ATTENUATED SALIVARY CORTISOL SECRETION UNDER CUE EXPOSURE IS ASSOCIATED WITH EARLY RELAPSE


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Abstract — Aims: To test whether the risk of relapse in alcohol dependence is predicted by the subjective experience of cue exposure (CE) and/or cortisol reactivity to alcohol cues. Methods: Salivary cortisol and self-ratings of ‘tension’ and ‘desire to drink’ were measured in 32 detoxified alcohol-dependent inpatients during CE sessions conducted in the first and third week of motivation enhancement therapy. Subjects completed the Toronto Alexithymia Scale (TAS-20) and the Abbreviated Alcohol Expectancy Questionnaire (B-AEQ) towards the end of the inpatient treatment to measure emotional self-awareness and the expected positive effects of alcohol. Results: Six weeks after the end of the inpatient treatment, 15 patients were abstinent. Relapse was verified or was presumed for 17 patients. Those who had relapsed had shown an attenuated response to CE in the third week as an inpatient but did not differ from abstainers in terms of subjective reaction to cues. Subjective ratings of CE were not related to salivary cortisol or relapse but showed several associations with factors one and two of the TAS-20. The expectancy of enhanced social contacts by using alcohol (factor 1 of the B-AEQ) correlated negatively with the decline in salivary cortisol during the CE session in the third week of treatment. Subjective ratings of CE correlated with Alexithymia scores. Conclusions: Alcoholic patients who use alcohol to enhance their social contacts typically lack hypothalamic-hypophyseal-pituitary-adrenocortical (HPA) reactivity in the early period of abstinence. They are at an increased risk of early relapse and perhaps use alcohol to increase cortisol secretion again.

INTRODUCTION

Detoxified alcohol-dependent patients go through a phase of attenuated hypothalmo-hypophysal-pituitary-adrenocortical (HPA) axis reactivity (Errico et al., 1993; Ehrenreich et al., 1997; Lovallo et al., 2000). Such an attenuated cortisol response is associated with an increased risk of early relapse (Junghanns et al., 2003). However, the applied stressor in all these studies has not been alcohol-specific. Cortisol reactivity upon exposure to disorder-specific cues has been explored in several non-alcoholic disorders. Thus, a study on veterans with a post-traumatic stress disorder (a result of their wartime combat experiences), showed heightened responsivity to trauma-related cues in some of the investigated response modalities, among others in skin conductance, heart rate and catecholamines but not in cortisol (Liberson et al., 1999). In detoxified cocaine users, the exposure to cocaine-related cues elicited a rise in cortisol and adrenocorticotropic hormone (ACTH) along with anxiety and craving that were evaluated using visual analogue scales (VAS). Although anxiety and craving could be reduced by haloperidol, the rise in cortisol and ACTH could not be antagonized (Berger et al., 1996). However, this increased reactivity in cocaine users has not been cue-specific (Sinha et al., 2000, 2003).

Cue exposure (CE) as a drug-specific confrontation is an effective measure in the treatment of alcohol-dependent patients (Drummond and Glautiler, 1994; Monti and Rohsenow, 1999). CE in alcoholics is associated with subjective and some physiological responses. Thus, Monti et al. (1993) found an increase in salivation in 70% and an increased urge to drink (as marked on a 10-point Likert scale) in 65% of detoxified alcoholics upon exposure to his/her preferred alcoholic drink. Stormark et al. (1995) found an increased heart rate acceleration response and increased skin conductance in alcoholics exposed to the olfactory stimulus of high-potency alcohol (Stormark et al., 1995). Szegedi et al. (2000) investigated the effect of cue exposure on electrodermal activity, saliva production, electrocardiogram, neck electromyogram and respiratory frequency and compared it with subjective parameters. They found a significant increase in the ‘urge to drink’ as rated on a VAS by confrontation with alcohol-related cues. This response correlated with spontaneous fluctuations in the electrodermal activity only. Although 42% of their sample showed a physiological response, only 22% of the patients were both subjective and physiological responders to the presentation of alcohol. This discrepancy between physiological and self-reported response is also reflected in a meta-analysis of cue-reactivity studies across different addict groups (Carter and Tiffany, 1999). In a study on eight male alcohol-dependent inpatients who abstained from alcohol, the presentation and consumption of non-alcoholic beer that was believed to be alcohol-containing did not result in an alteration of cortisol secretion, but the cortisol level was decreased in comparison to nine moderate drinkers (Dolinsky et al., 1987). The physiological response to CE can be associated with the outcome of treatment. Thus, Drummond and Glautiler found an association of skin conductance during CE with latency to heavier drinking (Drummond and Glautiler, 1994). Cortisol reactivity to mere CE and its association with relapse has not been explored yet. Assuming that CE might be regarded as an alcohol-specific stressor, we were interested to explore whether cortisol reactivity to CE would yield similar results with respect to relapse as those found with the non-specific stressor applied in our previous study.

