Brain-Derived Neurotrophic Factor Serum Levels in Alcohol-Dependent Subjects 6 Months After Alcohol Withdrawal

Marie-Agnès Costa, Murielle Girard, François Dalmay, and Dominique Malauzat

Background: Diagnosing alcohol dependence is based on clinical signs and on the measured levels of biological markers of alcohol consumption. However, these markers are neither sufficiently sensitive nor specific enough to definitively determine alcohol dependence. The neuro-adaptive changes associated with alcohol dependence involve markers such as brain-derived neurotrophic factor (BDNF), which regulate neuronal plasticity. Serum levels of BDNF have been reported to decrease during alcohol dependence and may be restored to normal soon after alcohol is withdrawn. However, the long-term relationship between serum BDNF levels and abstinence status is unknown.

Methods: We investigated serum BDNF levels in 101 abstinent and relapsing alcohol-dependent subjects at the moment of hospitalization for alcohol withdrawal (M0) and 6 months later (M6) and compared them to the serum BDNF levels of 41 nondependent subjects. The BDNF levels of the alcohol-dependent subjects were compared to their serum gamma glutamyl transferase (GGT) levels, mean corpuscular volume (MCV) values, and their score on the Beck Depression Inventory (BDI) questionnaire.

Results: Forty-four percent of the alcohol-dependent participants remained abstinent during the 6 months following alcohol detoxification. Serum BDNF levels of the abstinent group at M6 were significantly higher than those of the original group of alcohol-dependent subjects at M0 (p = 0.034). Only the abstinent group had higher BDNF levels than the control group (p < 0.001). Serum BDNF levels increased to a greater extent in the abstinent group than in the nonabstinent group (p = 0.016). No correlations were found between serum BDNF levels and GGT level, MCV value, or BDI score.

Conclusions: Our data confirm that serum BDNF levels do not correlate with either chronic alcohol consumption or peripheral toxicity but may be linked to neuronal aspects of alcohol consumption and dependence. The increased serum levels of BDNF may reflect the concomitant activation of BDNF synthesis that accompanies the neuronal remodeling triggered by alcohol withdrawal and suggests that BDNF synthesis may have a role in the long-term maintenance of abstinence. Monitoring the serum BDNF levels of alcoholics undergoing treatment could help to characterize alcohol dependence profiles and predict relapse.

Key Words: BDNF, Alcohol Dependence, Withdrawal, Neuronal Plasticity.

Alcohol dependence is a worldwide public health problem. According to the World Health Organization, it represents the fifth highest risk factor of premature death and incapacity in the world and is the principal cause of death and incapacity in developing countries that have low mortality rates.

Diagnosis of alcohol dependence is based on clinical signs and on the measurement of biological markers of hepatic injury such as gamma glutamyl transferase (GGT) and mean corpuscular volume (MCV). These markers are neither sufficiently sensitive nor specific enough for determining alcohol dependence, and their levels do not change rapidly in response to abstinence or relapse (Reynaud et al., 2000a,b; Schwan et al., 2004).

Excessive alcohol consumption can cause liver injury as well as brain toxicity and brain degeneration (de la Monte et al., 2009; Ward et al., 2009). In addition, long-term exposure to ethanol results in dependence, tolerance, and withdrawal syndrome, which result from functional, neurochemical, and cellular adaptation mechanisms in the brain (Moonat et al., 2010). Abstinence may reverse the destructive neurological
mechanisms that arise as a consequence of chronic alcohol consumption and lead to improved cognitive performance and memory (Bartels et al., 2007; Harper, 1998; Nixon et al., 2008; Sullivan et al., 2000). The adaptive changes that occur in the brain during alcohol withdrawal are associated with neurodegeneration as well as with neurogenesis (Crews et al., 2004, 2005), which together make up the process of neuronal plasticity.

The molecular mechanisms involved in reorganizing and modifying synaptic connections are numerous and complex, but some pivotal molecules have been described (McClearn and Nestler, 2008). Notably, brain-derived neurotrophic factor (BDNF) has been cited as a major regulator of synaptic plasticity (Kalivas and O’Brien, 2008).

Modifications of centrally synthesized and peripheral levels of BDNF have been observed in central nervous systems altered by neurodegeneration (Connor et al., 1997; Howells et al., 2000). Variations in BDNF levels in the circulation were found to be associated with psychiatric pathologies such as schizophrenia (Huang and Lee, 2006; Toyooka et al., 2002), with depression and anxiety (Martincovich and Lu, 2008), with Parkinson’s disease (Parain et al., 1999), and with Alzheimer’s disease (Connor et al., 1997). BDNF is a neurotrophin that is involved in neurodegenerative processes as well as in neoneurogenesis (Duman, 2005).

