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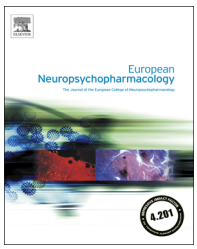

Leukocyte telomerase activity and antidepressant efficacy in bipolar disorder

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Abstract
Telomeres are DNA-protein complexes that cap linear DNA strands, protecting DNA from damage. Recently, shorten telomeres length has been reported in bipolar disorder (BD) and depression. The enzyme telomerase regulates telomeres' length, which has been associated with cellular viability; however it is not clear how telomerase may be involved in the pathophysiology and therapeutics of BD. In the present study, leukocyte telomerase activity was assessed in 28 medication-free BD depressed individuals (DSM-IV-TR criteria) at baseline and after 6 weeks of lithium therapy (n=21) also matching with 23 healthy controls. There was no difference between telomerase activity in subjects with BD depression (before or after lithium) and controls. Improvement of depressive symptoms was negatively associated with telomerase activity after 6 weeks of lithium therapy. This is the first study describing telomerase activity in BD research. Overall, telomerase activity seems not directly involved in the pathophysiology of short-term BD. Lithium's antidepressant effects may involve regulation at telomerase activity. Further studies with larger samples and long-term illness are also warranted.
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1. Introduction

Bipolar disorder (BD) is a serious and chronic psychiatric disorder, with high rates of comorbidities related to "accelerated aging" (Sodhi et al., 2012). Recently, leukocyte telomeres were suggested as a novel locus linking mood disorders and accelerated aging (Everson-Rose and Lewis, 2005; Simon et al., 2006; Penninx et al., 1998; Martinsson et al., 2013; Wassertheil-Smoller et al., 2004; Kinser and Lyon, 2013; Sodhi et al., 2012; Wolkowitz et al., 2010, 2011b). Telomere dysfunction has been associated with multiple environmental and biological stressors (Everson-Rose and Lewis, 2005; Epel et al., 2010; Penninx et al., 1998; Heidinger et al., 2012; Wassertheil-Smoller et al., 2004; Zglinicki, 2002; Sodhi et al., 2012; Epel et al., 2004; Ilmonen et al., 2008; Kotrschal et al., 2007; Shlush et al., 2011; Price et al., 2013) and eventually can result in programmed cell death (apoptosis) (Wong and Collins, 2003). Few studies on peripheral blood mononuclear cells (PBMCs) suggest altered telomere function in mood disorders. In depression and BD, shorter mean telomere length has been reported (Everson-Rose and Lewis, 2005; Simon et al., 2006; Penninx et al., 1998; Hartmann et al., 2010; Wassertheil-Smoller et al., 2004; Hoen et al., 2011; Sodhi et al., 2012; Wikgren et al., 2012; Rizzo et al., 2013). The mechanism that leads to telomere shortening in mood disorders is not clear; also it is not known how mood stabilizers influence telomerase length activity.

Telomeres are DNA nucleoprotein complexes at the end of chromosomes, which protect DNA from deterioration and fusion with other chromosomes (Everson-Rose and Lewis, 2005; Penninx et al., 1998; Blackburn, 2001; Wassertheil-Smoller et al., 2004; Sodhi et al., 2012). Telomere length and telomerase activity are two distinct processes. Telomere length declines with cell replication, and is replenished by its enzyme telomerase, which adds six-base DNA repeats onto the telomeric ends of chromosomes (Simon et al., 2006; Feng et al., 1995; Martinsson et al., 2013; Blackburn, 2001; Kinser and Lyon, 2013; Wolkowitz et al., 2010, 2011b). In addition, telomerase activity regulates transcription of growth factors in adverse conditions (Epel et al., 2010, 2004; Sung et al., 2005; Heidinger et al., 2012; Calado and Young, 2009; Zglinicki, 2002; Ilmonen et al., 2008; Kotrschal et al., 2007; Shlush et al., 2011; Price et al., 2013). Hippocampal telomerase was shown to modulate depressive-like behaviors (Wong and Collins, 2003; Everson-Rose and Lewis, 2005; Zhou et al., 2011; Blackburn, 2001; Penninx et al., 1998; Wassertheil-Smoller et al., 2004; Sodhi et al., 2012). Recently, an increase in telomerase activity in MDD was described, also associated with depression severity and predicting response to sertraline (Everson-Rose and Lewis, 2005; Feng et al., 1995; Simon et al., 2006; Wolkowitz et al., 2012; Penninx et al., 1998; Blackburn, 2001; Hartmann et al., 2010; Wassertheil-Smoller et al., 2004; Hoen et al., 2011; Sodhi et al., 2012; Wikgren et al., 2012; Rizzo et al., 2013).

