Neuroendocrine Assessment of Serotonergic, Dopaminergic, and Noradrenergic Functions in Alcohol-Dependent Individuals

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Background: Alcohol dependence has been associated with reduced function of serotonin, dopamine as well as noradrenaline activities in several neuroendocrine studies. To our knowledge, there is, however, no study investigating all these 3 systems with the use of neuroendocrine methods in one and the same alcohol-dependent individual.

Methods: Alcohol-dependent individuals (n = 42) and controls (n = 28) participated in the neuroendocrine test series. Central serotonergic neurotransmission was assessed by the prolactin (PRL) response to citalopram (CIT). The postsynaptic DRD2 function was measured by the growth hormone (GH) response to apomorphine (APO) and the postsynaptic α2-adrenoceptor function by GH response to clonidine (CLON).

Results: In the alcohol-dependent individuals, the PRL concentrations were significantly lower at the time points 240 minutes and 300 minutes after CIT administration and mean delta PRL value was significantly reduced by 45% in comparison with controls. There were no significant differences in APO-GH and CLON-GH concentrations at any time points or in mean delta GH values between the groups. An impaired monoaminergic profile, including all 3 systems, was significantly more frequent in alcohol-dependent individuals than controls (43% vs. 6% respectively).

Conclusions: The monoaminergic dysfunction was restricted to an impairment of the serotonergic system, suggesting that this system is especially vulnerable to long-term and excessive alcohol consumption. Moreover, impaired monoaminergic profiles, including low responses in 2 or 3 systems, were more frequently observed in alcohol-dependent individuals than in controls. Such impaired profiles may be of clinical importance, but further studies are needed.

Key Words: Alcoholism, Alcohol Dependence, Monoaminergic Function, Serotonin, Dopamine, Noradrenaline.

Several studies have found a relationship between functions in central monoaminergic systems and alcohol consumption. In animal studies, alcohol consumption has been shown to affect monoamines in a number of forebrain regions associated with hedonic, emotional, and integrative higher-order functions, possibly resulting in behavioral changes such as unhedonia, anxiety, and impulsive behaviors (Smith et al., 2008). In humans, there is also an association between excessive alcohol intake and function of the serotonergic, dopaminergic as well as the noradrenergic neurotransmitter systems measured by neuroendocrine challenge tests. With respect to the serotonergic system, studies have demonstrated reduced hormonal responses to serotonin (5-HT) releasing agents or receptor agonists, both during ongoing drinking (Balldin et al., 1994; Berggren et al., 2002a) and in abstinence periods (Buydens-Branchey et al., 1997; Farren et al., 1995; Lee and Meltzer, 1991; Pinto et al., 2002), although these results were not confirmed by Porter and colleagues (2008). The majority of the neuroendocrine studies give, however, support for the notion that excessive alcohol intake reduces serotonergic neurotransmission in the hypothalamic region. Furthermore, it should be noted that Nishikawa and colleagues (2009) found, by using positron emission tomography (PET), evidence for reduced 5-HT synthesis in the medial prefrontal cortex. This group also found negative correlations between regional 5-HT synthesis in the amygdala and the orbitofrontal region and measures of alcohol consumption. These latter results (Nishikawa et al., 2009) suggest that alcohol dependence is associated with serotonergic abnormalities in brain regions that are known to be involved in planning, judgment, self-control, and emotional regulation.
Whether reduced central serotonergic neurotransmission is preexisting or a consequence of long-term excessive alcohol consumption is, however, still a matter of debate. In favor of arguments of an alcohol-induced impairment of the serotonergic function are the findings by Berggren and colleagues (2002a), Berglund and colleagues (2006), and Heinz and colleagues (1998, 2000). These studies have shown that the longer the duration of excessive alcohol intake, the more pronounced is the loss of serotonergic transporters (Heinz et al., 1998, 2000) or, as assessed by neuroendocrine methods (Berggren et al., 2002a; Berglund et al., 2006), impairment of the serotonergic function. However, Gotjen and colleagues (2002) found no difference in central serotonergic neurotransmission between alcohol-dependent individuals, who had been abstinent for a mean of 3.5 years, and controls suggesting that alcohol-induced impairment of serotonergic neurotransmission is reversible after long-term abstinence. The relationships between excessive alcohol intake and the dopamine (DA) and noradrenaline (NA) systems have also been investigated using neuroendocrine methods. The postsynaptic dopamine D2 receptor (DRD2) function has thus been found to be reduced after 2 months (Baldin et al., 1992a) as well as after several years of sobriety (Baldin et al., 1993) in individuals with severe alcohol dependence. Reduced DRD2 function has also been shown to be related to severity of dependence, as assessed by relapse proneness (Schmidt et al., 1996). When using other techniques such as PET imaging, several studies have shown a decrease in the number of DRD2s and in the DA release in alcohol-dependent as well as in other drug-dependent individuals (Volkow et al., 2009). Consequently, both neuroendocrine and PET imaging studies support the notion of reduced DRD2 function in alcohol-dependent individuals. As for the noradrenergic system, neuroendocrine investigations have shown a reduction in the postsynaptic x2-adrenoreceptor function in alcohol withdrawal (Baldin et al., 1992b; Fahlke et al., 1999a,b; Matussek et al., 1984; Nutt et al., 1988). This reduction appears to be relatively long-lasting, because it can be demonstrated even after 6 months of sobriety (Berggren et al., 2000). In addition, long recovery time (about 5 years) of the alpha-2-adrenoreceptor function has been shown in long-term abstinent alcohol-dependent individuals as assessed by the sedative effect to clonidine (CLON) (Berggren et al., 2002b).