BDNF has also been implicated in addiction processes, including alcohol dependence and alcoholism (Bolaños and Nestler, 2004; Davis, 2008; Moonat et al., 2010). Plasma BDNF levels measured in alcohol-dependent patients were lower than in nonalcoholic patients (Joe et al., 2007; Lee et al., 2009), with the lowest plasma levels found in patients who had a family history of alcohol dependence (Joe et al., 2007). BDNF has been shown to be involved in gating alcohol intake (Jeanblanc et al., 2009; Logrip et al., 2008, 2009) and thus may be linked to alcohol consumption behaviors. It has been reported that serum BDNF levels increase soon after alcohol withdrawal (Huang et al., 2008; Lee et al., 2009), and at later times (Joe et al., 2007). A potential direct link between BDNF levels and depression has been recorded for alcohol-dependent subjects (Ostacher, 2007; Pettinati, 2004; Umenegaki et al., 2009), thus additional factors may be involved in the relationship between BDNF and alcohol dependence. Nevertheless, the issue of whether BDNF synthesis is connected to the eventual outcomes of alcohol withdrawal, which includes the possibility of relapse, has not been addressed.

To investigate whether the changes in serum BDNF levels were associated with the abstinence status of alcohol-dependent subjects, we measured BDNF concentrations in the serum of alcohol-dependent subjects at the time they were hospitalized for alcohol withdrawal (M0) and after a subsequent 6-month period (M6) and compared these values to the serum BDNF levels of 41 control participants. The BDNF levels of the alcohol-dependent subjects were also compared to their serum levels of GGT, MCV values, and their score to the Beck Depression Inventory (BDI) questionnaire.

MATERIALS AND METHODS

Participants

Alcohol-Dependent Participants. This study was an ancillary part of an open longitudinal study developed at the Esquirol Psychiatric Hospital Center in Limoges, France. It received legal authorization from the French Health and Solidarity Minister and the local government-authorized ethics committee. Three hundred thirty alcohol-dependent patients admitted to the hospital for alcohol detoxification were included in this study (M0) wherein each patient was to undergo 4 follow-up examinations at a 6-month frequency to determine their outcome at 2 years. At the first 6-month follow-up (M6), BDNF levels were measured and the subjects were evaluated for the possibility of relapse. All participants signed an informed consent form. Criteria for inclusion in the study consisted in a diagnosis of alcohol dependence, which was determined using the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV-TR) criteria and a positive CAGE questionnaire (Mayfield et al., 1974; Ewing, 1984). Patients were excluded if they presented a lethal organic pathology with a term of less than 6 months, were under the age of 18, were without health insurance or a postal address, or were unable to understand either French or the principles of the study. Among the 330 patients recruited for the longitudinal study, 101 patients (84 men and 17 women) were retained for the present study and were characterized by a follow-up at M6 which consisted of complete available clinical and biological data, and the absence of any psychiatric comorbidity (e.g., major depression, schizophrenia). Mean age was 45.2 ± 8.8 years for all participants. As our objective was to study variations in serum BDNF concentrations under conditions close to those of clinical practice, all alcohol-dependent participants remained under treatment. For analysis, the treatments were classified according to major therapeutic classes. Special attention was paid to participants who were receiving antidepressants and/or neuroleptics because of the possible effects of these drugs on BDNF levels (Gervasoni et al., 2005; Gonul et al., 2005; González-Pinto et al., 2010; Rizos et al., 2010; Shimizu et al., 2003).

Controls. Control participants were recruited from blood donors who were between the ages of 18 and 60, had no chronic or psychiatric disease, and were not receiving any therapeutic treatment. They agreed to participate in the study and signed an informed consent form. Whole blood (5 ml) was collected just before the blood donation and was immediately centrifuged. The only data collected from this group were age and gender. An agreement was made with the French Establishment of Blood Transfusion to test the donor blood samples for pathogens and pathological conditions after the samples were centrifuged. Thirty-nine participants (28 men and 11 women) were chosen to match the age and gender of the alcohol-dependent group. The mean age was 43.1 ± 7.1 years old.

