli as well as shorter SCR latencies and slower habituation rates of the SCR in non-alcoholic sons of male alcoholics compared to controls with no family history of alcoholism. According to Finn et al. (1990), this response pattern ‘may reflect a relative lack of inhibition, an increased sensitivity to stimulation, an increased distractibility, or an increased responsivity to novel stimuli’ (p. 84). These speculations are in accordance with the results of studies concerning spontaneous EDA and the concept of electrodermal response (EDR) lability (for a review, see Crider, 1993). The frequency of NSRs under resting conditions seems to be a psychophysiological trait reflecting habitual engagement in orienting activity. Subjects who emit great numbers of NSRs during resting periods differ from their counterparts with respect to elicitation and habituation of the OR in the very same way as high-risk subjects from controls without a family history of alcoholism (e.g. Vossel and Zimmer, 1992).

An interpretation of the observed EDR lability in alcoholics with regard to general models of attention is consistent with assumptions about a basal regulatory deficit in alcohol-dependent subjects and their biological offspring. For example, according to Phil and Peterson (1992) alcoholics react to novel and potentially threatening stimuli in an overshooting way that hinders habituation. This hyper-reactivity is supposed to cause an overstimulation of specific brain regions, e.g. hippocampus and septum, as well as feelings of anxiety and tension, which are reduced by intake of alcohol and other anxiolytics.

**Autonomic reactivity**

No evidence for autonomic hyper-reactivity in alcohol-dependent men was found in the present study. Neither an acceleration of HR nor a decrease in DBVA was more pronounced in alcoholics compared to healthy controls. Surprisingly, alcoholics showed a decreased acceleration of HR during MA. Only in controls was a marked initial HR acceleration at trial onset evident. Furthermore, controls performed better on MA than alcoholics. To facilitate interpretation of these results, several additional analyses were conducted. Dependent measures were the maximum acceleration during MA (± 1 to 20), the latency of the maximum acceleration and the variability of latency. Latency was defined as the time from trial onset to maximum acceleration. As a measure of variability, the individual SD of latency was computed. Three separate univariate ANOVAs were employed including the factors diagnosis (alcoholics vs controls), drug order (lorazepam/placebo vs placebo/lorazepam) and drug (lorazepam vs placebo) each. The analyses revealed that alcoholics did not differ from controls with respect to maximum acceleration during MA or variability of peak latency, but HR acceleration...
reached its maximum later in alcoholics than in healthy controls (mean = 8.39 vs 6.42 s). Therefore, it can be ruled out that the absence of an initial HR acceleration in alcoholics was due to greater variability in HR reactivity within or between alcohol-dependent subjects.

To test the assumption that the differences in initial HR acceleration were due to task performance, mixed subgroups of alcoholics and controls according to the number of correct subtractions were formed. A univariate ANOVA with the between-factors performance (good vs poor) and diagnosis (alcoholics vs controls) revealed a significant main effect of performance on HR reactivity. Generally, subjects performing well on MA showed a prominent HR acceleration. Hence, the lower HR reactivity in alcoholics was probably due to their poor task performance.

Stress response dampening

The general effects of pharmacological challenge were minimal in both groups. Lorazepam had no effect on self-reported mood or the number of NSRs. Most drug × drug order interactions indicate a reduced autonomic reactivity on the second day and might reflect adaptation or habituation. The attenuated HR response during MA on the second day therefore seems to be due to the combined effects of adaptation and pharmacological challenge. One possible explanation for these negative findings might be that the pre-experimental session was not effective in familiarizing subjects with the novel environment. According to Newlin and Pretorius (1991), the pharmacological effect of alcohol is often underestimated in experimental research, because subjects are not usually acclimatized to the experimental setting before testing. The results of another study (Marinkovic, 1993) indicate that changes in resting baseline levels between sessions reflect familiarity with experimental setting and regime. Marinkovic (1993) reported a decline in the number of NSRs as well as for the mean amplitude of NSRs after an initial introductory visit to the laboratory. Both measures remained constant throughout four subsequent experimental sessions. Although psychophysiological measures were not obtained during the pre-experimental session in the present study, the stable baseline levels across experimental sessions suggest that subjects became familiar with the setting, otherwise baseline levels should have declined from the first to the second experimental session.

