INTRODUCTION

It is well known that alcohol influences several central neurotransmitter systems during periods of intoxication (Eckardt et al., 1998). Functions in some of these systems are apparently restored during acute or prolonged withdrawal periods, whereas other neurotransmitter systems seem to remain affected even during sobriety. Among the systems that are affected during withdrawal is postsynaptic \( \alpha_2 \)-adrenoceptor function. Sensitivity in postsynaptic \( \alpha_2 \)-adrenoceptors can be assessed by a neuroendocrine test measuring growth hormone (GH) response to the \( \alpha_2 \)-agonist clonidine (CLON). Results of studies using this method have provided evidence for reduced postsynaptic \( \alpha_2 \)-adrenoceptor function in the acute and a longer alcohol-withdrawal period and even after a 6-month period of sobriety (Matussek et al., 1984; Nutt et al., 1988; Glue et al., 1989; Balldin et al., 1992a; Berggren et al., 1999; Fahlke et al., 1999; see also Müller et al., 1989).

Few studies have investigated the relationship between alcohol-induced psychopathology and changes in pre- and post-synaptic \( \alpha_2 \)-adrenoceptor function during the withdrawal period or in sobriety (Borg et al., 1983). In two recent studies, Berggren et al. (1999) and Fahlke et al. (1999) found a reduced postsynaptic \( \alpha_2 \)-adrenoceptor function and moderate to severe depressive symptomatology or anxiety immediately after a period of heavy alcohol intake. However, no relation was found between psychopathology and postsynaptic \( \alpha_2 \)-adrenoceptor function. Interestingly, during sobriety, patients’ postsynaptic \( \alpha_2 \)-adrenoceptor function remained low, even when all psychiatric symptoms had disappeared.

Bokström et al. (1989) have investigated different aspects of mental well-being in the early alcohol-withdrawal period using the Swedish Mood Adjective Check List (MACL; Sjöberg et al., 1979). Low levels in several mood dimensions were found on the first day of sobriety after cessation of a period of heavy alcohol consumption. One week later, results of self-report of moods indicated a profound improvement in mental well-being in these alcohol-dependent patients.

Although no relation between psychopathology and reduced postsynaptic \( \alpha_2 \)-adrenoceptor function has thus far been found, it cannot be excluded that such a relation may exist between \( \alpha_2 \)-adrenoceptor...
function and the momentary state of mood during the early withdrawal period. To our knowledge, this question has not been investigated and is therefore the subject of the present study.

METHODS

Patients

Patients admitted to a psychiatric hospital for treatment of alcohol-withdrawal symptoms were considered for the study. The inclusion criteria were: (1) the DSM-IV criteria (American Psychiatric Association, 1994) for alcohol dependence (303.90); (2) intake of alcohol in amounts exceeding 100 g of pure ethanol daily for at least 6 days prior to admission; (3) no interruption of alcohol intake earlier than 24 h before the start of the study; (4) DSM-IV (American Psychiatric Association, 1994) criteria for the non-delirium withdrawal syndrome (291.8). The exclusion criteria were somatic or psychiatric disorders or symptoms not associated with alcohol dependence or withdrawal.

Fifteen patients (13 men and 2 women), who fulfilled the above criteria were included in the study. Their age [mean ± SD (range)] was 42 ± 7 (33–54) years; the total length of time of alcohol abuse was 10 ± 8 (1–25) years; the length of time of last drinking episode was 22 ± 32 (6–129) days, and the estimated daily consumption of pure ethanol during this period was 250 ± 93 (118–384) g.

CLON/GH tests, assessments of mental well-being, and withdrawal psychopathology, together with venesections for determination of liver function and blood-glucose levels were made on days 1 and 7 after the end of alcohol intake. In addition, urine analyses for determination of narcotic drugs (including benzodiazepines) were performed before all challenge tests.

Challenge tests

CLON/GH tests were performed between 08:00 and 09:00 after an overnight fast (from 24:00). The patients were supine and a cannula was inserted into a brachial vein. A blood sample was drawn for analyses of GH, blood-glucose concentrations and liver parameters immediately before the CLON administration (at time 0). Clonidine hydrochloride (Catapres®; 150 µg/ml; 1.5 µg/kg body weight, dissolved in 10 ml of saline) was administered i.v. slowly for 10 min. The CLON dose was selected because it is commonly used in CLON/GH tests. In addition, previous studies have shown that this dosage does not have a serious effect on blood pressure (Müller et al., 1989; Tulen et al., 1992).

