Research paper

Serum and plasma brain-derived neurotrophic factor and response in a randomized controlled trial of riluzole for treatment resistant depression

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ABSTRACT

Background: Serum brain-derived neurotrophic factor (BDNF) is decreased in individuals with major depressive disorder (MDD). Pre-clinical and clinical reports suggest that the glutamate release inhibitor riluzole increases BDNF and may have antidepressant properties. Here we report serum (sBDNF) and plasma (pBDNF) levels from a randomized controlled, adjunctive, sequential parallel comparison design trial of riluzole in MDD.

Methods: Serum and plasma BDNF samples were drawn at baseline and weeks 6 and 8 from 55 subjects randomized to adjunctive treatment with riluzole or placebo for 8 weeks.

Results: Riluzole responders had lower baseline serum (19.08 ng/ml [SD 9.22] v. 28.80 ng/ml [9.63], $p = 0.08$) and plasma (2.72 ng/ml [1.07] v. 4.60 ng/ml [1.69], $p = 0.06$) BDNF compared to non-responders at a trend level. This pattern was nominally seen in placebo responders for baseline pBDNF to some degree (1.21 ng/ml [SD 1.29] v. 3.58 ng/ml [SD 1.67], $p = 0.12$) but not in baseline sBDNF.

Limitations: A number of limitations warrant comment, including the small sample size of viable BDNF samples and the small number of riluzole responders.

Conclusions: Preliminary evidence reported here suggests that lower baseline BDNF may be associated with better clinical response to riluzole.

1. Introduction

Major depressive disorder (MDD) is a substantial public health problem, affecting over 300 million people globally each year (Depression Fact Sheet, 2018). Unfortunately, its pathogenesis remains poorly understood. The monoaminergic hypothesis, which has dominated the field of mood disorders research for many decades, does not fully explain the underlying neurobiology of MDD, as demonstrated by the modest and delayed effects of monoaminergic-based antidepressants. Emerging evidence supports the basis of a neurotropic hypothesis, which posits that mood disorders may result from neuronal atrophy induced by chronic stress (Duman et al., 1997, 2016; Pittenger and Duman, 2008). In animals, models of chronic stress result in a variety of pathologic effects in brain regions implicated in MDD, most notably the hippocampus, medial prefrontal cortex, amygdala, and nucleus accumbens (Gray et al., 2013; Berton et al., 2006; Bessa et al.,

2013). In the medial prefrontal cortex (mPFC), chronic stress is associated with decreased dendritic branching and spine density. Similar changes are noted in the hippocampus with respect to overall size and new neuron number (Gray et al., 2013). In contrast, chronic stress is associated with dendritic hypertrophy in the nucleus accumbens and amygdala (Bessa et al., 2013; Mitra et al., 2005; Christoffel et al., 2011). It is hypothesized that reversal of a deficit or excess of trophic support in specific brain regions may ameliorate depressive symptoms (Duman et al., 1997; Bessa et al., 2013).

Additional support for the neurotrophic hypothesis comes from studies of brain-derived neurotrophic factor (BDNF), which has been shown to play a critical role in dendritic formation (Dijkhuizen and Ghosh, 2005), synaptogenesis (Aguado et al., 2003), and neurogenesis (Gray et al., 2013; Dijkhuizen and Ghosh, 2005). BDNF may also play an important role in the relationship among stress, neuronal atrophy, and depressive symptoms. A strong line of research supports this,

including evidence that chronic stress reduces hippocampal BDNF, reduced levels of hippocampal BDNF found in post-mortem analyses of brains from depressed patients (Karege et al., 2005), and infusion of BDNF in rodents resulting in increased hippocampal synaptic transmission and neuronal proliferation (Scharfman et al., 2005; Levine et al., 1995). Furthermore, serum BDNF levels have been shown to be consistently reduced in patients with depression compared to healthy controls and often increase following treatment with antidepressants (Bocchio-Chiavetto et al., 2010; Sen et al., 2008). Additionally, depressive response has been linked to BDNF Val66Met polymorphism, whereby Val66Met heterozygous patients have a higher response rate than Val66Met homozygous patients (Zou et al., 2010). Rodent models demonstrating decreased prefrontal synaptogenesis in Met/Met mice following antidepressant administration suggest that the BDNF Val66Met polymorphism may attenuate antidepressant response in part by blocking synaptogenesis (Liu et al., 2012).

Riluzole, an agent approved by the US Food and Drug Administration for the treatment of amyotrophic lateral sclerosis, has been shown to have neuroprotective properties and may help ameliorate deficits in trophic support through what are believed to be direct effects on the glutamatergic system resulting in decreased glutamate release (Risterucci et al., 2006; Wang et al., 2004; Stefani et al., 1997) and increased glutamate uptake (Azbill et al., 2000). Riluzole has been shown to stimulate neurotrophic growth factor expression, increase cell proliferation and enhance synaptic AMPA receptor activation (Katoh-Semba et al., 2002; Mizuta et al., 2001; Du et al., 2007), all potential neuroprotective and antidepressant mechanisms. Preclinical studies, open-label trials, and at least one placebo-controlled trial (Salardini et al., 2016) in humans have suggested that riluzole may have antidepressant effects (Coric et al., 2003), although a recent double-blind placebo-controlled study conducted by our group was negative (Mathew et al., 2017).

