REWARD CRAVING AND WITHDRAWAL RELIEF CRAVING: ASSESSMENT OF DIFFERENT MOTIVATIONAL PATHWAYS TO ALCOHOL INTAKE

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Abstract — Aims: Craving for the rewarding effects of alcohol may be evoked by conditioned alcohol-like effects whereas conditioned compensatory responses may induce withdrawal relief craving. We tested the hypothesis that drinking in positive emotional states is associated with appetitive reactions to alcohol-associated cues and contributes to reward craving, while conditioned withdrawal is associated with drinking in negative situations and distressful, obsessive preoccupations with alcohol. Methods: In 38 detoxified alcoholics, the Obsessive Compulsive Drinking Scale was used to assess the craving factors ‘impaired control’, ‘interference with social functioning’ and ‘obsession’. Affective responses to alcohol-associated visual stimuli were measured with the affect-modulated eyelblink startle reflex, positive and negative drinking situations with the Inventory of Drinking Situations (IDS) and withdrawal-like symptoms preceding alcohol intake with the revised Clinical Institute Assessment for Alcohol Scale (CIWA-Ar). Results: Appetitive reactions to alcohol-associated cues correlated positively with drinking in positive situations and contributed significantly to the craving factor ‘interference’ with social and work functioning. The severity of withdrawal-like symptoms preceding alcohol intake contributed to the craving factor ‘obsession’; however, contrary to our hypothesis, this measure of conditioned withdrawal correlated with drinking not only in negative but also in positive situations. Conclusions: Drinking in positive and negative situations, appetitive reactions to alcohol and withdrawal-like symptoms contributed differentially to the craving factors ‘obsession’ and ‘interference’, supporting the notion of different craving factors with separate underlying mechanisms.

INTRODUCTION

Craving for alcohol can be elicited by exposure to alcohol and alcohol-associated stimuli in abstinent alcoholics (Niaura et al., 1988; O’Brien et al., 1998; Carter and Tiffany, 1999). There is a controversy regarding the exact mechanisms involved in cue-induced alcohol and drug craving. Wikler (1948) observed that drug-associated stimuli, which have regularly been paired with opiate intake, evoke conditioned physiological reactions that oppose drug effects. Such conditioned compensatory responses help to maintain a homeostatic balance during drug or alcohol intake and may manifest as conditioned withdrawal if alcohol-associated cues are presented but not followed by actual drug intake (Siegel, 1983). In alcoholism, conditioned withdrawal may be caused by an imbalance between central glutamatergic and γ-aminobutyric acid (GABA)-ergic neurotransmission. Acute alcohol intake potentiates GABAergic sedation and inhibits glutamatergic excitation (Koob, 1992; Tsai et al., 1995). Chronic alcohol intake down-regulates GABA receptors and thus ensures homeostatic regulation (Abi-Dargham et al., 1998). When the sedative effects of alcohol are suddenly withdrawn during detoxification, reduced GABAergic inhibition and increased glutamatergic excitatory neurotransmission may manifest as anxiety, seizures and autonomic dysregulation (Tsai et al., 1995). Cues associated with prior alcohol intake that are not followed by actual alcohol consumption, stress exposure, or negative mood states may induce conditioned withdrawal and withdrawal relief craving (Siegel, 1983; McCusker and Brown, 1990; Cooney et al., 1997). Alcohol consumption may then be reinstated to reduce withdrawal stress, thus acting as a negative reinforcer (Edwards, 1990). Acamprosate, a drug used to reduce craving in abstinent alcoholics (Sass et al., 1996), blocks glutamatergic N-methyl-D-aspartate receptors and may exert its therapeutic effects by decreasing stress- and cue-induced conditioned withdrawal and withdrawal relief craving (Littlton, 1995; Spanagel and Zieglgänsberger, 1997).