Blood samples for GH determination were collected 30 and 45 min after the start of CLON injection. Blood for GH measurement was centrifuged and the serum was kept at −20°C until assay. GH was determined by a double-antibody radioimmunoassay method described earlier (Balldin et al., 1982). All values for serum GH concentrations are given in mU/l; 1 mU/l corresponds to 0.5 ng/ml.

The baseline serum GH concentration was defined as the value at time 0. Baseline GH concentrations above 6 mU/l were regarded as too high (Checkley et al., 1981), and results of the corresponding loading tests were therefore excluded from statistical calculations. The maximum GH response was defined as the difference between the highest post-injection GH concentration and the baseline level. Blunted GH response was defined as a maximum GH response of less than 8 mU/l (Hunt et al., 1986; Balldin et al., 1993).

Patients were treated for withdrawal symptoms with decreasing doses of clomethiazole, oxazepam, or a combination of chlorprothixen and carbamazepine, together with vitamins during the treatment period. The medication was reduced each day and the dosage was minimal the day before the second challenge test. Medication was terminated each day at 20:00. No medication was given on the day of the challenge tests until the mood ratings were completed in the afternoon (13:00–14:00).

Liver function tests

Blood samples for assessment of liver function were obtained at the start of the challenge tests and included determinations of serum concentrations of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and γ-glutamyltransferase (GGT). The upper reference limits of the laboratory for these three tests were 0.65 ukat/l, 0.65 ukat/l, and 0.90 ukat/l, respectively.

Mood ratings

Self-reports of mood were performed using the Mood Adjective Check List (MACL). This Swedish MACL was designed to give a bipolar comprehensive assessment by self-report of mental well-being (Sjöberg et al., 1979). The MACL consists of a questionnaire with 71 mood-associated
adjectives, arranged in a symmetrical response format with two acceptance and two rejection categories. The subjects decided whether the various adjectives corresponded to their momentary mood state.

The adjectives are subdivided into six bipolar dimensions: (1) pleasantness/unpleasantness (‘happy’, ‘sad’ etc.); (2) activation/deactivation (‘active’, ‘drowsy’ etc.); (3) extraversion/introversion (‘talkative’, ‘silent’ etc.); (4) calmness/tension (‘calm’, ‘nervous’ etc.); (5) positive/negative social orientation (‘co-operative’, ‘unreasonable’ etc.); (6) control/lack of control (‘self-confident’, ‘insecure’ etc.). The dimensions pleasantness/unpleasantness, activation/deactivation, and calmness/tension are considered basic mood dimensions. The other dimensions are aspects of mood more closely related to social situations.

MACL has been validated in double-blind studies for its capacity to differentiate between well-known drugs and placebo (Svensson et al., 1980). The replicability was tested in a study on mood following intake of various quantities of alcohol (Persson et al., 1980). A group of 225 normal subjects were also tested with MACL, which makes it possible to compare patient group values with those of a control group (Persson and Sjöberg, 1981).

A psychologist introduced the MACL questionnaires to the patients at 13:00–14:00 on the day of the hormonal tests.

Psychopathology

The psychopathology of alcohol withdrawal was assessed immediately before the hormonal tests by trained staff members using the rating scale for Alcohol Withdrawal Psychopathology (AWIP; Bokström and Balldin, 1992). The AWIP scale comprises 17 items and has a total range of scores of 0–102. Ten items on this scale are identical to items on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). The total range of scores on the latter is 0–60. A total MADRS score of 20–34 indicates moderate, and a score of 35 or more severe, depressive symptomatology (Snaith et al., 1986).

Statistics

The Spearman rank correlation test was used for evaluating correlations between GH responses to CLON and the six mood dimensions and the 71 separate mood-associated adjectives. Because of the large number of comparisons, $P < 0.01$ was chosen as the level of significance. Student’s $t$-test was used to compare mean values for the mood dimensions of the patient group with those of the 225 normals. The Wilcoxon rank sum test was used to compare maximum GH responses to CLON on days 1 and 7. In all tests two-tailed levels of significance were used.