It should be emphasized that in all these aforementioned neuroendocrine studies, only 1 monoaminergic system has been investigated in each study. Thus, none have to our knowledge investigated 5-HT, DA, and NA in one and the same alcohol-dependent individual. Such a design would address the question whether 1, 2, or all 3 systems are affected by excessive alcohol consumption. The aim of this study was, therefore, to investigate all 3 monoaminergic systems in one and the same individual within a group of alcohol-dependent individuals and compare results with controls with nonharmful alcohol consumption. The hypothesis based on earlier findings (e.g., Baldin et al., 1992a,b, 1994; Berggren et al., 2002a,b; Fahlke et al., 1999a,b) was that functions in all 3 monoaminergic systems would be reduced in the alcohol-dependent individuals. It cannot, however, be overlooked that there may be a variety of individual patterns of low function in the 3 monoaminergic systems. Therefore, an additional aim was to investigate this question and to compare possible differences in monoaminergic profiles between the groups.

MATERIALS AND METHODS

This study is part of an ongoing longitudinal study (Gothenburg Alcohol Research Project [GARP]; Berglund, 2009), which aims to investigate psychological/psychiatric and neurobiological/genetic characteristics in alcohol-dependent individuals and to evaluate whether these variables influence treatment outcome.

Subjects

For this part of the project, adult women and men with diagnoses of alcohol dependence (n = 42; women: n = 10, men: n = 32) were recruited from 3 different outpatient treatment units for alcoholism. The inclusion criteria were the following: (i) individuals had to meet the DSM-IV criteria for alcohol dependence (APA, 1994), (ii) they should be without ongoing physical disorders, and (iii) without psychiatric disorders other than alcohol and nicotine dependence.

As a control group for the neuroendocrine challenge tests, adult women and men (n = 28; women: n = 9, men: n = 19) were recruited. They were examined by an experienced physician and were found to be psychiatrically and somatically healthy and with no histories of previous psychiatric or major somatic illnesses. Their alcohol consumption was assessed by the Alcohol Use Disorder Identification Test (AUDIT; Reinert and Allen, 2007). All were found to have total AUDIT scores below 8 (men) and 6 (women), and they were thus considered as nonharmful drinkers (Reinert and Allen, 2007). In addition, harmful alcohol consumption was screened with the use of carbohydrate-deficient transferrin (CDT). None of the controls had CDT values above the upper laboratory reference limit (1.2% for both genders) supporting the results of the AUDIT questionnaires.

Procedure

All individuals (alcohol dependent and controls) were invited to participate in 3 different neuroendocrine challenge tests performed with at least 1 week intervals. One test assessed central serotonergic neurotransmission, that is the prolactin (PRL) response to citalopram (CIT). Another challenge test assessed central postsynaptic DRD2 function, that is growth hormone (GH) response to apomorphine (APO) and a third postsynaptic x2 adrenoreceptor function (that is GH response to CLON). Alcohol-dependent individuals who had a current drinking episode were instructed to end their alcohol intake during the day before any of the neuroendocrine challenge tests. When arriving to the laboratory, alcohol-dependent individuals were examined physically and psychiatrically using a semi-structured interview by the experienced physician. They had to provide urine for toxicology screening of substances of abuse and were also submitted to a Breathalyzer test. Negative test results were required for inclusion in the study. Blood samples for the determination of CDT were also collected.