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In order not to confound the effect of CE with the stress of an inserted intravenous cannula (Vitiello et al., 1996; Prinz et al., 2000) we chose to assess cortisol levels in saliva. Salivary cortisol free cortisol which on account of its small size and high lipid-solubility rapidly diffuses from the blood stream via passive intracellular diffusion through the lipid-rich cell membranes of the acinar cells of the salivary glands into saliva. Its concentration in saliva is therefore not dependent on saliva flow-rate as demonstrated by several research groups, and it is a reliable tool for investigations of HPA axis activity (Kahn et al., 1988; Kirschbaum and Hellhammer, 1989). Salivary cortisol concentrations correlate well with serum concentrations (Aardal and Holm, 1995).

Furthermore, we wanted to explore whether the cortisol response to CE correlated with the subjective ratings during the sessions or with the expected (and in the past, already experienced) positive effects of drinking alcohol. Since it could be demonstrated that the physiological and cognitive reactions to CE are not necessarily correlated (Bradizza et al., 1999; Szegedi et al., 2000), we additionally used the Toronto Alexithymia Scale (TAS-20, Bagby et al., 1994, German version: Bach et al., 1996) to test the hypothesis whether the subjective ratings are more associated with emotional self-awareness than with cortisol response.

MATERIALS AND METHODS

The study started with the approval of the local ethics committee and upon receipt of the written informed consent of the participating patients.

All alcoholics fulfilled the DSM-IV criteria for alcohol dependency. They were consecutively recruited from our inpatient motivation enhancement therapy, which is a standardized three-week cognitive behavioural programme begun after detoxification. All patients were assessed by a structured psychiatric interview that included the primary questions on psychiatric diagnoses of the structured clinical interview for DSM-IV and ICD 10 diagnoses (SCID, German version Wittchen et al., 1997). Neither in the interview nor during their three-week treatment did they show any clinical signs of a major psychiatric disorder or illicit drug use. None of the participating subjects fulfilled the criteria of an antisocial personality disorder. Additionally, a complete medical history was taken and a complete physical examination performed. For inclusion into the study, the patients had to have no major comorbid organic disorder and to be unmedicated for at least one week prior to the study and be able to participate in the follow-up six weeks later. Patients who would predictably enter another inpatient therapy within this time span were excluded.

Altogether, 32 alcohol-dependent patients—5 females and 27 males, were recruited. The mean age was 45.9 ± 8.1 years, the mean duration of alcohol dependence was 13.5 ± 8.9 years and the reported mean amount of alcohol consumed daily prior to the last detoxification was 231.6 ± 177.2 g. The mean period of abstention from alcohol was 14.8 ± 9.9 days at the time of inclusion into the study.

The programme was offered in a group format that had new members in the same group setting and in the same room but was not supervised by a therapist. The other three CE sessions that were not supervised by a therapist were organized by staff without a preceding explanation of the rationale. In order not to confound the effect of CE with the stress of an inserted intravenous cannula (Vitiello et al., 1996; Prinz et al., 2000) we chose to assess cortisol levels in saliva. Salivary cortisol free cortisol which on account of its small size and high lipid-solubility rapidly diffuses from the blood stream via passive intracellular diffusion through the lipid-rich cell membranes of the acinar cells of the salivary glands into saliva. Its concentration in saliva is therefore not dependent on saliva flow-rate as demonstrated by several research groups, and it is a reliable tool for investigations of HPA axis activity (Kahn et al., 1988; Kirschbaum and Hellhammer, 1989). Salivary cortisol concentrations correlate well with serum concentrations (Aardal and Holm, 1995).

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The programme was offered in a group format that had new patients entering the therapy every Tuesday, which was on the day before their first CE session. CE was offered twice per week and all patients participated in six cue exposure sessions during their stay. The first CE session of each week was always supervised by a therapist and proceeded in the following manner: the rationale of CE was explained and discussed from 2:45 to 3:30 PM. CE was introduced as a means to cope better with high-risk situations of relapse. Patients were asked to evoke an intense desire to drink alcohol or to try to imagine the relapse situation as intensely as possible during the immediately ensuing CE session. It was explained to them that by provoking tension and/or an intense desire to drink without actually drinking, they would in the end probably experience a decline in tension and/or desire and thus make the positive experience that they can resist drinking even with the typical relapse drink in front of them. Furthermore, it was explained that repeated CE would increase the chances of successful coping in high-risk situations.