Clinical Assessments for Alcohol-Dependent Participants

At the beginning of the study, socio-demographic and ongoing therapeutic treatment data were collected from the patients, and they were evaluated for any psychiatric comorbidities. Tobacco and cannabis use data, if available, were also recorded at M0 and M6. Alcohol dependence intensity was verified at M0 using the Alcohol Use Disorders Identification Test (AUDIT) questionnaire (Fiellin et al., 2000; Gache et al., 2006; Ramirez et al., 1990; Saunders et al., 1993).

The BDI questionnaire was used at M0 and M6 to determine depression intensity (Beck et al., 1961; Beck and Beamesderfer, 1974; Delay et al., 1963; McPherson and Martin, 2010).

Alcohol abstinence at M6 was defined by no consumption of alcohol (as evaluated by the referent practitioner), by an MCV value
below 96 $\mu$3, and GGT levels that were either below 52 IU/l for men or 32 IU/l for women, or that were 50% lower than their GGT levels at M0 (Niemelä, 2007).

**Biological Assessments for Alcohol-Dependent Participants**

Blood samples from fasting alcohol-dependent patients were collected on the day immediately after admission at M0 and at M6. Urine samples were collected when possible. Platelet counts were also determined because platelets are a potential reservoir of BDNF (Fujimura et al., 2002) and they are affected during chronic alcohol consumption (Mikhailidis et al., 1986). MCV and platelet counts were measured on a Cobas Argos automated hematology analyzer (Horiba ABX, Montpellier, France). Serum GGT levels were measured on a Cobas Mira S+ (Roche Diagnostics GmbH, Mannheim, Germany). Serum samples were stored at −40°C before BDNF measurement. Because cannabis use may influence serum BDNF levels (Angelucci et al., 2008; D’Souza et al., 2009), toxicology screening for cannabinoids was performed on urine using the Cedia immunoassay from Microgenics (Fremont, CA) adapted for Cobas Mira S+.

BDNF levels at M0 and M6 were measured in duplicate in diluted serum (1/100) by ELISA using the BDNF Emax ImmunoAssay System provided by Promega (Madison, WI). Because we were interested in the magnitude of serum BDNF variations, BDNF changes for each participant were determined by the following ratio: (BDNF M6 − BDNF M0)/BDNF M0.

**Statistical Analyses**

All quantitative data are given as means ± standard deviation (SD). Comparisons between groups (alcohol-abstinent, nonalcohol-abstinent, alcohol-dependent, and controls) were made using either Student’s t-test for MCV values, BDI, platelet counts, and AUDIT scores or the Mann–Whitney test for BDNF levels, GGT levels, and BDNF ratio. Comparisons between M0 and M6 in the same group were made using either a paired t-test or the Wilcoxon test, depending on the normality of the distribution. Data from qualitative variables were made using Pearson’s chi-square test or, if presented as sample sizes (% on benzodiazepines medication (% on neuroleptic medication (% on antidepressant medication (% on electroconvulsive therapy (% on smoking, therapeutics, gender). Spearman’s coefficient was used to test a correlation between 2 continuous variables.

The level of significance was set at 5%. Statistical analyses were carried out using SAS 9.1.3 software (SAS Institute, Cary, NC).

**RESULTS**

Clinical and biological data for chronic alcohol consumption markers and serum BDNF levels for the control group and the alcohol-dependent group at M0, and for the abstinent group and the nonabstinent group at M6 are summarized in Table 1.

Forty-four percent of the participants remained alcohol-abstinent at M6. Whereas the serum BDNF levels in the abstinent group and the nonabstinent group were equivalent at M0, and the levels had increased for both groups at M6, the serum BDNF levels of the abstinent group at M6 were significantly higher than those of the nonabstinent group ($p = 0.034$). At M6, the BDNF ratio was also higher in the abstinent group than in the nonabstinent group ($p = 0.016$). MCV values decreased significantly with time in both groups ($p < 0.001$), whereas GGT levels decreased only in the abstinent group between M0 and M6 ($p < 0.001, r = 0.39$) and at M6 ($p = 0.008, r = 0.34$). The platelet counts for the abstinent and nonabstinent groups were similar, suggesting that different platelet counts were not alone responsible for the serum BDNF differences observed for these 2 groups.

