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Mood Stabilizers for Alcoholism: BDNF Hypothesis

Takeshi Terao[1] and Lorenzo Pesaresi[2]

[1]Department of Neuropsychiatry, Oita University Faculty of Medicine
[2]Department of Psychiatric Sciences and Psychiatric Medicine
University of Rome "La Sapienza"

Takeshi Terao, MD, PhD, Professor of Neuropsychiatry, Oita University Faculty of Medicine
Oita 879-5593, Japan, E-mail: terao@med.oita-u.ac.jp

Abstract

The aim of pharmacotherapy for alcoholism is to increase sustained abstinence during and after treatment and to reduce relapse. There is accumulating, but not convincing, evidence showing the effects of mood stabilizers on alcohol dependence. Moreover, several studies suggest that brain-derived neurotrophic factor (BDNF) may be directly or indirectly associated with alcohol dependence, and mood stabilizers have been reported to increase BDNF. Taken together, it can be tentatively hypothesized that mood stabilizers increase BDNF and thereby, albeit partially, treat alcohol dependence which may be associated with low BDNF. Further studies are required to confirm this hypothesis (German J Psychiatry 2008; 11: 16-20).

Keywords: alcoholism, mood stabilizers, BDNF

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Introduction

The aim of pharmacotherapy for alcoholism is to increase sustained abstinence during and after treatment and to lessen the likelihood of relapse. Taking various findings into consideration, it seems possible that mood stabilizers have prophylactic effects not only on mood but also on alcoholism. Mood stabilizers have therefore already been investigated as a treatment for alcoholism.

In this review, the prophylactic effects of lithium, carbamazepine, valproate and topiramate on relapse prevention in alcoholism are reviewed from a literature search of available randomized, double-blind, placebo-controlled studies and their mechanism of action is discussed from the viewpoint of brain-derived neurotrophic factor (BDNF). Finally, we tentatively propose a "BDNF hypothesis".

Mood Stabilizers for Alcohol Dependence

The main findings of the following studies are summarized in Table 1.

Lithium

Klein et al. (1974) defined disabling drinking as 'drinking to the point of interference with normal daily life or necessitating admission to hospital for detoxification' and performed a randomized, double-blind, placebo-controlled, cross-over study of 73 patients suffering from chronic alcoholism and comorbid nonpsychotic depression. Although 43 (59%) failed to take medication as prescribed during the first follow-up period of 48 weeks, of the remaining 30 patients, lithium significantly prevented disabling drinking than placebo during the 48-week follow-up period, suggesting lithium prophylactic effects for alcoholism.

Table 1.

Author (year)	Drug	Subject (N)	Effect
Klein et al. (1974)	lithium	placebo (14) vs. lithium (16)	Nine subjects (64%) from the placebo group had disabling drinking, whereas only 4 (25%) of lithium group did so during 48-week follow-up period.
Merry et al. (1976)	lithium	placebo (18) vs. lithium (20)	Lithium had no significant effect on alcohol consumption of the non-depressive patients against placebo, but those patients rated as depressive showed a very significant decrease in days on which they consumed alcohol (48 days on placebo vs. one day on lithium).
Dorus et al. (1989)	lithium	placebo (229) vs. lithium (228)	Compared with placebo, lithium was not effective in either depressed or non-depressed alcoholics in reducing the number of individuals who failed to remain abstinent, the number of days of drinking, the number of alcohol-related hospitalizations, or the severity of alcoholism.
Fawcett et al. (2000)	lithium, buspirone	placebo (52) vs. lithium (56) vs. buspirone (48)	At the end of 3 months, lithium group had a non-significantly higher retention rate (lithium, 61%; placebo, 52%; buspirone, 44%). After 6 months, lithium group still had the highest retention rate (lithium 46%; placebo 38%; buspirone 27%), which was significant only among non-depressed subjects (lithium 45%; placebo 45%; buspirone 16%).
Mueller et al. (1997)	carbamazepine	placebo (16) vs. carbamazepine (13)	During the first few months, carbamazepine showed a trend toward lengthening the time of return to drinking and significant reduction in time to first heavy drinking episode and some other drinking behaviours.
Brady et al. (2002)	valproate	placebo (15) vs. valproate (14)	Compared with placebo, valproate did not have significant effect in decreasing alcohol consumption over 12 weeks.
Salloum et al. (2005)	valproate	placebo (30) vs. valproate (29)	Valproate group had a significantly lower proportion of heavy drinking days and a trend toward fewer drinks per heavy drinking day and fewer drinks per drinking day.
Johnson et al. (2003)	topiramate	placebo (75) vs. topiramate (75)	Topiramate was significantly more effective than placebo at improving drinking outcomes on drinks per day, drinks per drinking day, percentage of heavy drinking days, and percentage of days abstinent.

Merry et al. (1976) measured how many days each alcoholic patient had drank alcohol since his last visit and how many of those days he was incapacitated by alcohol in a randomized, double-blind, placebo-controlled study. Concurrently, each patient was asked to complete the Beck Depression Inventory to assess his mood. The findings showed that lithium had no significant effect on daily alcohol consumption in the non-depressive patients in comparison to placebo, but those patients rated as depressive showed a very significant decrease in the number of days that they consumed alcohol. These findings indicate that lithium may prevent alcoholism via improving depression.