This study was approved by the Ethics Committee of the Göteborg University, Sweden. Informed consent was obtained from all subjects.

RESULTS

Fifteen patients participated in all challenge tests and ratings on day 1. High baseline serum GH concentrations were observed in five patients on day 1 (6.2–19.4 mU/l) and thus only test results from 10 patients could be evaluated then. On day 7, two patients had high baseline values (9.4 and 14.4 mU/l) and four had left the hospital earlier than planned. Therefore, results from nine patients were evaluated on day 7.

Urine analyses for narcotic drugs and benzodiazepines revealed no positive findings in any patient on either of the two test occasions. Blood-glucose levels at the start of all CLON/GH tests were well within the laboratory limits for fasting individuals.

Results of ratings for psychopathology showed that the total mean ± SD scores for AWIP was $34 ± 14$ on day 1 and $7 ± 5$ on day 7. Corresponding figures for MADRS was $25 ± 9$ and $4 ± 3$ respectively.

Values for baseline GH concentrations, maximum GH responses, and liver function tests on days 1 and 7 are shown in Table 1. The mean values for ASAT, ALAT, and GGT were elevated on day 1, but lower on day 7, though not significantly. The mean value for maximum GH response to CLON was higher on day 7 but did not differ significantly from that on day 1. This slightly higher mean level of maximal GH secretion can be explained by one patient having a much higher GH response (17.3 mU/l), compared to all other patients. Other than this high GH response, all other GH responses were blunted (< 8 mU/l) on both days of investigation.

Table 2 shows the values for six mood dimensions on days 1 and 7 and also those from a control
group (Persson and Sjöberg, 1981). Except for the
dimension positive/negative social orientation, the
values for all mood dimensions were significantly
($P < 0.01$) lower than those of controls on day 1,
whereas no significant differences were observed
on day 7.

There were no correlations between values for
GH responses to CLON and the values for the six
mood dimensions on day 1. When values for GH
responses to CLON were correlated with values for
all the separate adjectives, significant correlations
were observed for two adjectives in the mood
dimension extraversion/introversion (adjectives	nos 15 ‘witty’, $r = 0.79$; $P < 0.01$ and 37 ‘social’,

$r = 0.79$; $P < 0.01$) and for one adjective in the
dimension activation/deactivation (adjective no. 16
‘interested’, $r = 0.86$; $P < 0.01$).

On day 7, there were significant negative correla-
tions between values for GH responses to CLON
and the mood dimensions pleasantness/unpleasant-
ness and activation/deactivation (Fig. 1). As seen in
Table 3, several correlations were found within
these two mood dimensions between values for

**Discussion**

The present study has some limitations and
should therefore be regarded as a preliminary in-
vestigation. First, the number of patients evaluated
was small. Fifteen patients fulfilled the inclusion
criteria, but only nine patients were evaluated
because the limits for highest acceptable level of
baseline GH (6 mU/l; Checkley et al., 1981) were
surpassed. Hohe et al. (1988) used a higher upper
limit for baseline GH in CLON/GH challenge tests (10 mU/l). Using such a higher criterion additional patients could have been included in this study. However, the time period preceding a challenge test may be extremely stressful for some patients. Such a situation may cause a considerable increase in baseline levels of GH, which inhibits its own secretion and thereby reduces the CLON-induced hormonal responses. It was also important not to use stress-induced GH responses, since those results should be compared with figures for mood ratings obtained during non-stressful circumstances. The lower baseline limit of 6 mU/l was therefore chosen in the present study.