Neuroendocrine Challenge Tests

The individuals were kept fasting after 12.00 pm the night before the day of the challenge tests. No smoking or alcohol intake was allowed in the morning of the day for the challenge test, which started at 9.00 am. The individuals were placed in a supine position and a cannula was inserted into a brachial vein. Blood was collected...
according to the protocols below and thereafter centrifuged and serum kept at −70°C until assayed.

**Citalopram Protocol**

Central serotonergic neurotransmission was assessed by the PRL response to CIT (Gotjen et al., 2002). Blood samples for the determination of PRL were collected at the time point 0 minute (baseline) and every 60 minutes thereafter for 5 hours. CIT was administered orally in the dose of 40 mg after collection of the blood sample at time 0 minutes. Light nontryptophan-containing caffeine-free snacks were provided during the test period to prevent dehydration and possible hypoglycemic effects of the challenge drug.

PRL in serum was analyzed using the Architect Prolactin kit on the Architect i2000SR instrument (Abbott Laboratories, Abbott Park, IL). The upper laboratory reference limit is 300 mU/l for normal men and women. Results from challenges tests in individuals with baseline values above this limit were excluded from this study (n = 5).

**Apomorphine Protocol**

The postsynaptic DRD2 function was assessed by the GH response to APO (Balldin et al., 1992a, 1993). Blood samples for the determination of GH were collected at the time point 0 minute (baseline) and 30, 45, 60, 90, and 120 minutes thereafter. As this challenge test is age dependent (Balldin et al., 1992a), APO was administered slowly intravenously in a dose of 0.18 mg to individuals below the age of 50 years or 0.24 mg to older individuals after collection of the blood sample at time 0 minutes.

GH in serum was analyzed using the Access Ultrasensitive hGH assay on the Beckman Coulter Access 2 instrument (Beckman Coulter, Inc., Brea, CA). All values for serum GH concentrations are given in mU/l; 1 mU/l corresponds to 0.5 ng/ml. Baseline GH concentrations above 10 mU/l were regarded as too high, that is, the occurrence of spontaneous bursts could not be excluded (Hoehe et al., 1988). Therefore, results from such challenge tests were not used (n = 1).

**Clonidine Protocol**

The postsynaptic α2 adrenoceptor function was assessed by the GH response to CLON (Balldin et al., 1992b). Blood samples for the determination of GH were collected at the time point 0 minutes (baseline) and every 15 minutes thereafter for 60 minutes. CLON was administered slowly intravenously for 10 minutes in a dose of 2 μg/kg body weight after collection of the blood sample at time 0 minutes. For the determination of GH, see the above protocol for APO. One individual had to be excluded because of baseline GH concentrations above 10 mU/l.

**Statistics**

For each individual, the hormonal level at time point 0 minutes (that is immediately before challenge drug administration) was defined as the baseline level. The difference between these baseline hormonal levels and the highest hormonal levels after challenge drug administration was calculated and defined as the hormonal response (the delta value). Baseline and delta values were used in the statistical analyses for comparisons between the alcohol-dependent individuals and controls. In addition, alcohol-dependent individuals and controls were also defined as high or low responders in each of the neuroendocrine test. This definition was based on a median split procedure for the delta values in the controls. Individuals with low responses in 2 or 3 of the investigated neurotransmitter systems were defined as having an impaired monoaminergic profile.

Independent t-test, χ²-test, or Spearman’s rank correlation test were used when appropriate. Significance level of p < 0.05 was chosen. To investigate whether the delta values in the challenge tests were associated with alcohol dependence, a forward likelihood ratio logistic regression was used. A power analysis was also performed to determine the number of individuals required for each challenge test to detect significant differences between the groups.

This study was approved by the Ethics Committee of the University of Gothenburg, Sweden and was in compliance with the Helsinki Declaration of 1975. Informed written consent was obtained from all individuals.

**RESULTS**

In this study, all the 42 alcohol-dependent individuals and the 28 controls participated in at least 1 neuroendocrine test (for number of individuals participating in the various tests, see Table 1). The mean age (±SD) of the alcohol-dependent individuals was 46 ± 10 years and for the controls 41 ± 11 years. There was a significant difference in age between alcohol-dependent individuals and controls (t = 2.19, p < 0.05), but not in gender distribution.