Dorus et al. (1989), however, failed to find lithium effects in 457 male alcoholics in a randomized, double-blind, placebo-controlled study. The outcome measures included; number of alcoholics abstinent, number of days of drinking, number of alcohol-related hospitalizations, changes in rating of severity of alcoholism, and change in severity of depression. Subsequently, 286 alcoholics without depression and 171 alcoholics with depression began the 52-week outpatient study, 172 alcoholics without depression and 108 alcoholics with depression completed the study. There were no significant differences between lithium group and placebo group, regardless of whether they had depression or not. Similarly, no significant differences were found when the 82 alcoholics compliant in taking lithium, and the 89 alcoholics compliant in taking placebo were considered separately. These findings suggest that lithium does not improve the course of alcoholism in either depressed or non-depressed alcoholics.

Fawcett et al. (2000) also failed to show lithium effects in 156 alcohol dependent male subjects in a randomized, double-blind, placebo-controlled, three-arm parallel group study. The indicators measured included frequency of drinking days, quantity consumed on drinking days, and drug use since last visit. The subjects were randomized to lithium, buspirone, and placebo treatment groups. There were no significant findings supporting lithium effects in comparison to placebo or buspirone in the indicators measuring drinking behaviours.

In sum, the evidence supporting lithium effects on the prevention of alcohol dependence has yet to be conclusively established.

Carbamazepine

Mueller et al. (1997) investigated carbamazepine effects on 29 alcoholics in a randomized, double-blind, placebo-controlled study. They examined mean time to first drink, mean time to return to heavy drinking (defined as more than four drinks in a day for women and five for men), drinks per drinking day, and maximum number of heavy drinking days. During the 4-month follow-up, the survival curves for time for first drink showed a strong trend to significance supporting carbamazepine versus placebo, and a significant difference for time to first heavy drinking episode favouring carbamazepine.

Although this study is small, these findings suggest carbamazepine has an effect on the prevention of alcohol dependence and warrants further study.

Valproate

Brady et al. (2002) studied valproate effects in 29 alcohol dependent individuals in a randomized, double-blind, placebo-controlled study. They measured drinks per drinking day, percentage of days drinking, percentage of days heavy drinking (defined as more than or equal to 5 drinks in a 24h period), the percentage of subjects who relapsed to any drinking, percentage of relapse to heavy drinking, and alcohol craving. During a 12-week follow-up, there were no significant differences between valproate and placebo groups.

Salloum et al. (2005) investigated valproate effects in 59 subjects with alcohol dependence and bipolar I disorder in a 24-week, randomized, double-blind, placebo-controlled study. All subjects received treatment as usual, including lithium and psychosocial interventions. Kaplan-Meier survival curve for time to sustained heavy drinking revealed that valproate significantly prolonged the mean time before relapse to sustained heavy drinking to 93 days compared with 62 days in the placebo group. With regard to mood outcome, there was no difference between the placebo group and the valproate group. Levels of manic symptoms decreased substantially in both groups whereas depressive symptom levels remained at relatively high for both groups. Manic and depressive symptoms were highly associated with alcohol use outcomes and daily functioning. These findings suggest a possibility that valproate in combination with lithium may decrease heavy drinking in patients with comorbid bipolar disorder and alcohol dependence.

Topiramate

Johnson et al. (2003) studied 150 individuals with alcohol dependence in a randomized, double-blind, placebo-controlled study. During 12-week follow-up, participants on topiramate, compared with those on placebo, had fewer drinks per day, fewer drinks per drinking day, fewer heavy drinking days, and more days abstinent. These findings suggest that topiramate is more effective than placebo at reducing drinking and promoting abstinence in alcohol-dependent individuals who are seeking treatment.

In summary, there is accumulating, but not convincing, evidence showing the effects of mood stabilizers on alcohol dependence and further studies are warranted.

Brain-derived Neurotrophic Factor (BDNF) and Alcohol Dependence

Brain-derived neurotrophic factor (BDNF) is the most widely expressed member of the nerve growth factor family of growth regulators, collectively termed the neurotrophins. Neurotrophins play a critical role in the development of the brain and continue to have a seminal role in shaping plasticity in the mature nervous system. BDNF has a well-established role in the development, survival and differentiation of select populations of neurons and is capable of augmenting ongoing neurogenesis in the adult brain. BDNF has also been shown to elicit rapid action potentials thus influencing neuronal excitability and it has a demonstrable role in activity-dependent synaptic plasticity events like long-term potentiation, learning tasks and memory (Nair and Vaidya, 2006).

BDNF signalling may also be involved in affective behaviours and environmental stresses such as immobilization, which induces depression, and is accompanied by decreased BDNF mRNA. Existing treatments for depression are thought to act primarily by increasing endogenous monoaminergic synaptic transmission, and recent studies have shown that effective antidepressants increase BDNF mRNA and protein (Binder and Scharfman, 2004). Recently, it has become generally recognized that BDNF is associated with mood disorders and important in their treatment (Duman and Monteggia, 2006).