Because enhanced SRD in high-risk subjects is a rather robust phenomenon (e.g. Sher and Levenson, 1982; Finn and Pihl, 1987, 1988; Levenson et al., 1987; for a negative finding see Sayette et al., 1994), it was expected that lorazepam-induced SRD should be more pronounced in alcohol-dependent subjects, than in controls. This assumption could not be confirmed. A possible explanation for this failure to replicate the findings of Finn and Pihl in a sample of alcohol-dependent men is suggested by the results of pharmacological studies. The supposed premorbid sensitivity for the anxiolytic effects of alcohol might have been covered by an acquired cross-tolerance for benzodiazepines. Despite the fact that cross-tolerance between alcohol and benzodiazepines is well documented (for a review see Boisse and Okamoto, 1980) lorazepam was given in small doses (0.5 mg) to avoid the sedation and cognitive impairment observed after administration of large doses.

Experimental studies concerning pharmacological SRD in alcohol-dependent subjects have to deal with the dilemma of increased dispositional or functional (cross-)tolerance to alcohol or other anxiolytics on one hand, and the problems arising from sedation and cognitive impairment after administration of large doses on the other. In preparing a pharmacological challenge, researchers have to consider that interpretation of results may be hampered by possible sedating effects of alcohol or other CNS depressants. For example, lorazepam produces profound amnesia which persists for 8 h or more after oral doses of 1–4 mg (Mallick et al., 1993). Especially, if the experimental regime involves active coping — as in the present study — sedation and subjects’ awareness of cognitive impairment, e.g. increase of reaction time or short-term memory decrements, may induce additional stress originally not intended (for a review of the effects of benzodiazepines on human performance, see Johnson and Chernik, 1982). On the other hand, empirical evidence suggests that men at high risk for the development of alcohol dependence must consume at least moderately high doses of alcohol (e.g. 0.75 ml/kg body weight) in order to obtain its negatively reinforcing effects (e.g. Stewart et al., 1992) and it seems likely that sedation occurs at the resulting BACs. According to speculations by Bernston et al. (1997), the anxiolytic effects of benzodiazepines are due to an impairment of attention and information processing. Consequently, SRD may be assumed to be a secondary phenomenon depending on sedation. But this point of view is questionable, because some highly effective anxiolytics produce no, or only a moderate, sedation (e.g. Seidel et al., 1985). Further research is needed to clarify the nature of SRD induced by anxiolytics such as alcohol or benzodiazepines. Moreover, group-specific tolerance to the pharmacological effects of CNS depressants has to be taken into account, otherwise the detection of aetiological important differences regarding the potentially reinforcing consequences of alcohol consumption may be difficult. The use of other objective measures of intoxication besides BAC, e.g. the so-called equally effective alcohol dose (see Mizoi et al., 1969, cited in Naitoh, 1972), could be helpful in determining the adequate doses for experimental studies concerning SRD in alcoholics compared to non-alcoholics controls.

GENERAL CONCLUSIONS AND COMMENTS

Experimental manipulations induced an increase of autonomic activity as indicated by elevation of HR and reduction of DBVA. The incentive RT task produced a larger cardiovascular response than the non-incentive task. These general findings are in accordance with the results of previous studies. But the results of the present investigation are not in accord with the assumption that alcoholics show a response pattern of autonomic hyper-reactivity and increased SRD. On the contrary, alcoholics showed a decreased acceleration of HR during MA compared with healthy controls. This attenuation of HR reactivity in alcoholics seems to reflect their poor performance in this task. Furthermore, no evidence for enhanced SRD was found. These unexpected results may be due to the discussed methodological limitations of the present study. Alternatively — or additionally — a mix-up of different subgroups of alcoholics might have led to the negative findings.
Finn and Pihl (1987, 1988) reported that only high-risk subjects with a dense (multigenerational) family history of alcoholism showed increased psychophysiological reactivity and high sensitivity for the rewarding effects of alcohol. In the present study, alcohol-dependent subjects were included regardless of their family history of alcoholism. Despite the fact that information about family history was drawn mainly from routine records and only available for 33 patients, all statistical analyses were repeated for subgroups of alcoholics with \( n = 14 \) and without \( n = 19 \) a family history of alcoholism. The analyses revealed a main effect of family history on the HR acceleration during MA \( F(1,29) = 13.06; P = 0.001 \). Elevation of HR was more pronounced in alcoholics with a family history of alcoholism than in patients without an alcohol-dependent relative \( \text{mean} = 8.21 \text{ vs} 2.87 \text{ bpm} \). Subsequent analyses ruled out the possibility that this effect was due to differences in task performance. Furthermore, it was not limited to trial onset. No signs of SRD were found in either group of alcoholics.

This result should be interpreted with caution, because available information about family history in the present study is of low validity and the subgroup numbers are very small. But, taken as a preliminary result, this finding suggests that future research should address the psychophysiological response patterns of specific subgroups of alcohol-dependent subjects. In other fields of addiction research, subtyping of patients has already proven valuable in understanding the aetiology of substance misuse and improving treatment outcome (e.g. Lesch and Walter, 1996).

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