BDNF levels and BDNF ratios in either alcohol-dependent group at M6 and at M0 were unrelated to therapeutic

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### Table 1. Clinical and Biological Data in the Control Group and the Alcohol-Dependent Group at M0, and in the Abstinent Group and the Nonabstinent Group at M6

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Alcohol-dependent</th>
<th>Nonabstinent</th>
<th>Abstinent</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>43.1 ± 7.1</td>
<td>45.2 ± 8.8</td>
<td>44.14 ± 8.8</td>
<td>46.5 ± 8.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Gender (male/female)</strong></td>
<td>28/11</td>
<td>84/17</td>
<td>44/13</td>
<td>40/4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>% Smokers (n)</strong></td>
<td>79 (56)</td>
<td>10 (7)</td>
<td>75 (42)</td>
<td>79 (33)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>% Positive cannabinoids detection (n)</strong></td>
<td>27 (8)</td>
<td>14 ± 7</td>
<td>13 (5)</td>
<td>6 (2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BDI score (mean ± SD)</strong></td>
<td>–</td>
<td>–</td>
<td>8.1 ± 7.1</td>
<td>6.6 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>% on antidepressant medication (n)</strong></td>
<td>–</td>
<td>44.6 (45)</td>
<td>60 (34)</td>
<td>45 (20)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>% on neuroleptic medication (n)</strong></td>
<td>–</td>
<td>14.8 (15)</td>
<td>23 (13)</td>
<td>20 (9)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>% on benzodiazepines medication (n)</strong></td>
<td>–</td>
<td>89.1 (90)</td>
<td>65 (37)</td>
<td>50 (22)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MCV (µl) (mean ± SD)</strong></td>
<td>–</td>
<td>97 ± 7</td>
<td>96 ± 7</td>
<td>92 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>GGT (IU/l) (mean ± SD)</strong></td>
<td>–</td>
<td>282 ± 542</td>
<td>208 ± 569</td>
<td>43 ± 83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Platelet count (×10^12/mm^3) (mean ± SD)</strong></td>
<td>–</td>
<td>214 ± 79</td>
<td>240 ± 86</td>
<td>260 ± 65</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BDNF (pg/ml) (mean ± SD)</strong></td>
<td>24.2 ± 5.1</td>
<td>22.98 ± 7.95</td>
<td>27.5 ± 10.4</td>
<td>31.9 ± 10.1</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>(BDNF M6 − BDNF M0)/BDNF M0 (mean ± SD)</strong></td>
<td>–</td>
<td>–</td>
<td>0.261 ± 0.453</td>
<td>0.462 ± 0.442</td>
<td>0.016</td>
</tr>
</tbody>
</table>

AUDIT, Alcohol-Use Disorders Identification Test; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; GGT, gamma glutamyl transferase; MCV, mean corpuscular volume; M0, time of hospitalization for alcohol withdrawal; M6, end of the 6-month period subsequent to M0; NS, nonsignificant difference between the abstinent group and the nonabstinent group; $p$, probability for a difference between the abstinent group and the nonabstinent group at M6. Significant if <0.05.
treatments (neuroleptics, antidepressants, or benzodiazepines), BDI scores, smoking, or detection of cannabis use.

The abistent group and the nonabistent group were equivalent in terms of gender, tobacco smoking, detection of cannabis use, and therapeutic treatment at M6 and at M0. There were no differences in the AUDIT scores at M0 for both groups, indicating they both had similar levels of alcohol dependence at M0. BDI scores did not differ between groups at M0 and M6, but BDI scores had decreased significantly for both groups at M6 ($p < 0.001$).

To better characterize the increase in BDNF levels of the abistent group, we compared the serum BDNF levels of alcohol-dependent patients to those from the control group. No statistically significant difference was found at M0 between the control group and the entire alcohol-dependent group, or between the control group and either the future abistent group or the future nonabistent group. However, the mean levels of BDNF at M6 were significantly higher in the alcohol-dependent groups ($p = 0.014$) than in the control group. This statistical difference was largely driven by the abistent groups, as the mean BDNF level for the abistent subjects, but not the nonabistent subjects, was substantially and significantly higher than the mean BDNF level for the control group ($p < 0.001$). This confirms that serum BDNF levels increased after alcohol withdrawal to a greater extent in abistent subjects than in nonabistent subjects.

**DISCUSSION**

We found that serum BDNF levels in alcohol-dependent subjects increased to a greater extent in subjects who had remained abstinent at M6 than in subjects who had relapsed. We found no correlation between BDNF levels and either GGT levels or MCV values, which confirms that BDNF levels were not representative of chronic alcohol consumption or peripheral toxicity, although GGT levels and MCV values were used to define abstinence status. Our data also revealed that basal BDNF levels in alcohol-dependent subjects at the time of hospitalization were not different from those of control subjects, which was also reported by Huang and colleagues (2008) and Heberlein and colleagues (2010). These results do not support the concept that molecules related to neuronal plasticity break down during alcohol dependence and contrast with reports that low levels of BDNF in subjects with major depression seem to reflect the absence of neurogenesis and neuronal plasticity (Castrén and Rantamäki, 2010; Dwivedi, 2009).