Most of the alcohol-dependent individuals were working (86%) and had permanent residences (93%). Forty-eight percent of them were cohabitants. Their duration of excessive drinking was 12 ± 8 years (women, 4 ± 3 and men 14 ± 8; t = 5.75, p < 0.001), and their average alcohol intake during the last year before the investigation was 759 ± 564 g pure alcohol per week. The CDT levels before start of the first challenge test was 1.4 ± 1.0%. There were no gender differences in alcohol intake or in CDT levels. The individuals self-reported posttreatment sobriety of 132 ± 110 days before their first challenge test. Thirty-one of 41 subjects (76%) self-reported abstinence more than 1 month (that is they were in early full remission according to DSM-IV criteria) before the first challenge test. However, of those, only 23 individuals had CDT values below the upper reference limit. Consequently, 23/41 (56%) subjects were in early full remission as ascertained by both self-reports and by CDT tests. On the other hand, of those who self-reported drinking within the last month 9/10 (90%) had CDT values above the upper limits.

The baseline hormonal values did not differ significantly between the alcohol-dependent individuals and the controls in any of the challenge tests (see Figs. 1–3). There was a significant correlation between baseline GH values in the

<table>
<thead>
<tr>
<th>Neurotransmitter System</th>
<th>Alcohol-Dependent Individuals (%)</th>
<th>Controls (%)</th>
<th>Chi²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>29/36 (80)</td>
<td>12/23 (52)</td>
<td>5.33</td>
<td>0.021</td>
</tr>
<tr>
<td>DA</td>
<td>24/36 (66)</td>
<td>13/25 (52)</td>
<td>1.33</td>
<td>ns</td>
</tr>
<tr>
<td>NA</td>
<td>19/27 (70)</td>
<td>12/24 (50)</td>
<td>2.21</td>
<td>ns</td>
</tr>
<tr>
<td>5-HT + DA</td>
<td>17/31 (55)</td>
<td>5/20 (25)</td>
<td>4.41</td>
<td>0.036</td>
</tr>
<tr>
<td>5-HT + NA</td>
<td>14/24 (58)</td>
<td>3/20 (15)</td>
<td>8.64</td>
<td>0.003</td>
</tr>
<tr>
<td>DA + NA</td>
<td>15/26 (58)</td>
<td>7/22 (32)</td>
<td>3.21</td>
<td>ns</td>
</tr>
<tr>
<td>5HT + DA + NA</td>
<td>10/23 (43)</td>
<td>1/18 (6)</td>
<td>4.71</td>
<td>0.030</td>
</tr>
</tbody>
</table>

5-HT, serotonin; DA, dopamine; NA, noradrenaline.

For definition of low responders, see Statistics.
CLON and APO challenge tests in the total sample (alcohol-dependent individuals and controls; $r = 0.37$, $p < 0.01$). Furthermore, delta values in the CLON and APO challenge tests were also significantly correlated ($r = 0.38$, $p < 0.01$). In the controls, the hormonal responses were significantly increased after drug administration in all 3 challenge tests, demonstrating challenge drug responses (CIT-PRL: $t = 2.07$, $p = 0.05$; APO-GH: $t = 4.67$, $p < 0.001$; CLON-GH: $t = 3.23$, $p < 0.004$). No difference in time to peak hormonal concentrations after drug administration was observed between the groups in any of the challenge tests, suggesting that the drug absorption and/or metabolism were similar in both groups. In addition, there were no differences in baseline values or hormonal responses after any of the challenge drug administration between men and women in either group. The data of men and women were, therefore, not separated in the following statistical analyses.

As seen in Fig. 1, the PRL concentrations were lower at the time points 180 minutes ($t = 1.88$, $p = 0.07$), 240 minutes ($t = 2.15$, $p < 0.05$), and 300 minutes ($t = 2.33$, $p < 0.05$) after CIT administration in the alcohol-dependent group compared to the controls. Moreover, the delta PRL values were significantly lower in the alcohol-dependent group (47 ± 48 mU/l) as compared to the controls (86 ± 67 mU/l; $t = 237$, $p < 0.02$; see Fig. 1). The mean delta PRL value was thus reduced by 45% in the alcohol-dependent individuals. There was no difference in delta PRL values in individuals with alcohol dependence who were in early full remission (neither when self-reported nor when ascertained by CDT tests) and those who were not. Neither were significant correlations observed between age and delta PRL values in the alcohol-dependent individuals nor in the controls. No significant correlation between length of sobriety (days) or severity of alcohol dependence (assessed by the
number of DSM-IV criteria) and delta PRL values was observed.