In BD, studies on telomere dysfunctions were limited to investigation on telomere length in leukocytes, which does not necessary reflect telomerase activity. These studies report reduced telomere length in BD (Simon et al., 2006; Elvsåshagen et al., 2011; Rizzo et al., 2013). Also, a high number of short telomeres were found in bipolar II disorder (BD-II), associated with lifetime number of depressive episodes (Epel et al., 2010, 2004; Elvsåshagen et al., 2011; Heidinger et al., 2012; Zglinicki, 2002; Ilmonen et al., 2008; Kotrschal et al., 2007; Shlush et al., 2011; Price et al., 2013). Telomerase activity may reduce the impact of oxidative stress, conferring resistance to physical and chemical stressors (Sung et al., 2005; Rubio et al., 2004; Calado and Young, 2009). Although lithium has been widely used as an antidepressant in BD (Yatham et al., 2013; Machado-Vieira et al., 2009), its long term use was associated with longer telomeres (Martinsson et al., 2013).

To date, no study on telomerase activity has been performed in BD. Also, lithium seems to regulate telomere length in BD but its association with telomerase activity is not known. Thus, we aimed to investigate the leukocyte telomerase activity in bipolar depression before and after a six-week trial with lithium, also matching with a healthy control group.

2. Experimental procedures

Subjects were evaluated between August 2010 and June 2012 at the Institute of Psychiatry, University of Sao Paulo, Brazil. Twenty-eight patients, 21 (70%) women, age 28.5($\pm$5.3) years with bipolar I disorder (BD-I) (39%) or BD-II (61%), current episode depressive, as diagnosed by Structured Clinical Interview for Axis I DSM-IV-TR Disorders (SCID) entered the study. Patients had a score greater than or equal to 18 on the 21-item Hamilton Depression Scale (HDRS) and Young Mania Rating Scale baseline score lower than 7 (except for 2 patients). Also, before the treatment was started 24 (85%) patients were drug-free for at least 6 months. At day one, patients were given lithium at a dosage of 450 mg/day, and subsequent dosage adjustment was allowed at a flexible manner, according to clinical response and serum levels. Mean serum lithium level at the endpoint was 0.48 mEq/L (mean dose: 728.5 mg$\pm$118.9). Seven patients dropped out the study or had adjunctive medications and thus were not included. All patients evaluated here were in lithium monotherapy (six used hypnotics as needed for a maximum of 5 days). In order to avoid other potential confounding factors, patients had no severe medical illness, were free of comorbid substance abuse or dependence, and had no axis I comorbidity.

Twenty-three age-matched healthy controls were evaluated (10 women; age 27.1$\pm$6.6 years). Controls were excluded if they had lifetime history of any axis I psychiatric disorder (by SCID-I), or any first-degree relative with a mental disorder. The local institutional ethics committee approved the study and all patients provided written consent before they enter in the study. Clinical response was defined as a decrease of 50% or more in the Hamilton Depression Rating Scale (HDRS) at endpoint and remission as HDRS$<$8 at endpoint.

2.1. Procedure

Psychometric assessments were made at baseline, on week 1, week 2, week 4, and week 6 (endpoint). Assessment of symptoms was performed with the HDRS. The Young Mania Rating Scale (YMRS) was used to evaluate potential switch to mania. Blood samples of patients were collected for this objective at baseline (before treatment) and at endpoint (week 6), while healthy controls had only one-point sample collection.

2.2. PBMC collection

Blood was collected in EDTA tubes between 8:00 a.m. and 10:00 a.m. PBMCs were isolated using ficoll-hypaque gradient centrifugation

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