At the end of this explanation the patients put their typical relapse drink in front of themselves and collected the first cortisol sample (first week: W1-1 and third week: W3-1). In a staggered approach (first looking at the bottle or can, then putting it in one’s hand, then opening and smelling it, pouring the content into a glass, then putting the glass to one’s lips without drinking, while imagining a typical relapse situation) with a standardized time schedule, the patients were confronted with the drink and their desires. Just before discarding the drink, the patients collected the second saliva sample (first week: W1-2, third week: W3-2). Each CE session lasted for one hour. Besides the assessment of salivary cortisol the patients scored their tension and desire to drink alcohol and to smoke before, during and at the end of CE. We used a six-box VAS with only the extremes marked (from left to right) as ‘no tension’ and ‘very tense’ or ‘very strong desire’ and ‘no desire’ to drink alcohol or smoke, respectively. The other three CE sessions that were not supervised by a therapist were organized by staff members in the same group setting and in the same room but without a preceding explanation of the rationale.

Two days later that same week, the patients collected another sample at 4:30 PM (first week: W1-3, third week: W3-3) during an occupational therapy session when they had been woodworking in a relaxed atmosphere and had not been smoking for at least one hour.

At the end of the inpatient treatment, the 20-item TAS-20 and the German version of an abbreviated Alcohol Expectancy Questionnaire (B-AEQ) were administered to assess the emotional status and the expectancy concerning with respect to the positive effects of alcohol (Demmel and Hagen, 2003). The latter questionnaire comprised 19 items in a dichotomous (yes/no) answer format out of which two factors can be calculated: factor 1 has a high internal consistency (Cronbach’s alpha = 0.90), whereas factor 2 has a low internal consistency (Cronbach’s alpha = 0.70). Retest reliability is 0.88 for factor 1 (enhancement of social contacts) and 0.79 for factor 2 (reduction of tension and regulation of affect). It is based on the American Alcohol Expectancy Questionnaire (AEQ, Brown et al., 1987).

Six weeks after discharge from hospital, 21 patients were interviewed in person about relapse, the reports being compared using breathalyzer and blood samples assessing gamma-glutamyl transferase, mean corpuscular volume of the erythrocytes and carbohydrate-deficient transferrin. The interviewer was blind to the results of the CE. Relapse was defined as the consumption of at least one alcoholic beverage since discharge from the hospital. In addition, confirmation of
the interview data was collected by a third person. No patient denied a relapse when faced with incongruent laboratory data or third-party reports. The day of the first drink was calculated with the time line followback strategy. Of these 21 patients, six had had a relapse whereas 15 had not.

Eleven patients failed to show up for follow-up despite repeated efforts to get in touch with them by phone or mail. Patients who did not attend the follow-up were counted as relapse, so that the overall relapse rate after 6 weeks was calculated as 53.1%. Relapsers and abstainers did not differ with respect to age (mean age 45.9 years, \( T = 0.003, P = 0.998 \)) or gender (three of five females had relapsed as compared to 15 of 29 males, \( \chi^2 = 0.112, P = 0.737 \)).

Saliva specimens were stored at \(-20^\circ C\) until an analysis was done; prior to assay, they were thawed, mixed and centrifuged at 10 000 \( g \) for 10 min. Cortisol concentration in centrifugation supernatants was measured by a commercial direct solid-phase radioimmunoassay (Coat-A-Count Cortisol, DPC Biermann, Bad Nauheim, Germany) using appropriately diluted (1:10 with water) standardized solutions, 200 \( \mu l \) sample volume, and equilibrium binding conditions (incubation of sample and \( ^{125}I \)-labelled tracer (1000 \( \mu l \)) for 24 h at room temperature). Under these conditions, the measurable range extended from 2 to 150 nmol/l. Intra- and interassay precisions were <9% at 11 nmol/l and <7% at 34 nmol/l mean cortisol concentrations. Recovery of standardized cortisol added to saliva samples was 93–101%. According to information given by the manufacturer, antiserum crossreactivity to endogenous steroids other than cortisol is generally below 1% with the only exception of 11-deoxycortisol (11.4%). The assessor was blinded to the participating subjects and their diagnosis.

Age and cortisol data were normally distributed whereas subjective ratings were not. Consequently nonparametric tests were applied when ratings were involved, whereas parametric tests were used when salivary cortisol was assessed. The differences between abstainers and relapsers with respect to the data on cortisol were analysed by applying analysis of variances (ANOVA) with repeated measurements for the two CE sessions with \( t \)-tests as post-hoc tests. For the calculations the statistical program SPSS version 11.0 was used with a two-sided alpha of 0.05.