An alternative hypothesis suggests that alcohol craving is induced by the mood-enhancing, positive-reinforcing effects of alcohol and drug intake (Stewart et al., 1984; Wise, 1988; Koob and Le Moal, 1997). Craving for the rewarding effects of alcohol can be mediated by opioidergic and dopaminergic neurotransmission in the ventral striatum (Spanagel et al., 1992; Di Chiara, 1995; Volpicelli et al., 1995). Associative learning may transform positive mood states and previously neutral environmental stimuli into alcohol-associated cues that acquire positive motivational salience and induce reward craving (Robinson and Berridge, 1993). Among alcoholics, the appetitive character of alcohol-associated visual stimuli was indicated by an attenuation of the eyelblink startle response (Mucha et al., 2000; Grüsser et al., 2002). The motivational effects of positive mood states and external alcohol-associated cues on alcohol craving and consumption may be blocked by naltrexone (Monti et al., 1999).

Anton et al. (1996) constructed the Obsessive Compulsive Drinking Scale (OCDS) which focuses on obsessive–compulsive aspects of alcohol craving. A factor analysis revealed that three factors contribute to alcohol craving as assessed with the OCDS: ‘control impairment’, ‘obsession’ and ‘interference’. ‘Obsession’ describes the distress or anxiety caused by a pre-occupation with alcohol-associated ideas or impulses, ‘control impairment’ the lack of success in the control of alcohol intake, and ‘interference’ the degree of interference with social or work functioning (Roberts et al., 1999). Naltrexone medication was associated with reduced scores for ‘control impairment’ but not the other two craving factors (Roberts et al., 1999).
Recently, Verheul et al. (1999) suggested that reward craving, withdrawal relief craving and obsessive craving are not mutually exclusive concepts, but, rather, describe different types of alcohol craving with distinguishable neurobiological correlates. The individual response to naltrexone or acamprosate medication may depend upon the relative strength of the respective alcohol craving type and its neurobiological foundation.

For the clinical identification of alcohol craving types, we measured different aspects of alcohol craving with the Obsessive Compulsive Drinking Scale (Anton et al., 1996). We tested the hypothesis of Verheul et al. (1999) that subjects who crave for the rewarding effects of alcohol mainly consume alcohol in emotionally positive situations and show appetitive responses to alcohol cues, whereas subjects suffering from withdrawal relief craving drink mainly in negative situations and report unpleasant, withdrawal-like symptoms preceding alcohol intake. We also tested the hypothesis that negative mood states and conditioned withdrawal contribute to distressful obsessive alcohol craving (factor ‘obsession’ in the OCDS) and that appetitive reactions to alcohol cues and drinking in positive situations contribute to ‘control impairment’ and ‘interference’ with social and work functioning.

SUBJECTS AND METHODS

Subjects

Thirty-eight abstinent alcoholics who fulfilled diagnostic criteria for alcohol dependence according to ICD-10 (World Health Organization, 1992) were included in the study. The mean ± SD age of the patients was 44 ± 13 years. Patients had been detoxified on a ward and participated in a supervised treatment programme. All psychological and psychophysiological testing was performed on the same day after 1–3 weeks of supervised abstinence; abstinence was controlled with random alcohol blood and breath testing and urine drug assessment. Standardized clinical assessment was performed with the ‘Manual for the Assessment and Documentation of Psychopathology’ (Fühndrich and Stieglitz, 1997); patients had no axis I psychiatric disorders according to ICD-10 and no previous substance dependence or current substance misuse other than alcoholism (random urine drug testing). Patients with neurological or hepatic impairment (e.g. liver cirrhosis) were excluded. The amount of lifetime alcohol intake was measured with the Lifetime Drinking History (LDH; Skinner and Sheu, 1982). Patients reported an average lifetime chronic alcohol intake of 560 ± 419 kg. Within the last 6 months prior to detoxification, the patients were drinking on average on 134 ± 54 out of 180 days with 17 ± 12 standard drinks per drinking day (see Table 1). All subjects were free of psychotropic medication and had not received benzodiazepines or clomethiazole for ≥7 days. The study was approved by the Ethics Committee of the Mannheim Faculty of Medicine at the University of Heidelberg and informed written consent was obtained from all participants.