Concerning APO-GH (Fig. 2) and CLON-GH (Fig. 3), there were no significant differences in GH concentrations at any time points between the alcohol-dependent individuals and the controls. Neither were there any differences in mean delta GH values between the groups. No correlations were found between the delta values and age, length of sobriety (days), or severity of alcohol dependence in any of the challenge tests.

To characterize the monoaminergic profiles for each individual, the median delta values for the controls were calculated and were the following: CIT-PRL = 74 mU/L, GH-APO = 8.3 mU/L, and GH-CLON = 2.75 mU/L. As seen in Table 1, more alcohol-dependent individuals had a combined low response of 5-HT and DA than controls (55% vs. 25%, respectively, \( p < 0.04 \)). A similar pattern was seen for the combination 5-HT and NA (58% vs. 15%, respectively, \( p < 0.01 \)). An impaired monoaminergic profile, including all 3 systems, was significantly more frequent in alcohol-dependent individuals than controls (43% vs. 6%, respectively, \( p < 0.05 \)).

A forward likelihood ratio logistic regression was used to determine whether the delta values of the challenge tests, independently as well as in combinations with each other, could predict a diagnosis of alcohol dependence. The only significant predictor for a diagnosis of alcohol dependence was the CIT-PRL delta values (\( p < 0.05 \)), see Table 2. The odds ratio for this variable was 0.986 with a 95% CI of 0.973 to 0.998. The nonsignificant predictors that were used in the model were: APO-GH and CLON-GH delta values as well as combinations of those values (Table 2).

**DISCUSSION**

This is an experimental study using a neuroendocrine approach to investigate, within short-time intervals, all 3 central monoaminergic systems (5-HT, DA, and NA) in one and the same alcohol-dependent individual. These individuals could be characterized as high functioning because most of them were working and had a permanent residence (Berglund et al., 2009). About half (56%) had been abstinent for at least 1 month before start of the challenge test series as ascertained by both self-reports and CDT values. That group was thus in early full remission according to DSM-IV criteria (APA, 1994). There was, however, no difference in delta values between those who were in early full remission and the remaining individuals, making an influence of prior alcohol intake on results of these challenge tests unlikely.

When comparing the alcohol-dependent individuals with controls, we found that alcohol dependence was associated with a significant reduction (45%) in central serotonergic neurotransmission in both genders, as assessed by the PRL responses to CIT. On the other hand, there were no differences in central postsynaptic DRD2 or \( \alpha_2 \)-adrenoceptor functions. When performing a logistic regression analysis in all individuals, we only found an association between the diagnosis of alcohol dependence and PRL responses to CIT. Thus, alcohol dependence was found to be associated with reduced central serotonergic neurotransmission but not with changes

<table>
<thead>
<tr>
<th>Variables</th>
<th>B (SE)</th>
<th>Wald</th>
<th>df</th>
<th>Odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIT-PRL delta</td>
<td>−0.15 (0.006)</td>
<td>5.05</td>
<td>1</td>
<td>0.986</td>
<td>0.025</td>
</tr>
<tr>
<td>Constant</td>
<td>1.28 (0.549)</td>
<td>5.46</td>
<td>1</td>
<td>3.605</td>
<td>ns</td>
</tr>
</tbody>
</table>

CIT, citalopram; PRL, prolactin.

\( R^2 = 0.18 \) (Hosmer & Lemeshow), 0.14 (Cox & Snell), 0.18 (Nagelkerke).

Model \( \chi^2 (1) = 6.17, p < 0.05 \).
in postsynaptic DRD2 or z2-adrenoceptor functions. To our knowledge, no previous study has investigated all 3 monoaminergic systems in one and the same alcohol-dependent individual. One study, investigating heroin-dependent individuals, has however, used similar neuroendocrine techniques and design (Gerra et al., 2003). Notably, also they found a reduction in the serotonergic function but not in postsynaptic DRD2 or z2-adrenoceptor functions. Taken together, the findings in these 2 studies may, therefore, suggest that reduced central serotonergic neurotransmission but not of DA or NA is a common denominator in various types of substance dependencies.

The alcohol-dependent women and men differed substantially in their mean duration of excessive drinking (4 and 14 years, respectively). Despite this difference in duration, both genders had a similar high alcohol intake during the last year before the investigation (about 750 g/wk). The finding of no difference in serotonergic function between alcohol-dependent women and men, thus in spite of the much shorter duration of excessive alcohol intake in women, suggests that the so-called telescoping effect in women (Schuckit et al., 1995) may also be applied here, at least for the serotonergic neurotransmission. This indicates that even short-term (about 4 years) excessive alcohol consumption may be deleterious in women (see also Mann et al., 2005).