**RESULTS**

**Results on salivary cortisol**

Levels of salivary cortisol were highest after an explanation of the rationale was made to the patients at the start of both investigated sessions (W1-1 and W3-1). At the end of the respective sessions, mean salivary cortisol values were significantly lower (W1-2 and W3-2). ANOVA with repeated measurements yielded a significant time and time \( \times \) group effect for these two sessions combined (time effect: \( F = 10.04, P = 0.001 \), time \( \times \) group effect: \( F = 3.44, P = 0.023 \)). Post hoc \( t \)-tests showed a significant group difference for salivary cortisol values in the third week (see Table 1).

Relapsers had a significant decline in salivary cortisol values at the start of CE from the first to the third week (cortisol at W1-1 vs. W3-1, \( T = 3.08, P = 0.007 \), paired \( t \)-test) but did not sustain the significant decrease during the third week’s session (W3-1 to W3-2, \( T = 0.102, P = 0.92, t \)-test of paired samples). Abstainers, in contrast, maintained a significant decline during the CE session (W3-1 to W3-2: \( T = 4.77, P = 0.001 \)) owing to a higher cortisol at the start of the session (W3-1) (see Figure 1). The ‘resting-value’ from the first to the third week (W1-3 as compared with W3-3) did not change significantly (\( T = 1.84, P = 0.07, \) paired \( t \)-test).

Factor 1 of the B-AEQ summarizes positive answers with respect to the alcohol-related enhancement of social contacts and correlated negatively with the decline found in salivary cortisol in the third week (\( r = -0.44, P = 0.019 \)). However, the differences between relapsers and abstainers were not significant on this score.

**Ratings of CE and Alexithymia scores**

In contrast to salivary cortisol, ratings of tension and desire to consume alcohol increased during CE but declined again at the end (Figure 2). There was no difference between relapsers and abstainers with respect to these aspects at any one of the two sessions assessed. The tension rated at the start of each session decreased significantly from the first to the third week (\( Z = -2.97, P = 0.003, \) Wilcoxon test) whereas the decrease in the desire to drink alcohol was not significant. The desire to smoke increased from the start to the end of both CE sessions with a strong effect of time (\( P < 0.01, \) ANOVA with repeated measurements) but no effect of group for each session.

There was no correlation between subjective ratings and cortisol values. In contrast, TAS-20 factors 1 and 2 correlated with the subjective ratings: the higher the subjective ratings with respect to tension, desire to drink alcohol and desire to smoke, the more problems there were in identifying and describing emotions. This was especially marked at the beginning of the CE session in the third week (Table 2). Again, however, abstainers and relapsers did not differ with respect to the Alexithymia scores.

**DISCUSSION**

A greater risk of relapse was associated with a smaller decrease in cortisol during CE in the third week. This is in

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<th>Table 1. Salivary cortisol at the start and end of CE in the first and the third week (means ± SD)</th>
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<td><strong>Salivary cortisol</strong></td>
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<tr>
<td>Whole sample (n = 32)</td>
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<tr>
<td>Relapsers (n = 17)</td>
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<td>Abstainers (n = 15)</td>
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Statistics: \( t \)-test of paired samples for whole sample, \( t \)-test of independent samples comparing relapsers and abstainers with respect to difference between W1-1 and W1-2 and between W3-1 and W3-2.
accordance with our previous study (Junghanns et al., 2003) where we used a stressor that was not alcohol-specific. In contrast to this difference in cortisol reactivity, both those who later relapsed and those who abstained rated their intensity of the elicited desire to drink alcohol and the tension experienced in the session similarly. These subjective ratings showed the expected increase–decrease course during CE sessions and also showed a significant decline in tension from the first to the third week. This decline was in line with the overall improvements seen in the patients over the three weeks of treatment but we cannot rule out if the ratings were a measure of social conformity.

We do not think that we should attempt a discussion on craving in our study. Not only is the concept of craving deemed complex (Wetterling et al., 1997; Sayette et al., 2000) but it was also not assessed adequately with the rating scales applied here. We also think that a necessary (and not sufficient) criterion of craving is a high-intensity desire to drink. Consequently, the low intensities of desire to drink alcohol and of perceived tension as rated in real time on a VAS in this study do not allow a discussion of any provoked craving at all.