Psychological testing

On the test day, patients were first interviewed and then the eyeblink startle response was measured in the psychophysiological laboratory. Craving for alcohol was measured with the OCDS (Anton et al., 1996). Mood states during alcohol intake were assessed with the Inventory of Drinking Situations (IDS; Victorio-Estrada et al., 1996); previous analysis showed that drinking situations mainly load on two factors, positive and negative mood states (Victorio-Estrada and Mucha, 1997). With the IDS, patients were assessed with respect to typical drinking situations during the last 12 months. Patients were also asked for withdrawal-like symptoms that regularly precede alcohol intake, which were experienced in a typical drinking situation in the last 3 months prior to detoxification. Patients’ reports of symptom severity were rated with the revised Clinical Institute of Alcohol Withdrawal Scale (CIWA; Sullivan et al., 1989). In a pilot study, the CIWA score was applied twice within two consecutive days in 10 alcoholics who had abstained from alcohol for 1–2 weeks, and the test–retest reliability of this procedure was ρ = 0.926. The non-parametric correlation coefficient ρ was selected, because of the non-normal distribution and the ordinal nature of the CIWA scales. To test for the adequacy of the linear interpretation of the CIWA total score, we transformed it to a quantitative discrete scale and correlated this with the original total scores. The correlation of ρ = 0.915 shows the adequacy of our linear interpretation of the CIWA total score.

Psychophysiological assessment

The appetitive or aversive nature of alcohol-associated cues was measured with the affectively modulated eyeblink startle response (Lang et al., 1990). A potentiation of the startle response by the induction of negative mood states and an attenuation of the startle response by positive mood states have been widely described in studies among healthy volunteers and patients with different neuropsychiatric disorders (Vrana et al., 1988; Bradley et al., 1990; Cook et al., 1992). In alcoholics, two studies reported an attenuation of the startle response during the presentation of alcohol-associated stimuli, compared with emotionally negative and neutral stimuli (Mucha et al., 2000; Grüsser et al., 2002).

Eight slides showing alcoholic beverages were randomly presented along with eight neutral, eight unpleasant and eight pleasant objects and 30 startle probes. The pleasant, unpleasant and neutral pictures were taken from the International Affective Picture System (IAPS; Lang, 1995) and were separately selected for male and female subjects. Pleasant, unpleasant, neutral and alcohol-associated stimuli were matched for arousal

Table 1. Patients’ demographic and other characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 13</td>
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<tr>
<td>Age of onset of alcoholism (years)</td>
<td>28 ± 10</td>
</tr>
<tr>
<td>Lifetime alcohol consumption (kg)</td>
<td>560 ± 419</td>
</tr>
<tr>
<td>Drinking days (last 6 months)</td>
<td>135 ± 54</td>
</tr>
<tr>
<td>Standard drinks per drinking day</td>
<td>17 ± 12</td>
</tr>
<tr>
<td>CIWA total score</td>
<td>7.4 ± 5.7</td>
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<tr>
<td>IDS positive score</td>
<td>1.35 ± 0.85</td>
</tr>
<tr>
<td>IDS negative score</td>
<td>1.47 ± 0.57</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/l)</td>
<td>34 ± 24</td>
</tr>
<tr>
<td>γ-Glutamyltranspeptidase (U/l)</td>
<td>88 ± 155</td>
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</tbody>
</table>

Values are means ± SD of 38 subjects (six females and 32 males).

CIWA, Clinical Institute Assessment for Alcohol; IDS, Inventory of Drinking Situations.
ratings; valence and arousal data were taken from the IAPS and controlled for in our patient sample. Alcohol craving was rated with the OCDS immediately before picture presentation.