However, our results are consistent with previous studies which reported that BDNF levels increase after 24 hours of abstinence (Lee et al., 2009) or after 1 week of abstinence (Huang et al., 2008) and suggest a role for BDNF in neuro-adaptation during alcohol withdrawal. Nevertheless, it is not possible to determine from our data whether the increased levels of BDNF observed at M6 correspond to elevated BDNF synthesis that occurred immediately after withdrawal. In fact, in alcohol-dependent subjects, BDNF levels were reported to decrease 1 month after withdrawal when compared to nonalcoholic volunteers (Joe et al., 2007) and were reported to remain unchanged during the first 2 weeks of withdrawal (Heberlein et al., 2010). Whether the increase in the level of BDNF began immediately after alcohol withdrawal or was maintained during the 6 months afterward remains to be determined.

Many studies of BDNF levels in alcohol-dependent individuals have not addressed the eventual outcome of the participants, which includes the possibility of relapse after the BDNF analysis was performed. Monitoring BDNF levels in relation to alcohol relapse may be important because a BDNF polymorphism (Val66Met) has been associated with dependence and with a higher risk of relapse during the year following withdrawal (Wojnar et al., 2009). We can thus hypothesize that the level of BDNF over time may be important for the long-term success of alcohol abstinence.

Reversal of neuroadaptive phenomena following chronic alcohol consumption and dependence is linked to neoneurogenesis and cerebral plasticity (Crews and Nixon, 2009). Activation of BDNF signaling pathways in rodents decreases alcohol intake and reward, probably through the activation of the dopaminergic D3 system (Ghitza et al., 2010; Jeanblanc et al., 2006, 2009; Logrip et al., 2008, 2009; McGough et al., 2004). Because BDNF seems to regulate the gating of alcohol intake in rodents (Jeanblanc et al., 2009), it has been suggested that endogenous BDNF reduces the reinforcing effect of ethanol, thereby preventing the development of addiction and dependence. The progression and persistence of addiction appear to be coupled with dysregulation of BDNF homeostasis (Crews and Nixon, 2009), and we hypothesize that abstinence should restore this homeostasis, resulting in increased BDNF synthesis and serum concentrations.

Altered BDNF-related systems may contribute to the maintenance of addictive behaviors without being directly involved in the initial processes that occur at the time of withdrawal. This hypothesis may be supported by the results of studies in animal models, where the efficiency of BDNF injection as a treatment for drug dependence depended on the addiction phase, and on the length of time between the injection and the assessments of the animals behaviors linked to reward and relapse (Ghitza et al., 2010). In mice, reduced hippocampal neurogenesis was observed only after 14 days of abstinence, but not after 24 hours. Low neurogenic activity in the hippocampus is associated with depression-like behavior and supports the hypothesis that functional and behavioral changes occur during abstinence, but may need to take place over a long period of time to have a lasting effect (Stevenson et al., 2009). Further investigations will be needed to assess whether altered BDNF pathways correspond to a time-dependent response that determines abstinence stability or whether they depend on the continuation of addictive behavior.

We also investigated other variables that could possibly affect BDNF levels such as age, gender (Karege et al., 2002a,b; Lommatzsch et al., 2005), nicotine dependence (Bhang et al., 2010; Kim et al., 2007), and cannabis use (D’Souza et al., 2004). Because BDNF seems to regulate the gating of alcohol intake in rodents (Jeanblanc et al., 2009), it has been suggested that endogenous BDNF reduces the reinforcing effect of ethanol, thereby preventing the development of addiction and dependence. The progression and persistence of addiction appear to be coupled with dysregulation of BDNF homeostasis (Crews and Nixon, 2009), and we hypothesize that abstinence should restore this homeostasis, resulting in increased BDNF synthesis and serum concentrations.
None of them was found to influence or correlate with BDNF levels. Depression intensity was measured to evaluate the potential effect of mood alterations (Brunoni et al., 2008; Calabrese et al., 2009) on our results, despite the fact that subjects with major depression and established mood disorders were excluded from the study. BDI scores indicated that the basal level of depression was higher at M0 than at M6 and decreased significantly after the time of hospitalization for alcohol withdrawal. Similar to the findings of Joe and colleagues (2007), we detected no link between serum BDNF level and the level of depression in alcohol-dependent subjects. A study in rodents showed that depressive- and anxiety-like behaviors are induced by daily alcohol consumption (Getachew et al., 2008) and may explain the high level of depression for the alcoholic group at M0. Abstinence did not seem to influence depressivity, as it decreased in a similar manner for both groups of alcohol-dependent subjects. This was likely a result of factors other than abstinence such as antidepressant treatments (Pettinati, 2004) and psychotherapies. This observation strongly suggests that depressive mood is related to alcohol consumption, but not to its dependence.