Table 2. Correlations of the intensity of tension (1 = no tension, 6 = very strong tension), desire to drink alcohol or smoke cigarettes (1 = very strong, 6 = no desire) at the start of the CE session in the third week with TAS-20 factors 1 (difficulty in ID of emotions) and 2 (difficulties in description of emotions)

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<th></th>
<th>Tension</th>
<th>Desire to drink</th>
<th>Desire to smoke</th>
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<tr>
<td>(TAS-20 factor 1)</td>
<td>0.496**</td>
<td>−0.367*</td>
<td>−0.697**</td>
</tr>
<tr>
<td>(TAS-20, factor 2)</td>
<td>0.562**</td>
<td>−0.613***</td>
<td>−0.522**</td>
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Correlations calculated with Spearman’s ρ. *P < 0.05, **P < 0.01.
in line with our expectations, the cortisol reaction was different: it was higher at the start than at the end of the session. We suppose that this was due to an expectancy effect: all patients had been ‘primed’ by the explanation of the CE rationale. At that point in time they knew that they were about to be confronted with their typical relapse drink and presumably anticipated the CE physiologically. Such an interpretation is tentatively supported by a study of Weinstein et al. (1998) who demonstrated that the imagination of a drinking situation can lead to the same physiological response as actual presentation of an alcoholic beverage. Although in our study this physiological reaction remained unchanged in the abstainers until the third week of treatment, it was lost in those who were to relapse later. The loss of a stress response at this time of abstention was already found to be a risk factor for an early relapse in a previous study of ours (Junghanns et al., 2003). Newlin found a decreased heart rate and increased skin conductance upon CE and interpreted this as a conditioned antagonistic response to an anticipated alcohol ingestion (Newlin, 1985). In line with this interpretation, a decreased cortisol response might be interpreted as a reactivated antagonistic conditioned response in the later relapsers. This hypothesis would to some degree be further supported by the results of O’Malley et al. (2002) who found an increase in cortisol secretion that was associated with a diminished craving for alcohol as assessed with the alcohol urge questionnaire. A diminished cortisol response could be a sign of a physiologically (re-) increased ‘wanting’ (Robinson and Berridge, 2000) that increases the risk of relapse, although it is not perceived consciously. This would also be in accordance with the theory of Tiffany and Conklin on a possible dissociation of physiological and conscious experiences in alcohol-dependent patients (Tiffany and Conklin, 2000).

In this study we judged those who did not show up for follow-up as relapers, which carries the risk of counting abstaining patients as relapers. As the significant results with respect to cortisol reactivity were the same only if those who came to follow-up were included (ANOVA for repeated measurements), we think that our conservative estimation of the abstinence rate did not distort the results.

Although we think that the data of previous studies and the arguments presented speak in favour of a decline in cortisol reactivity among the later relapsers, no final decision on this question can be made. A controlled study with several assessments of salivary cortisol at the same time of the day but under conditions of rest is necessary to verify that the shown cortisol secretion under the conditions of CE was indeed a reaction to CE. But given that our hypothesis of the cortisol reaction to CE is true and will be confirmed by further studies, this would mean that cortisol reactivity to CE does not differ from that of non-alcoholic stressors. The fact of a similar stress reaction to unspecific and drug-specific cues was shown for cocaine-dependent patients (Sinha et al., 2000).

As with other studies (Szegedi et al., 2000), our data show a dissociation between subjective and objective parameters. Interestingly, the subjective ratings of tension and desire to drink alcohol or smoke correlated with the difficulties in identifying and describing emotions as assessed by the TAS-20. This observation complements the results of Bradizza et al. (1999), who found an association between self-consciousness and subjective cue ratings but none between these ratings and their physiological measure — saliva production. The Alexithymia scores were not associated with the risk of relapse, which suggests that a lack of self-awareness towards one’s own emotions during this time of abstinence does not allow prediction of relapse if the patient does not suffer from a comorbid affective or anxiety disorder. The latter two disorders are associated with an increased risk of relapse (Driessen et al., 2001) but were excluded in this study.

The exposure to drug-specific cues is regarded as a potential technique for having a positive influence on a patient’s capacity to cope with his dependence and specifically with situations carrying a high risk for relapse. Although no increase in abstinence could be shown, data suggest that this procedure can help to reduce the amount of drinking (Drummond and Glautier, 1994), especially if this procedure is accompanied by social-skills training (Monti and Rohsenow, 1999). Although the data of the present study cannot contribute to the question of an effect of CE on abstinence, we showed that the expectancy of enhanced social contacts by means of alcohol correlated with the attenuation of cortisol response to CE at the end of therapy, and that this cortisol response in turn was associated with an increased risk of relapse. This might mean that those who use alcohol to enhance their social contacts typically lack HPA reactivity at this early period of abstinence and perhaps use alcohol to increase cortisol secretion again. The causal connections between the HPA axis, alcohol expectancy and CE are thus a worthwhile target of further studies.

REFERENCES