The subjects were first prepared for recording from the left orbicularis oculi. To evoke the startle eyeblink response, white noise was presented via headphones with 95 dB while the subjects viewed the visual stimuli (Geier et al., 2000). Visual stimuli were presented for 7.5 s at intervals of 21 s on a high-resolution monitor (35.8 cm) of an Acer travelmate (7100TE) laptop placed 0.5 m in front of the subject. The startle probe was a 50 ms burst of white noise delivered over headphones on average 4 s after picture onset. The muscle activity was stored for off-line analysis (Geier et al., 2000), and the startle amplitude (peak activity) was used as the outcome measure. The startle response was standardized with a z-transformation with respect to intra-subject baseline level and variability to correct for varying signal quality.

Statistical analysis

In the confirmatory part of the statistical analysis of the results of the present study, the t-statistic for paired observations was used to decide whether the data contain sufficient evidence in favour of the following (alternative) hypotheses: (1) the startle response elicited during the presentation of alcohol-associated cues is reduced, compared with the response during the presentation of affectively neutral cues (Grüsser et al., 2002); (2) the startle response elicited during the presentation of alcohol-associated cues is reduced compared with the response during the presentation of affectively neutral cues (Mucha et al., 2000; Grüsser et al., 2002); (3) the startle response during the presentation of alcohol-associated cues is similar to the response to affectively positive stimuli among alcoholics (Grüsser et al., 2002). In order to keep the multiple type-I error risk <5%, the sequentially rejective procedure of Holm (1979) was applied. Accordingly, any of the significance statements made in the Results section refers to an experiment-rather than comparison-wise type-I error risk bounded by 5%.

Since the first two individual hypotheses are uni- rather than bilateral, both corresponding tests were performed in a one-sided manner. Furthermore, hypothesis 3 states equivalence of alcohol-associated and affectively positive stimuli. Hence, a testing procedure appropriate for the latter is the paired t-test for equivalence as described by Wellek (2002). In this approach, equivalence is defined through the standardized difference \( \delta / \sigma \) of the two means under assessment. The equivalence range for \( \delta / \sigma \) was specified (-0.5, 0.5), and the P-value computed from the non-central F-distribution with 1, n – 1 degrees of freedom and non-centrality parameter 0.25n.

At the exploratory level, the following additional analyses were performed. The correlation between (1) the startle response to alcohol cues and alcohol consumption in emotionally positive situations and (2) the severity of withdrawal-like symptoms before alcohol intake and emotionally negative drinking situations was measured by means of the ordinary product-moment correlation coefficient. Finally, linear multiple regression techniques were used to assess the association of: (1) the startle response to alcohol cues; (2) alcohol consumption during positive mood states; (3) negative mood states; (4) withdrawal-like symptoms, with the craving factors ‘obsession’, ‘control impairment’ and ‘interference’ (Roberts et al., 1999).

RESULTS

The startle response during the presentation of alcohol-associated pictures was found to be significantly decreased as compared to the response during presentation of affectively negative cues (\( t = -2.26, P = 0.0149 \); see Fig. 1). Whereas the analogous comparison with the measurements taken in the presence of neutral cues gave no significant result (\( t = -1.02, P = 0.1572 \)), we were able to establish equivalence of alcohol-related and affectively positive cues (\( t = 0.96, P = 0.0172 \)), confirming previous reports of the appetitive nature of alcohol-associated cues for alcoholics (Mucha et al., 2000; Grüsser et al., 2002).

As hypothesized, appetitive responses towards alcohol-associated cues, as indicated by a low startle response during the presentation of alcohol-associated cues, showed a positive correlation (\( r = 0.37, \) descriptive \( P < 0.05 \)) with drinking situations in positive mood states assessed with the IDS (Vicario-Estrada et al., 1996). Contrary to our hypothesis, the reported severity of withdrawal symptoms experienced before alcohol intake was only loosely associated with alcohol consumption in negative mood states (\( r = 0.2, \) descriptive \( P = 0.2 \)). Instead, withdrawal symptoms preceding alcohol intake showed a correlation of a moderate size (\( r = 0.57, \) descriptive \( P < 0.05 \)) with alcohol intake in emotionally positive situations.

