Telomerase Dysregulation in the Hippocampus of a Rat Model of Depression: Normalization by Lithium

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Abstract

Background: Telomeres are protective DNA-protein complexes at the ends of each chromosome, maintained primarily by the enzyme telomerase. Shortening of the blood leukocyte telomeres is associated with aging, several chronic diseases, and stress, eg, major depression. Hippocampus is pivotal in the regulation of cognition and mood and the main brain region of telomerase activity. Whether there is telomere dysfunction in the hippocampus of depressed subjects is unknown. Lithium, used in the treatment and relapse prevention of mood disorders, was found to protect against leukocyte telomere shortening in humans, but the mechanism has not been elucidated. To answer the questions whether telomeres are shortened and the telomerase activity changed in the hippocampus and whether lithium could reverse the process, we used a genetic model of depression, the Flinders Sensitive Line rat, and treated the animals with lithium.

Methods: Telomere length, telomerase reverse transcriptase (Tert) expression, telomerase activity, and putative mediators of telomerase activity were investigated in the hippocampus of these animals.

Results: The naïve Flinders Sensitive Line had shorter telomere length, downregulated Tert expression, reduced brain-derived neurotrophic factor levels, and reduced telomerase activity compared with the Flinders Resistant Line controls. Lithium treatment normalized the Tert expression and telomerase activity in the Flinders Sensitive Line and upregulated β-catenin.

Conclusion: This is the first report showing telomere dysregulation in hippocampus of a well-defined depression model and restorative effects of lithium treatment. If replicated in other models of mood disorder, the findings will contribute to understanding both the telomere function and the mechanism of lithium action in hippocampus of depressed patients.

Keywords: depression, animal model, lithium, telomerase, telomere, hippocampus
Introduction

Mammalian telomeres consist of tandem repeat DNA sequences (TTAGGG) and protective proteins at each chromosome end, preventing the chromosome from degrading or fusing with other chromosomes (Chan and Blackburn, 2004; Palm and de Lange, 2008). Telomere length (TL) varies between cell types (Friedrich et al., 2000), but the majority of studies have explored TL in peripheral blood leukocytes. Telomeres shorten with each cell division and are suggested to be an indicator of biological aging (Benetos et al., 2001; O’Donovan et al., 2011). Significantly, accelerated shortening occurs in chronic disease states (e.g., cardiovascular disease, diabetes, and cancer) with inflammation and metabolic stress, which through oxidative stress damage the telomeres (Price et al., 2013; Verhoeven et al., 2013). In recent years, a number of studies associated shorter blood leukocyte telomere length (LTL) with psychological stress, major depression, and posttraumatic stress disorder (Lung et al., 2007; Wolkowitz et al., 2011; Wikgren et al., 2012; Garcia-Rizo et al., 2013; Verhoeven et al., 2013). With regard to psychological stress and LTL, the results are not uniformly consistent; for example, no association was found between objectively recorded early-life stress (separation from parents) or self-reported significant stress across the life-span and LTL, and only in subjects reporting the combination of both factors could an association be ascertained (Savolainen et al., 2014). Further, Shalev and coworkers (2014) recently showed that persistent early internalizing disorder predisposed LTL shortening in men, but not in women, independently of childhood maltreatment. Accordingly, a large meta-analysis found that females have consistently longer telomeres compared with males (Gardner et al., 2014).

On the other hand, patients diagnosed with schizophrenia were found to have longer leukocyte telomeres compared with controls (Nierschiker et al., 2013). The authors suggested that a possible explanation could be use of psychotropic drugs, not controlled for in their cohort, that have antioxidative and thereby protective effects on the telomeres (Lung et al., 2007; Wolkowitz et al., 2011; Wikgren et al., 2012; Garcia-Rizo et al., 2013; Verhoeven et al., 2013). Interestingly, lithium, the drug of choice in the treatment and relapse prevention of mood disorders, was found to protect against LTL shortening in humans, but the mechanisms have not been elucidated (Martinsson et al., 2013).

