European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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Telomere length in bipolar disorder and lithium response

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Received 16 July 2015; received in revised form 8 October 2015; accepted 22 October 2015

KEYWORDS
Leukocyte telomere length;
Bipolar disorder;
Lithium;
Telomerase

Abstract
Telomeres consist of exanucleotide tandem repeats and proteins complexes at the end of chromosome ends. Telomeres shorten at each cell division, and as such telomere length is a marker of cellular age. Accelerated telomere shortening and cell senescence have been associated with a number of chronic medical conditions, including psychiatric disorders, where increased prevalence of age-related disorders and shorter telomere length have been reported. Shorter telomeres in psychiatric patients are thought to be the consequence of allostatic load, consisting in the overactivation of allostatic systems due to chronic exposure to severe medical conditions and failure to adapt to chronic stressful stimuli. Most of the studies on telomere length in psychiatry have focused on major depressive disorder, but recent findings have shown shorter leukocyte telomere length in bipolar disorder patients and suggested that lithium may counteract telomeres shortening. These findings provided new insights into the pathophysiology of bipolar disorder and the mechanism of action of lithium. In this review we will present findings from the literature on telomere length in bipolar disorder, with a specific focus on lithium. We will also discuss advances and limitations of published work as well as methodological issues and potential confounding factors that should be taken into account when designing research protocols to study telomere length.

1. Introduction

Bipolar disorder (BD) is a severe recurrent psychiatric disorder characterized by alternating manic and depressive episodes. It affects 0.8–1.2% of the general population (Merikangas et al., 2007, 2011) and is considered one of

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http://dx.doi.org/10.1016/j.euroneuro.2015.10.008
0924-977X/

Please cite this article as: Squassina, A., et al., Telomere length in bipolar disorder and lithium response. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.10.008

the most debilitating psychiatric disorders. BD is a cyclic disorder, but progression may be a key feature, as suggested by data showing a significant correlation between years of active disease and severity of symptoms, worsening of neurocognitive performance and increased risk of suicide (Mansur et al., 2013; Fries et al., 2012; Berk et al., 2010). It has been hypothesized that BD progression could be influenced by allostatic load (Mansur et al., 2013; Scott et al. 2013). Allostasis describes the physiological adaptation of biological systems to stress stimuli, but chronic exposure to stressors and perturbed activity of mediators of stress response lead, over time, to overactivation of the allostatic system causing allostatic load (McEwen, 2003, 2006). In psychiatry, allostatic load is useful to specifically describe biological degradation due to exposure to chronic, severe symptoms. Changes induced by allostatic load may affect functioning of specific brain regions involved in processing of emotions and cognition, leading to a progression of symptoms and increased vulnerability to stressors (Kapczinski et al., 2008). In patients with BD, recurrent mood episodes may be responsible for allostatic load, which in turn could determine accelerated cell senescence (Kapczinski et al., 2008). This allostatic-age model agrees with the hypothesis that BD is associated with accelerated aging, as supported by the findings of reduced life expectancy, premature mortality and high prevalence of comorbid age-related disorders in BD, such as cardiovascular conditions, metabolic imbalance and immunoscenescence (Rizzo et al., 2014).

An important biological marker of cellular aging is telomere length (TL) (Blackburn, 2000; Aubert and Lansdorp, 2008). Telomeres are nucleotide repeat regions at the ends of eukaryotic chromosomes that shorten with each cell division, regulate specific cell functions, prevent replication of damaged or genomically unstable cells, and exhibit different length dynamics by cell type. Accelerated telomere shortening can be caused by exposure to stress and has been observed in several chronic and age-related disorders, including psychiatric disorders. Whether telomere shortening is a risk factor, a consequence or a correlate of psychiatric disorders is still not clearly understood, but in the last decade a growing research effort has been put forth to untangle this question.

2. Telomere dynamics

Telomere shortening is a mechanism that prevents uncontrolled cell replication, as TL under a certain threshold causes telomeric instability, and thereby probabilistic cell senescence (Blackburn, 2000). However, in proliferative tissues (such as in male germ cells, activated lymphocytes, and certain types of stem cell populations) where TL is essential for prolonged persistence and genetic stability (Flores et al., 2006, 2008), telomere shortening is counteracted by telomerase. Telomerase is an RNA-dependent DNA polymerase that synthesizes telomeric DNA sequences. Telomerase is active through embryogenesis, but not in most adult somatic cells, where telomeres shorten with each cell division.

TL loss is accelerated by cellular or organismal stress (e.g. oxidative, inflammatory, chemical, hormonal), by mutations in telomerase relevant genes, and depletion or sequestration of telomeric proteins (Aubert and Lansdorp, 2008). Oxidative stress is highly detrimental, as it causes DNA damage that is irreparable specifically within telomeres (Fumagalli et al., 2012; Rossiello et al., 2014). This agrees with observations that telomeres in stressed cells have preferentially elevated persistent telomere DNA damage responses (Hewitt et al., 2012) and impaired telomere maintenance (Kawanishi and Oikawa, 2004; von Zglinicki, 2006). Such damage responses correlate with inflammatory cell phenotypes (Rodier et al., 2009; Ye et al. 2014). TL shortening is associated with chronic conditions that are thought to have inflammatory components, including cardiovascular disease, diabetes, cancer, and psychiatric disorders (Bojesen, 2013; Shalev et al., 2013).

The majority of studies on TL in human disorders measure leukocyte telomere length (LTL), and this is the case also in psychiatry. While the correlation between LTL and brain TL has not been largely investigated, LTL represents a valuable measure, as it is an easily accessible biomarker of cellular aging and correlates with TL in other somatic cells (Bodelon et al., 2014). A number of studies have reported shorter LTL in mental disorders. Most of these studies have been performed in major depressive disorder, but reports exist of shorter LTL in schizophrenia, bipolar, posttraumatic stress and anxiety disorders (Lindqvist et al., 2015). In this review, we will present and discuss salient research exploring TL in BD and lithium response.

3. TL in peripheral blood from BD patients

To date, six studies have explored TL in peripheral blood in BD (Table 1). In the first study, Simon et al. (2006) measured LTL by Southern Blot in 44 patients with chronic mood disorders (15 with major depression and 29 with BD) and 44 age-matched controls. After correcting for age, sex and smoking history, diagnosis of mood disorder was associated with shorter mean LTL ($p=0.001$). Although a subsequent study did not replicate this finding (Mansour et al., 2011), association between BD and shorter LTL has been reported in a number of recent studies.

Using quantitative PCR (qPCR), Lima et al. (2014) showed shorter mean LTL in BD patients compared to controls ($p<0.001$) in 85 patients and 95 healthy subjects. In a larger study comprising 286 BD patients and 139 healthy controls, Martinsson et al. (2013) found the contrary, showing that mean LTL was higher in BD ($p<0.0005$). In this study almost all patients were treated with lithium, an important factor not controlled for in previous studies.

To date, two studies explored TL in peripheral blood mononuclear cells (PBMC) from BD patients. Using quantitative fluorescence in situ hybridization (qFISH), Elvsåshagen et al. (2011) found a higher load of short (<3 kb) telomeres in 28 BD type 2 patients compared to 28 controls, with no difference in mean PBMC-TL. However, this result was marginally significant. Shorter TL in PBMCs from 22 female BD patients compared to 17 age-matched controls was also found by Rizzo et al. (2013) using qPCR. The use of PBMC in the studies by Elvsåshagen et al. and Rizzo et al. represent an important difference with other

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