In a multiple linear regression analysis, appetitive responses to alcohol-associated cues, alcohol consumption during positive and negative mood states, and withdrawal-like symptoms explained 52% of the variance of the craving factor ‘obsession’. The severity of withdrawal-like symptoms that precede alcohol intake (CIWA score) was the only factor that substantially contributed to explaining the variance of ‘obsessive craving’ (\( \beta = 0.59, r_{\text{par}} = 0.59, \) descriptive \( P < 0.005 \)); post-hoc analysis showed that, in most patients, symptoms such as ‘paroxysmal sweats’ (\( r = 0.58, \) descriptive \( P = 0.001 \)) and ‘auditory disturbances’ (\( r = 0.55, \) descriptive \( P = 0.001 \)) contributed to this association, whereas patients hardly ever reported ‘agitation’.

![Fig. 1. Affect-modulated startle reaction.](image)

For the convenience of the reader, the values were normalized to a mean of 100 and an SD of 10.
Drinking in positive \((\beta = 0.21, r_{\text{part}} = 0.18, \text{descriptive } P = 0.4)\) and negative situations \((\beta = 0.02, r_{\text{part}} = 0.02, \text{descriptive } P = 0.9)\) and appetitive responses to alcohol-associated cues \((\beta = -0.04, r_{\text{part}} = -0.04, \text{descriptive } P = 0.8)\) proved to be of little, if any, relevance for predicting the intensity of obsessive alcohol craving.

‘Interference’ with social and work functioning was also explained to a relevant extent by the factors of appetitive responses to alcohol-associated cues, alcohol consumption during positive and negative mood states, and withdrawal-like symptoms \((r^2 = 44\%)\). Alcohol consumption in positive mood states was the only factor which showed some association with ‘interference’ \((\beta = 0.61, \text{partial } r_{\text{part}} = 0.44, \text{descriptive } P < 0.05)\). Neither drinking in negative situations \((\beta = -0.07, r_{\text{part}} = -0.07, \text{descriptive } P = 0.8)\) nor appetitive responses to alcohol-associated cues \((\beta = 0.15, r_{\text{part}} = 0.17, \text{descriptive } P = 0.5)\) or withdrawal-like symptoms preceding alcohol intake \((\beta = 0.02, r_{\text{part}} = 0.02, \text{descriptive } P = 0.9)\) could be used to explain a substantial proportion of the variance of the interference of alcohol intake with social and work functioning. Finally, in a linear model relating ‘control impairment’ to all four covariables taken into account, only \(r^2 = 29\%\) of the variance of the dependent variable could be explained by the regression function.

DISCUSSION

We were able to confirm some, but not all, of the hypotheses regarding reward craving and withdrawal relief craving as two different craving types (Verheul et al., 1999). Craving for the rewarding properties of alcohol consumption may be facilitated in emotionally positive situations, and in accordance with that hypothesis, a history of drinking in positive situations during the last 12 months as assessed with the IDS (Victorio-Estrada et al., 1996) was significantly correlated with appetitive responses to alcohol-associated stimuli assessed with the emotionally modulated eyelink startle reflex (Mucha et al., 2000; Grüsser et al., 2002). Withdrawal relief craving, on the other hand, showed a more complex interaction with positive and negative mood states. Since conditioned withdrawal is unpleasant, we expected that negative mood states may trigger or enhance withdrawal relief craving. Indeed, negative mood states, such as anxiety and depression, can prime cue-induced alcohol craving (Cooney et al., 1997). However, conditioned drug-opposite effects may be evoked in any situation previously associated with alcohol intake, and our results indicate that withdrawal-like symptoms are also associated with alcohol intake in positive situations.