Shorter telomeres may result from excessive attrition due to decreased telomerase activity. Telomerase is a ribonucleoprotein consisting of a catalytic subunit with reverse transcriptase activity (TERT) and an RNA subunit (TERC) that serves as a template for DNA synthesis. TERT expression is stringently regulated and of the several splicing forms the full-length mRNA correlates positively with telomerase activity (Kaneko et al., 2006; Boillmann, 2013). Telomerase counteracts the telomere shortening by adding TTAGGG repeats to the chromosome ends (Blackburn and Collins, 2011). In addition to maintaining TL, telomerase is involved in other biological activities, most prominent being mitochondria protection from oxidative stress, DNA repair, antiapoptosis, stimulation of cell proliferation, and stem cell activation (Boillmann, 2008; Cong and Shay, 2008). In the adult rodent and human brains, telomerase is expressed mainly in regions where adult neurogenesis occurs, such as the subgranular zone of the hippocampus (Hermann et al., 2006). TERT also plays important roles in neuroprotection (Fu et al., 2000; Wolf et al., 2011; Li et al., 2013), and it was recently shown that disruption of the telomerase activity in mouse hippocampus led to depression-like behavior, which could be rescued by the antidepressant fluoxetine and by Tert-expressing viral vector injection, coupled with the upregulation of telomerase activity (Zhou et al., 2011). In a small open-label study of 16 depressed outpatients treated with sertraline for 8 weeks, there was no overall effect of treatment on telomerase activity. However, those with both low pretreatment telomerase activity and large increase in leukocyte telomerase activity exhibited the largest response to treatment (Wolkowitz et al., 2012). Lithium was previously shown to inhibit glycogen synthase kinase-3β (GSK-3β) (Pasquali et al., 2010), which results in retention of β-catenin (Gould et al., 2004). Lithium-induced upregulation of β-catenin was shown to upregulate hTERT transcription in cancer cell lines (Zhang et al., 2012). Lithium has also been reported to promote expression of brain-derived neurotrophic factor (BDNF) which, in turn, enhanced Tert expression (Fu et al., 2002).

While shorter telomeres in leukocytes were reported to be associated with major depression, it is not clear whether the same holds true for their respective brains. Two studies (Teyssier et al., 2010; Zhang et al., 2010) reported normal TL in occipital cortex and cerebellum, respectively, of postmortem brains from major depression patients. Szebeni et al. (2014) showed that oligodendrocytes but not astrocytes from depressed individuals displayed shorter TL and reduced hTERT expression compared with corresponding postmortem white matter from control brains. Tert transcript is highly conserved between human and rodents (Kaneko et al., 2006), thus enabling translational studies in rodent models. The Flinders Sensitive Line (FSL) is a genetic rat model of depression-like behavior and is often compared to the Flinders Resistant Line (FRL). The FSL rats display characteristics that resemble human depression with good face validity, including psychomotor retardation, circadian rhythm disturbances, and cognitive impairment (Overstreet et al., 2005; Overstreet and Wegener, 2013), and have been extensively used to study antidepressant effects of both pharmacological and nonpharmacological treatment modalities, such as antidepressants, ECS, physical activity, and deep brain stimulation (Bjornebekk et al., 2005, 2010; Jimenez-Vasquez et al., 2007; Eriksson et al., 2012; Melas et al., 2012; Rea et al., 2014).

In light of the above, we asked the questions whether telomeres are shortened and the telomerase activity changed in the depressed hippocampus and if so, whether lithium would reverse the process. We attempted to answer these questions by using the FSL rats and treated the animals with lithium. First we investigated if the telomeres were shorter in the hippocampus of the FSL rats, compared with FRL, and if that co-occurred with disturbance of Tert expression and telomerase activity. Second, since hippocampi from the FSL rats showed reduced levels, we investigated if lithium treatment would affect these telomere-related measures in the FSL rats. Finally, we investigated expression levels of putative mediators, β-catenin, and BDNF, of lithium’s effect on telomerase activity, both in naïve FSL/FRL and vehicle-/lithium-treated FSL.

Methods

Animals and Lithium Treatment

Male FSL and FRL rats were kept under controlled conditions of temperature (22 ± 1°C), relative humidity (45–55%) and daylight cycle (12:12 h, lights on at 6:00 AM). Normal rat chow and tap water were available ad libitum. A group of FSL rats was randomly assigned to a 6-week treatment with either 2.19 g Li2SO4/
kg or vehicle admixed to the rat chow. The lithium-treated rats showed no overt symptoms of toxicity; normal grooming and sleeping behavior were observed. The experimental design was based on our previous studies; under such conditions, lithium serum concentration is within the therapeutic range (Husum et al., 2001; Angelucci et al., 2003). Hippocampi from all the rats were dissected and immediately stored at -80°C until subsequent analyses. All experiments met the guidelines by the Danish National Committee for Ethics in Animal Experimentation and the Ethical Committee for Protection of Animals at the Karolinska Institutet.