Second, patients were given different types of medication during the withdrawal period (mainly clomethiazole or a combination of chlorprothixen and carbamazepine). However, the medication was reduced each day during the treatment period and dosages given were minimal the day before the second challenge test. As no medication was given after 20:00 on the day before each challenge test, patients were medication-free at the time of the challenge tests and for the period until the mood ratings were completed in the afternoon (13:00–14:00). Furthermore, different types of medication have not been found to influence significantly baseline or CLON-induced changes in GH (Balldin

**Table 3. Correlation between values for growth hormone responses to clonidine and levels of mental well-being in six mood dimensions from the Mood Adjective Check List (MACL) as reported by nine alcohol-dependent patients on day 7 of alcohol withdrawal.**

<table>
<thead>
<tr>
<th>Mood dimension</th>
<th>Correlation coefficient (r)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleasantness/unpleasantness</td>
<td>-0.86</td>
<td>0.01</td>
</tr>
<tr>
<td>39 depressed (negative)</td>
<td>0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>45 harmonious (positive)</td>
<td>-0.83</td>
<td>0.01</td>
</tr>
<tr>
<td>49 optimistic (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>51 pessimistic (negative)</td>
<td>0.87</td>
<td>0.01</td>
</tr>
<tr>
<td>52 ill at ease (negative)</td>
<td>0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>55 cheerful (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>61 worried (negative)</td>
<td>0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>Activation/deactivation</td>
<td>-0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>6 concentrated (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>26 lively (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>30 unconcentrated (negative)</td>
<td>0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>57 unenterprising (negative)</td>
<td>0.89</td>
<td>0.01</td>
</tr>
<tr>
<td>59 indifferent (negative)</td>
<td>0.83</td>
<td>0.01</td>
</tr>
<tr>
<td>Extraversion/introversion</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>Calmness/tension</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>Positive/negative social orientation</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>17 obliging (positive)</td>
<td>-0.82</td>
<td>0.01</td>
</tr>
<tr>
<td>Control/lack of control</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>20 self-assured (negative)</td>
<td>0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>23 self-confident (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>38 insecure (negative)</td>
<td>0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>41 carefree (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
<tr>
<td>69 independent (positive)</td>
<td>-0.84</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Correlations for all mood dimensions and for the adjectives with levels of significance $P < 0.01$ (Spearman rank correlation test) are given. For each adjective, the MACL number and in parentheses, the character of the adjective are given.
Finally, assessment of mood was only performed once during days 1 and 7, a few hours after the challenge tests. Since MACL only reflects a momentary state of mood, it may be assumed that results of the self-reports did not correspond to the mood state when the challenge tests were performed. However, no differences have been found between morning and evening MACL values for ratings performed during early alcohol withdrawal (Bokström et al., 1989), suggesting a stable state of mood each day during the withdrawal phase. Since CLON has a sedative effect, it may be assumed to affect the levels of the mood dimensions. The drug was therefore administered 4–6 h before self-ratings of moods were performed. Moreover, the fact that the level of the mood dimension calmness/tension, which contains adjectives reflecting sedation (e.g. ‘calm’, ‘relaxed’, ‘tense’, ‘strained’), did not differ from controls on day 7 argues against the sedative effects of CLON. Additionally, the lower dosage of CLON usually used in challenge tests (1.5 μg/kg body weight used in the present study, vs 2 μg/kg) was selected to further avoid such late effects on state of mood. Some patients may feel uncomfortable prior to and during the challenge tests due to reasons other than the effects of CLON. Such effects on levels of self-reported moods were also eliminated by administering the mood questionnaires several hours after the hormonal tests.

The present study confirms previous studies of blunted GH response to CLON in the early alcohol-withdrawal phase after a period of heavy alcohol intake, suggesting a subsensitive α2-receptor function in early alcohol withdrawal (Matussek et al., 1984; Nutt et al., 1988; Balldin et al., 1992a; Berggren et al., 1999; Fahlke et al., 1999). Results from the AWIP rating scale revealed that patients immediately after the end of alcohol intake had a moderate to severe level of psychopathology, consisting mainly of depressive symptoms assessed through the MADRS scale. Almost all symptomatology was remitted on the last day of the investigation. This supports earlier findings of a rapidly reduced degree of psychopathology during the earlier alcohol-withdrawal phase (Balldin et al., 1992b; Davidson, 1995; Berggren et al., 1999; Fahlke et al., 1999).