With regard to the association between BDNF and alcohol, MacLennan et al. (1995) showed that chronic ethanol administration (28 days) decreased BDNF gene expression in the rat hippocampus. In addition, Hensler et al. (2003) revealed that BDNF heterozygous mice exhibited increased ethanol intake. McGough et al. (2004), however, found that acute exposure of hippocampal neurons or striatal slices to ethanol increases the expression of BDNF via the scaffolding protein RACK1 and that voluntary consumption of ethanol also resulted in increased levels of BDNF in the striatum. They also found that similar increases in the expression of BDNF in the striatum were detected after systemic administration of Tat-RACK1. Moreover, increasing BDNF expression, via increasing the protein levels of RACK1, decreased ethanol consumption and sensitization whereas decreasing the levels of BDNF increased ethanol consumption as well as ethanol-induced place preference and sensitization (McGough et al., 2004). These results indicate that BDNF may act to decrease the rewarding effects of alcohol, concomitantly decreasing alcohol consumption.

Also, Allen et al. (2004) showed that in alcohol-treated rats suprachiasmatic nucleus levels of BDNF were significantly decreased and were characterized by a loss of circadian

rhythmicity relative to those observed in control animals and that hippocampal levels of BDNF were slightly lower in alcoholic-treated animals than in control group. Bonthius et al. (2003) revealed that BDNF had a neuroprotective effect, reducing alcohol-induced neuronal losses.

In some alcoholics, pre-existing conditions of high anxiety levels are important in the initiation of alcohol drinking. The amygdaloid structures have been shown to be centre for emotion and anxiety and also play a role in motivational aspects of alcohol drinking behaviours (Janak et al., 2006). Pandey et al. (2003) suggest that decreased cAMP response binding (CREB) protein phosphorylation in the central, but not in basolateral amygdala, may be associated with high anxiety and alcohol preference and dependence. Since BDNF gene is regulated by the CREB gene transcription factor, decreased phosphorylation at CREB may decrease BDNF in the central amygdala. Therefore, BDNF may be associated with alcohol dependence either directly and/or indirectly.

Discussion

Not only antidepressants, but also mood stabilizers such as lithium and valproate have been reported to increase BDNF (Fukumoto et al., 2001; Jacobsen and Mørk, 2004). For example, Fukumoto et al. (2001) showed that chronic lithium treatment significantly increased the expression of BDNF in hippocampus, temporal cortex and frontal cortex and that chronic valproate treatment also increased the expression of BDNF in frontal cortex and hippocampus. Carbamazepine protects against abnormal expression of BDNF (Lavebratt et al., 2006). Lavebratt et al. (2006) showed that BDNF mRNA was increased in CA3 (>3-fold), dentate gyrus (>3-fold), ventral cortex (>4-fold), amygdale (>3-fold) and CA1 (plus 0.9 fold) in megencephaly (*mceph/mceph*) mice compared to wild type mice and that carbamazepine treatment not only normalized *mceph/mceph* BDNF mRNA signals to wild type levels in all these areas but also decreased it to below wild type levels in CA1 and CA3. At the moment, to our knowledge, there is no report regarding topiramate effects on BDNF. If mood stabilizers do improve alcohol dependence, taking the above findings together, it can be tentatively hypothesized that mood stabilizers may increase BDNF and thereby at least partially treat alcohol dependence which may be associated with low BDNF. Further possibilities are that mood stabilizers directly improve alcohol dependence and/or that mood stabilizers improve mood and thereby indirectly treat alcohol dependence. However, there is also the potential that all of these possibilities interact with each other.

A final consideration is that clozapine and olanzapine which are initially recognized as antipsychotics but recently considered as mood stabilizers have been reported to improve alcohol dependence (Green et al., 2003; Hutchison et al., 2001) and have been shown to increase BDNF (Bai et al., 2003; Grillo et al., 2007). Such findings further support the above hypothesis.

The limitations of this hypothesis are that it is uncertain how the greater ethanol intake, showed in alcoholics, changes pathways signalling and reduces BDNF in the brain, and that it is unknown why increased BDNF does not always express its beneficial and protective effects in some subjects that may develop alcohol abuse. Of note, naltrexone which has μ-opioid receptor antagonistic effect and is used for alcoholism has been reported to reverse BDNF mRNA increased by β-endorphin (Zhang et al., 2006). Although this review emphasizes BDNF as having an important role in the pathophysiology and treatment of alcohol dependence, other factors, such as psychosocial and other biological factors are likely to be involved. Therefore, comprehensive investigation, including a rage of factors such as these is required to the effects of mood stabilizers on alcohol dependence.

In conclusion, it can be tentatively hypothesized that mood stabilizers increase BDNF and thereby, albeit partially, treat alcohol dependence which may be associated with low BDNF. Further studies are needed to investigate this hypothesis.

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Dept. of Psychiatry, The University of Göttingen, von-Siebold-Str. 5, D-37075 Germany; tel. ++49-551-396607; fax: ++49-551-392004; e-mail: gjpsy@gwdg.de