Previous studies have shown that riluzole enhances the expression and release of BDNF (Katoh-Semba et al., 1997), suggesting it may serve as a marker of therapeutic response (Moghaddam, 1993; Bartanusz et al., 1995; Sapolsky, 2000). Most studies investigating the relationship between MDD and BDNF have evaluated serum BDNF (sBDNF). Plasma BDNF (pBDNF) has more recently been investigated, and is also shown to be lower in MDD compared with healthy controls (Karege et al., 2005). BDNF is stored in platelets and released over time (Fujimura et al., 2002). Hence assays measuring plasma BDNF, which include platelets, may be less time-sensitive and easier to carry out in practical clinical settings. Here we report on serum (sBDNF) and plasma (pBDNF) levels of BDNF from a subset of subjects in a multi-site double-blind, randomized controlled trial of riluzole as an augmentation strategy in treatment-resistant MDD. We hypothesized that riluzole treatment would increase low baseline sBDNF and pBDNF levels and that these changes would correspond with improvements in depressive symptoms.

2. Methods

The study protocol was approved by the IRB at all involved institutions (Yale School of Medicine, Baylor School of Medicine, Massachusetts General Hospital [MGH]) and was registered on clinicaltrials.gov (NCT01204918). All subjects signed informed consent.

2.1. Participants

Adult outpatients ages 18–65 with a diagnosis of major depressive disorder (MDD), confirmed by the Structured Clinical Interview for DSM-IV were recruited for participation. Subjects were treatment-resistant, based on their non-response to 1–4 adequate antidepressant trials using the MGH Antidepressant Treatment Response Questionnaire. Participants were either already on a therapeutic dose of a standard antidepressant (selective serotonin reuptake inhibitor,

serotonin-norepinephrine reuptake inhibitor, or bupropion) or were prospectively treated with one prior to randomization.

2.2. Study design and assessments

Using a sequential, parallel comparison design (Fava et al., 2003), subjects ($n = 104$) were randomized (2:3:3) to 8 weeks of riluzole, 8 weeks of placebo, or 4 weeks of placebo followed by 4 weeks of riluzole. Oral riluzole (50 mg twice daily) was adjunctive to a standard antidepressant that subjects were already taking. The primary study outcome was change in Montgomery-Asberg Depression Rating Scale (MADRS) at 8 weeks. The full details of the trial methodology were published previously (Mathew et al., 2017).

2.3. BDNF samples

BDNF was analyzed using human free BDNF Immunoassay (Quantikine Elisa, R and D systems, Cat# DBD00) with a standard range of 62.5–400pg/ml, sensitivity of 20pg/ml, and sample dilution of 1/20. Samples of sBDNF and pBDNF levels were drawn at baseline, 6 and 8 weeks in a subset of the total sample. While most samples were drawn in the morning, there was variability in the time of sample collection. sBDNF samples were collected by drawing whole blood samples, allowing for a 40-min incubation period at room temperature, then centrifuging at 2000 g for 10 min at 4 °C. sBDNF values were normalized for total protein. For pBDNF samples, whole blood was collected and immediately centrifuged for 15 min at 3000 rpm. Plasma supernatant was then immediately transferred to new tubes and stored at −80 °C until processed. BDNF concentrations (serum and plasma) were determined via enzyme-linked immunosorbent assay. Samples from one site were not analyzable due to an error in the processing method.

2.4. Statistical analysis

Given that only a portion of subjects randomized contributed viable sBDNF or pBDNF samples, those who did and did not contribute BDNF samples were compared on demographic and clinical characteristics using two-sample, independent t tests (for continuous variables) or chi-square tests (for categorical variables). Linear regression was used to examine correlations among serum and plasma BDNF samples and change in depression severity. A general linear mixed model was used to examine BDNF trends over time. Statistical analyses were conducted using STATA 15.0 (College Station, TX).

3. Results

3.1. Demographics

Overall, 104 subjects were randomized, with the mean age being 46.1 years (SD 12.2), and 50 (48%) were males (Table 1). The mean (SD) number of adequate antidepressant treatment failures was 1.59 (0.80), with 42.3% of the sample having failed 2 or more adequate trials. The primary study outcome, which showed no evidence of riluzole having antidepressant effects over placebo in the total sample, has been reported previously (Mathew et al., 2017). Viable serum BDNF samples were collected and processed in 43 subjects with at least one time point and in 27 subjects at all 3 times points; viable plasma samples were collected in 27 subjects with at least one time point and in 17 subjects at all 3 time points. The mean (SD) age of the subjects with serum BDNF samples was 44.8 (10.6). The mean (SD) age of the subjects with plasma BDNF samples was 44.1 (10.9). Among the subjects who contributed a viable sBDNF sample, 51% were male; among the subjects who contributed viable pBDNF samples, 59% were male (Table 1).

Those who contributed viable BDNF samples were not different from those who did not in terms of age, gender, race, ethnicity, total