From a methodological point of view, it is of interest that there was no difference in baseline PRL levels between alcohol-dependent individuals and controls. On the other hand, the PRL response after pharmacological challenge with CIT was reduced to nearly half in the alcohol-dependent individuals. This clearly demonstrates the importance of using pharmacological challenge tests and not only baseline hormonal levels when investigating putative differences in monoaminergic functions. As expected, there was a correlation between baseline GH values in these 2 challenge tests. This could reflect stability in morning GH values over time. Interestingly, there was also a correlation between the GH responses to APO and CLON, suggesting an association between postsynaptic DRD2 and z2-adrenoceptor functions, at least in the hypothalamus. Whether these 2 monoaminergic systems are synchronized in this brain region has to be further investigated.

As mentioned previously, there were no differences in postsynaptic DRD2 or z2-adrenoceptor functions compared to controls in this study. It should, however, be noted that there appeared to be a tendency for smaller GH responses to APO and CLON in the alcohol-dependent individuals in comparison with controls (see Figs. 2 and 3). This observation raised the question whether the use of larger samples would have revealed statistically significant differences. Therefore, a power analysis was performed, which showed that there was only a 25% possibility to detect significant differences in the GH responses either to APO or to CLON between the alcohol-dependent individuals and the controls. It could be calculated that a total of 650 and 170 subjects would have been required for the tests of DRD2 and z2-adrenoceptor functions, respectively. Consequently, it cannot be excluded that differences might have been demonstrated if a substantially larger number of subjects had been included.

When constructing individual monoaminergic profiles, significantly more alcohol-dependent individuals had a combined low response of 5-HT and DA, 5-HT and NA, or 5-HT together with DA and NA than controls. One interpretation of these findings is that they are being driven by the 5-HT findings alone. A biological interpretation is that impaired serotonergic neurotransmission may be a condition precedent for a more general monoaminergic dysfunction in alcohol dependence. An impaired serotonergic neurotransmission may thus have consequences for the function of other neurotransmitter systems. In animal studies, depletion of 5-HT has indeed been reported to down-regulate brain DA receptors (Ashby et al., 1994; Ferron et al., 1982) and it has been suggested that 5-HT is a prerequisite for the maintenance of brain DRD2 numbers and/or function (Olausson, 2000). The direct evidence for an association of reduced serotonergic neurotransmission and the DRD2 function in alcohol-dependent subjects is, however, to our knowledge scarce. In an earlier report of ours (Berggren et al., 2000), which is a reevaluation of the earlier study by Baldlin and colleagues (1994), we found an association between low platelet monoamino oxidase (MAO-B) activity and reduced DRD2 function, as assessed by the GH responses to APO, in alcohol-dependent subjects. In this report, platelet MAO-B activity was considered an index for presynaptic DA function. However, platelet MAO-B activity has often been assumed to reflect central serotonergic neurotransmission (Oreland et al., 1981). If so, this finding by Berggren and colleagues (2000) could be taken as evidence that reduced central serotonergic neurotransmission is indeed associated with reduced central DRD2 function in alcohol-dependent individuals. Furthermore, during a trial of the effect of CIT medication on heavy alcohol consumption, only drinkers with DRD2 genotype A2/A2 reduced their alcohol consumption, also suggesting an association between the serotonergic and dopaminergic systems (Eriksson et al., 2001). More recently, Budde and colleagues (2010) have found that reduced DRD2 function, as assessed by the GH response to APO, was associated with the long allele of the promoter polymorphism of the 5-HT transporter gene further demonstrating an influence of serotonergic function on DRD2 sensitivity.

In conclusion, our hypothesis that all 3 monoaminergic systems would be reduced in a group of alcohol-dependent individuals could thus be confirmed. The monoaminergic dysfunction was restricted to an impairment of the serotonergic system, suggesting that this system is especially vulnerable to long-term and excessive alcohol consumption. Moreover, impaired monoaminergic profiles, with low function in 2 or all 3 systems, were more frequently observed in alcohol-dependent individuals than in individuals with nonharmful alcohol consumption. Such different profiles may be of clinical importance. Further studies are, however, needed because this, to our knowledge, is the first study investigating all 3 monoaminergic systems in one and the same alcohol-dependent individual.
ACKNOWLEDGMENTS

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