The only biological variable that correlated to serum BDNF level was platelet count. It has been reported that platelets contain essentially all the BDNF found in the serum (Fujimura et al., 2002) and internalize it from other compartments (e.g., immune cells, endothelial cells, etc.). However, this represents only a small proportion of the total BDNF (Donovan et al., 1995; Fujimura et al., 2002; Gielen et al., 2003; Kerschensteiner et al., 1999; Lommatzsch et al., 1999, 2005; Nakahashi et al., 2000). Whereas platelet levels can be affected by alcohol toxicity, in our study, they varied independently of abstinence status at M6. The correlation between the platelet counts and the serum BDNF levels is very weak, and thus platelet level variations may have contributed to the differences in BDNF levels we observed, but they were not entirely responsible for them. It is now widely accepted that peripheral concentrations of BDNF reflect the level of BDNF present in the brain or released by the brain (Karege et al., 2002a; Krabbe et al., 2007; Rasmussen et al., 2009; Sartorius et al., 2009). Although the BDNF gene is expressed in the liver, which is often damaged during alcohol dependence, production of BDNF protein is limited to the hippocampus, amygdala, cerebral cortex, and cerebellum (Pruunsild et al., 2007). If the elevated BDNF levels of the abstinence group were because of liver regeneration, they should have correlated with the levels of GGT, but this was not the case here. Some liver pathologies, such as carcinoma, are known to influence BDNF levels (Yang et al., 2005, 2006), but this pathology was an exclusion criterion for our study (i.e., a disease with a fatal outcome). Similarly, pancreatic, pulmonary, gastric, cardiovascular, or hepatic inflammation can account for elevated serum BDNF levels (Asami et al., 2006; Barouch et al., 2001; Kimata, 2003; Lewin and Barde, 1996; Nockher and Renz, 2006; Noga et al., 2001, 2003; Schulte-Herbrüggen et al., 2007). However, none of these conditions could have been the primary cause of the elevated BDNF levels we observed in our study because BDNF levels were measured in patients who served as their own control. The causes of these BDNF variations should relate to the general state of the patients during the 6 months between M0 and M6. This corresponded to changes in alcohol consumption habits rather than to the emergence of a somatic disease affecting BDNF synthesis. Thus, we conclude that the increased peripheral BDNF levels we detected in the abstinent group likely consisted of BDNF that was released from the brain as a direct or indirect consequence of the brain’s response to abstinence.

Our study has several limitations. First, we did not examine withdrawal intensity, which has been reported to be strongly linked to BDNF levels (Heberlein et al., 2010). Second, our control group was entirely comprised of healthy volunteers, which does not allow it to be strictly compared to our alcohol-dependent groups. In addition, some data were not collected from the controls, particularly their levels of nicotine dependence and alcohol consumption. Moreover, nicotine dependence and smoking cessations were not recorded for all subjects of our sample. However, we assumed that the data we obtained for a few subjects could be extrapolated to our entire sample, because the prevalence of smokers in our sample was similar to that of alcohol-dependent people in the general population (Kalman et al., 2005; Le Strat et al., 2010; Poirier et al., 2002), and the sample size for which we had smoking data was large enough to allow us to determine that the effect of smoking was statistically significant. Third, because the interval between alcohol withdrawal and M6 was long, various additional factors linked to the specific clinical setting of our sample may have affected our results. Such factors include the appearance of somatic comorbidities and the influence of hospital care. Cognitive and memory functions may improve in hospitalized patients, thus structural connections in their brains may be affected as a consequence of neural plasticity (Scholz et al., 2009; Takeuchi et al., 2010).

In conclusion, our results provide support for a previously hypothesized role for BDNF, primarily through its neurotrophic stimulation of neuronal plasticity, in the neuroadaptation that occurs in the brain after alcohol withdrawal, and they raise the possibility of a role for BDNF in maintaining abstinence. Monitoring serum BDNF concentrations could help to characterize alcohol dependence profiles in clinical practice, help predict relapses, and assist in adjusting care to prevent difficulties in alcohol withdrawal.

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