We used the CIWA score (Sullivan et al., 1989) to assess the severity of withdrawal symptoms that precede alcohol intake. This score was developed for observer rating of acute withdrawal severity and the use of this score as a retrospective instrument for the assessment of withdrawal symptoms is purely exploratory. Moreover, some items of this scale rate symptoms which are also found in anxiety or agitation. Conditioned withdrawal may be accompanied by anxiety and anxiety may be misinterpreted by alcohol-dependent subjects as a sign of withdrawal (Cooney et al., 1997; Verheul et al., 1999); therefore, it may be extremely difficult to separate effects of anxiety from conditioned withdrawal. However, in this study, the items in the CIWA score which mainly contributed to the association with ‘obsessive craving’ were ‘paroxysmal sweating’ and ‘auditory disturbances’ and not those such as ‘agitation’ or ‘anxiety’, which may reflect anxiety disorders, rather than conditioned withdrawal. Given the lack of standardized assessment procedures for conditioned withdrawal, the modification of established withdrawal scores may offer a viable way to measure conditioned compensatory responses (Siegel, 1983) in alcoholism and their association with drinking situations.

The craving factor ‘obsession’ in the OCDS (Anton et al., 1996) was associated with anxiety and distressful preoccupation with alcohol-related ideas and impulses (Roberts et al., 1999). Therefore, we hypothesized that withdrawal relief craving and drinking in negative situations contribute to this craving factor. This was confirmed for withdrawal relief craving, but not drinking in negative situations, confirming the observation that withdrawal relief craving is not exclusively associated with alcohol intake during negative mood states.

The craving factor of ‘control impairment’ decreases under naltrexone medication (Roberts et al., 1999), which blocks opioid receptors and inhibits pleasant emotions evoked by alcohol intake (Volpicelli et al., 1995). Therefore, we hypothesized that appetitive responses to alcohol-associated cues and drinking in positive situations may contribute to this craving factor, and that reward craving elicited by appetitive alcohol cues and positive mood states may also induce ‘interference’ with social and work functioning. Contrary to our hypotheses, drinking in positive situations and appetitive reactions to alcohol cues contributed to the craving factor ‘interference’ but not to ‘control impairment’. Both craving factors are derived from the OCDS and may not adequately reflect the concept of reward craving (Verheul et al., 1999). In any case, alcohol consumption in positive situations was associated with problems of role functioning, reflected in the craving factor ‘interference’ of the OCDS.

In summary, our study supports the notion of different pathways leading to different types of alcohol craving (Niaura et al., 1988; Verheul et al., 1999). We observed a correlation between appetitive reactions to alcohol cues and drinking in positive situations, which contributed to the impairment of social and work functioning. Withdrawal-like symptoms that precede alcohol intake contributed to obsessive alcohol craving, a distressful preoccupation with alcohol-related ideas and impulses to consume alcohol. Contrary to our hypotheses, withdrawal-like symptoms correlated not only with drinking in negative, but also positive, situations, indicating that conditioned withdrawal may be primarily associated with hedonic dysregulation, rather than the obsessive–compulsive aspects of alcohol craving per se. We used an exploratory method to assess withdrawal relief craving, namely the self-reported occurrence of withdrawal-like symptoms, which regularly precede alcohol intake. Conditioned alcohol-opposite psychophysiological responses may be better-suited to measure the severity of conditioned withdrawal; however, this approach is limited by the fact that alcohol-like and withdrawal-like psychophysiological reactions overlap clinically (Niaura et al., 1988). The assessment of drinking situations and of appetitive and withdrawal-like reactions to alcohol in association with neuroimaging (Volkow et al., 1996; Heinz et al., 1999).
1998; Braus et al., 2001) may be best suited to further explore the neurobiological pathways associated with different craving types and to select the appropriate anti-craving medication.

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REFERENCES