In the present study, we found that different aspects of mental well-being, as assessed by the MACL, were affected immediately after the period of heavy alcohol intake. Thus, levels of five mood dimensions (pleasantness/unpleasantness, activation/deactivation, calmness/tension, control/lack of control, and extraversion/introversion) were significantly lower than those of control subjects on day 1, indicating a profound disturbance in several aspects of mental well-being. This finding confirms our earlier observation of reduced levels in these dimensions (Bokström et al., 1989), with the addition of the extraversion/introversion dimension to those with low levels immediately after the end of alcohol intake. Similar results were obtained when using the self-report technique, Profile of Mood States (Freed et al., 1977; McMahon and Davidson, 1986).

In accordance with findings in our earlier study (Bokström et al., 1989), we found that levels in all dimensions of mood were no different from control subjects on day 7, indicating an impressive improvement in the state of mental well-being during a week of recovery following a period of heavy alcohol intake.

Overall, no correlations were found between GH responses to CLON and the various mood dimensions on day 1. Thus, in alcohol-dependent subjects, the lowered state of mental well-being appears to have no relationship to the postsynaptic α2-adrenoceptor status immediately following the end of alcohol intake. In addition to the findings of moderate to severe psychopathology in the early withdrawal phase after heavy alcohol intake (see Berggren et al., 1999; Fahlke et al., 1999), the present study adds further information about the considerably affected state of mental well-being for the same time period. To what extent these two aspects are based on functional disturbances in the same or different central neurotransmitter systems is unknown at present. However, the lack of correlation between postsynaptic α2-adrenoceptor sensitivity, as assessed by CLON/GH challenge tests and psychopathology (Berggren et al., 1999; Fahlke et al., 1999), or the present findings regarding mental well-being, are not in favour of such an explanation, at least in conjunction with postsynaptic α2-adrenoceptor sensitivity. Whether states of mood and psychopathology are linked together is unknown at present, and remains to be elucidated.
Relationships between $\alpha_2$-adrenoceptor status and different aspects of mental well-being were observed 1 week after the end of a period of heavy alcohol intake. Thus, patients with the lowest postsynaptic $\alpha_2$-adrenoceptor function reported the highest levels in the adjectives ‘harmonious’, ‘optimistic’, ‘cheerful’, ‘concentrated’, ‘lively’, ‘self-confident’, ‘carefree’ and ‘independent’, and the lowest levels in the corresponding negative adjectives. It must be emphasized that, 1 week after cessation of alcohol intake, these patients had no psychiatric or somatic symptoms and their self-reported mood levels were well within the normal range. Interestingly, however, the patients with the lowest GH responses to CLON described a state of mental well-being with features of slightly elevated states of mood as reflected in positive aspects in the dimensions pleasantness/unpleasantness, activation/deactivation, and control/lack of control. Lubman et al. (1983) reported symptoms of hypomania (grandiosity, irritability, and mildly increased psychomotor activity), possibly associated with an increase in central noradrenaline release, in a subgroup of patients during alcohol withdrawal. It is also of interest that low postsynaptic $\alpha_2$-adrenoceptor function, as assessed by the CLON/GH test, has been found in mania (Ansseau et al., 1987).

The findings in this and earlier studies (Matussek et al., 1984; Nutt et al., 1988; Glue et al., 1989; Balldin et al., 1992a; Berggren et al., 1999; Fahlke et al., 1999; see also Müller et al., 1989) indicate that postsynaptic $\alpha_2$-adrenoceptor function is subsensitive in an early, as well as a late, recovery period after heavy alcohol intake in alcohol-dependent subjects. Whether this sensitivity is downregulated before and during an intoxication phase is, at present, unknown. A finding of lowered state of mental well-being in conjunction with the end of a period of heavy alcohol intake cannot, according to the findings of this study, be associated with the low $\alpha_2$-adrenoceptor sensitivity. After recovery, the patients reported levels of mental well-being in agreement with normal levels, even though the postsynaptic $\alpha_2$-adrenoceptor function remains subsensitive. It is noteworthy that individuals who expressed the most subsensitive $\alpha_2$-adrenoceptor function are those with reports of the highest levels in those aspects of mental well-being that are considered to be basic mood dimensions. The strong relationship between the levels of basic mood dimensions and postsynaptic $\alpha_2$-adrenoceptor function in abstinence may suggest that $\alpha_2$-adrenoceptor function is fundamental for basal mood regulation at least in this patient group. The results from this preliminary study must, however, be confirmed with a larger patient sample.

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