Published in final edited form as:

Med Hypotheses. 2012 August ; 79(2): 280–283. doi:10.1016/j.mehy.2012.04.042.

Neuroprotective and Neurogenesis Agent for Treating Bipolar II Disorder: Add-On Memantine to Mood Stabilizer works

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Introduction

Bipolar disorder (BP) [1] characterized by a dysregulation of mood, impulsivity, risky behavior, and interpersonal problems, is a recurrent and often chronic psychiatric illness [1–2]. According to the World Health Organization (WHO), BP is the sixth leading cause of disability-adjusted life years worldwide among persons aged 15 to 44 years [3]. It is associated with functional impairment [4–5], elevated suicide rates [2, 5], and utilization of mental health systems [6].

The BP is known for recurrent depressive, manic, and mixed episodes, and divided into several categories. The two most common and severe subtypes are bipolar I disorder (BP-I) and bipolar II disorder (BP-II). BP-I is characterized by the occurrence of one or more manic episodes or mixed episodes, accompanied by one or more major depressive episodes, while BP-II requires the presence of one or more major depressive episodes and at least one hypomanic episode. Although some researchers have questioned whether BP-II is simply a milder form of BP-I or is a distinct disorder, more and more researchers have documented that BP-I and BP-II have different etiologies, including genetics, variation, and characteristics during the course of the illness [7–8]. Long-term follow-ups show that patients with BP-II have a more chronic course, more mood episodes, more major and minor depressive episodes, and shorter inter-episodes, which last longer than those of patients with BP-I [9–10]. The lifetime prevalence rate of BP-I is about 2.4% [11] while BP-II has been perceived as a common disorder with a prevalence of approximately 3–11% [12–13].

However, the BP, especially BP-II, is commonly under-recognized, even in psychiatric settings [14], and it may take years before those patients receive a correct diagnosis [15] and appropriate treatment [16]. In our previous study, we found that the misdiagnosis rate of different subtypes of BP is much higher in Taiwan than in Western countries [17]. The

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current DSM-IV diagnostic criteria for BP-I and BP-II are the same except for different durations of hypomania and manic episodes: for BP-I it is more than 7 days and for BP-II more than 4 days [18]. This may also account for the difficulty in differentiating BP-I and BP-II and for the frequent misdiagnosis of BP-II. Even when correctly diagnosed, fewer than 50% patients are successfully treated [19], and 10–15% may eventually die as a result of suicide. Psychosocial impairments also significantly increase with each increment in the severity of the symptoms of BP-II depressed [20].

Pathogenesis: bipolar disorder as a neurodegenerative disease

Increasing evidences suggest that neuronal degeneration may relate to the etiology and progression of bipolar disorder. Imaging studies suggested that ongoing neuronal atrophy accompanies the disorder. For instance, PET images of the cerebral blood flow and the rate of glucose metabolism, both indicative of brain activity, detected a reduced activity in the subgenual prefrontal cortex during the bipolar depression. This decrement in activity in part corresponds to a reduction of cortical volume, similar in a manner to that seen in magnetic resonance imaging demonstrating the reduced mean volume on grey matters. In BP, abnormalities of the third ventricle, frontal lobe, cerebellum, and possibly the temporal lobe are also noted. These observations suggested a neuronal dysfunction and possibly neuronal loss may be involved in the pathogenesis of BP [21–22]. Therefore, BP might represent a neuro-degeneration disease.

In addition, BP may be associated with induction of a lot of endotoxins and exotoxins which might increase neurotoxins as well as decrease of neurotrophic factors due to overactivate microglial cell and inhibit astroglia cell. Those effects may induce pre-inflammatory factors such as TNF- α , C-reactive protein, interleukins, etc. and decrease BDNF etc. which will cause neuron damage or necrosis. The vicious cycle will lead to progressive worsening of the disease.

Neuroinflammation and BDNF downregulation: The possible mechanisms underlying neuronal degeneration in bipolar disorder

Recent report suggests roles of neuroinflammation in the pathogenesis of BP and depression. Studies had shown higher plasma level of interleukin-6 and TNF- α in bipolar patients during manic and depressive episodes than those seen in normal controls [23]. Furthermore, elevated levels of protein and mRNAs coding for the IL-1 β receptor as well as some neuroinflammatory markers including inducible nitric oxide synthase (iNOS) and c-fos were found in postmortem frontal cortex of BP patients [24]. In our previous study, we found that the plasma BDNF levels in the BP (15.2 ± 0.95 , $n=203$) were significant lower compared to normal control (18.6 ± 1.0 , $n=93$) (Chen et al., unpublished data). Accumulating evidence suggests that BDNF might be a candidate molecule involved in the pathophysiology of BP. For instance, dysfunction of BDNF acting on primary sensory and cholinergic neurons of the basal forebrain might relate to mood disorders, schizophrenia, eating disorders, and addiction [25]. Thus, the plasma or brain BDNF level in those mental illness patients has been studied intensively. BDNF, a basic dimeric protein, is a member of the nerve growth factor family involving in neuronal survival, differentiation [26], synaptogenesis, and maintenance [27–29]. BDNF has to be maintained throughout life in order to preserve essential functions such as learning and memory. In human subjects, studies had shown that BDNF is expressed in postnatal brains with the highest mRNA levels in the hippocampus and neocortex of rodents [30–31] and humans [32–33]. The mRNA levels of BDNF are relatively low during infant and adolescent period, reaching peak during young adulthood, and are maintained at a constant level throughout adulthood [33]. Studies had shown that BDNF promoted the survival of a wide range of neuronal cells, like the dopaminergic

neurons of the substantia nigra [34], cerebellar granule neurons [35], motoneurons [36], and retinal ganglion cells [37] that are important to the mental status in humans. In manic and depressed BP patients, serum BDNF levels have been reported to decrease significantly [38–44], indicating the possible neurotrophic and neuronal dysfunction in BP patients.

The decrease of plasma BDNF protein level in human subjects might reflect the degree of neuronal degeneration in Alzheimer's disease. It was reported that BDNF could cross the blood brain barrier [45] and that BDNF levels in the brain and plasma underwent similar changes during the maturation and aging processes in rats [46] and rhesus macaques [47]. These results suggest that plasma BDNF levels may reflect BDNF levels in the brain. Thus, the plasma BDNF level might reflect the dysfunction of neurotrophic system as well as the degree of neuronal degeneration in BP. Therefore, we hypothesized that bipolar disorder BP might lead to an even lower level of BDNF contributing to advanced neuronal degeneration.

Treatment for BP-II: Beyond mood stabilizer or antipsychotics

While the pharmacological guidelines for treatment are well established [18, 48–51], treatment for BP remains less than ideal, especially BP-II. Before 2000, not only BP-II has been misdiagnosed but scholars also wonder whether BP-II need treatment [52]. Most individuals still have breakthrough episodes or significant residual symptoms while on medication [53]. In addition, functional deficits often remain even when patients are in remission [53]. Moreover, most BP-II patients who are newly diagnosed have not taken any mood stabilizer or antipsychotics in the past. Because many patients with BP remain symptomatic even when fully adherent to their medication regimens, greater understanding of the pathogenesis of this illness and novel treatment modality other than current regimen of mood stabilizers and antipsychotics is needed. In our studies, we found that after adequate treatment, the BP-II had better functional improvement than the BP-I while excluding comorbidities, such as substance abuse [54].

Memantine and neuroprotective, neurogenesis effect

Memantine used to be recognized as a noncompetitive N-methyl-D-aspartate receptor antagonist. It was found to have neuroprotective effect in several neurodegenerative diseases in the past years [55–57]. We found that memantine could inhibit brain inflammatory response through its action on neuroglial cells and provide neurotrophic effect. Studies on mechanism revealed that the high potency of small dosage of memantine is due to its dual actions: an anti-inflammatory effect by reducing the activity of microglia and an increase in the release of neurotrophic factors, such as BDNF, GDNF by astroglia [58] (For Hung-Ming Wu, Jau-Shyong Hong, Ru-Band Lu*. US Patent 2009-0118376 A1. May 07, 2009). Our research team also found that even 1/100 dosage of memantine (0.2mg/kg) may be effective in opioid addictive behavior in rat by conditioned place preference (Chen et al. 2011). Since memantine may not only inhibit overactivity of microglial cell, but also repair the damaged neurons and neurogenesis through activation of astroglial cell and release of neurotrophic factors, we propose that memantine with neuroprotective effect and neurotrophic effect may treat neurodegenerative diseases including BP-II.

Many patients with BP remain symptomatic even though they fully adherent to appropriate dosages of mood stabilizers. This suggests a possible ongoing neuronal degeneration in BP which cannot be prevented by mood stabilizer. Thus, adding neuroprotective and neurogenesis agents to the therapy might represent a better treatment paradigm for those patients. Memantine in higher doses (7.5–20 mg/kg; s.c.) was considered an NMDA receptor antagonist and an inhibitor of morphine-induced tolerance, physical dependence, and drug seeking effects in animal models [59–61]. However, we recently showed that using a low dose of memantine (0.02 mg/kg) abolished morphine-induced Conditioned place

preference behavior in rats via its IL-6-modulating effect in the medial prefrontal cortex [62]. Our clinic data show that 5 mg (0.1 mg/kg) of oral memantine added to the methadone maintenance therapy given to morphine dependency significantly attenuated the methadone replacement dose and the combined morphine use (Chen et al., unpublished data).

Conclusion

To sum up, the plasma BDNF levels may reflect the BDNF levels in the brain, and the dysfunction of neurotrophic system as well as the degree of neuronal degeneration in BP. Bipolar disorder might lead to an even lower level of BDNF contributing to advanced neuronal degeneration was then hypothesized.

Acknowledgments

This work was supported in part by grant NSC98-2314-B-006-022-MY3 (to RBL) from the Taiwan National Science Council, grant DOH 95-TD-M-113-055 (to RBL) from the Taiwan Department of Health, grant NHRI-EX-97-9738NI (to RBL) from the Taiwan National Health Research Institute, and the National Cheng Kung University Project for Promoting Academic Excellence and Developing World Class Research Centers. This research was also supported in part by the Intramural Research Program of the NIH/NIEHS.

We thank Dr. Liang-Jen Wang, Ms. Shin-Feng Yang and Huei-Yu Chuang for their assistance in preparing this manuscript.

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