**DNA/RNA Extraction and Reverse Transcription**

Genomic DNA and total RNA were extracted by AllPrep DNA/RNA/miRNA Universal Kit (Qiagen; Hilden, Germany) and concentrations were determined using the NanoDrop ND-1000 (NanoDrop Technologies Inc.). Complementary DNA was synthesized using the SuperScript III First-Strand Synthesis System for RT-PCR (Invitrogen; Life Technologies, Carlsbad, CA) according to the manufacturer's protocol. In brief, equal amounts of RNA were random-hexamer primed at 25°C for 10 minutes, followed by an incubation with SuperScript III RT at 50°C for 50 minutes and termination of the reaction at 85°C for 5 minutes. DNA/complementary DNA was stored at -20°C and RNA at -80°C until further processing.

**Gene Expression Analyses**

Amplification of target and reference genes was assessed using quantitative real-time polymerase chain reaction (qRT-PCR). All qRT-PCR amplifications were performed in triplicate using Power SYBR Green (Applied Biosystems; Life Technologies) on an ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems) with the following conditions: 95°C for 10 minutes, followed by 40 repeats of 95°C for 15 seconds and 60°C for 1 minute, and a final dissociation stage to monitor amplification specificity. Target genes included telomerase reverse transcriptase (Tert), brain-derived neurotrophic factor (BDNF), and catenin, beta 1 (Ctnnb1). Two reference genes (glyceraldehyde-3-phosphate dehydrogenase; Gapdh, and cyclophilin A; Ppia) were used for normalization of data. Relative quantification of gene expression was calculated using the qBase software (version 1.3.4; Hellemans et al., 2007). The tested genes and corresponding primer sequences were (written 5’3’): Tert Fw: GCCAGGCCAGAGAAGGA; Tert Rv: CCTACAGCCTGTACCCATAT; Bdnf Fw: GCCGCAAGAAGAAGAACAT; Bdnf Rv: AGCATCACC CGGGAATTGT; Cnmb1 Fw: GAAAAATGCTTGGTGCGCACG; Cnmb1 Rv: CGCACTGGCATTTAGCTC; Gapdh Fw: TCCGTTGTAACAGG ATTTGCGGG; Gapdh Rv: CCGTTGAACTTGCGGTGG; Ppia Fw: GCC TGATGCCAGGCCCTTGG; Ppia Rv: CGGTGTAAGTACACCTCCCTGGC.

**Protein Expression**

Protein levels were measured using a modified Western-blot protocol as previously described (Wei et al., 2014). Briefly, following sample homogenization and centrifugation, protein concentrations were measured using the Pierce BCA Protein Assay Kit (Thermo Scientific; Thermo Fisher Scientific Inc., Rockford, IL). After incubation at 95°C for 5 minutes, equal amounts of protein (30 µg) were loaded on a NuPAGE Novex 4 to 12% Bis-Tris Gel (Invitrogen). The separated protein was transferred to Amersham Hybond ECL Nitrocellulose Membrane (GE Healthcare; GE Healthcare UK Limited) at room temperature for 1.5 hour and then blocked with 5% nonfat milk for 1 hour at room temperature. Immunoblotting was performed overnight at 4°C with a monoclonal rabbit anti-beta catenin (β-catenin) antibody (1:20000 dilution; ab32572, Abcam; Abcam plc, Cambridge, UK), a monoclonal rabbit anti-BDNF antibody (1:1000 dilution; ab108319, Abcam) and, separately, with a mouse monoclonal anti-beta actin antibody (1:10000; A5316, Sigma-Aldrich, Sigma-Aldrich Co., St. Louis, MO). After washing, the membrane for detecting β-catenin and BDNF was incubated with HRP-linked goat anti-rabbit secondary antibody (1:100000 for β-catenin, 1:50000 for BDNF; Santa Cruz Biotechnology; Santa Cruz Biotechnology Inc., Santa Cruz, CA) and the membrane for detecting β-actin was incubated with HRP-linked goat anti-mouse secondary antibody (1:100000; Santa Cruz Biotechnology) for 1 hour at room temperature. Finally, immunoreactive bands were visualized with the Amersham ECL Plus Western Blotting Detection System (GE Healthcare), exposed to Amersham Hyperfilm ECL (GE Healthcare), and optical densities were quantified using the NIH Image (v1.47 version). β-Catenin and BDNF protein levels were normalized to the levels of β-actin, and the data were presented as relative quantifications.

**Telomerase Activity**

The telomerase activity was detected by real-time telomeric repeat amplification protocol (RT-TRAP) (Hou et al., 2001) with some modifications. In brief, the rat hippocampus was lysed in CHAPS buffer, and the total protein concentration was measured by the Pierce BCA Protein Assay Kit (Thermo Scientific; Thermo Fisher Scientific Inc., Rockford, IL). Equal amount of protein (1.0 µg) from each sample was added to a reaction mix with a total volume of 25 µL containing 2.5 mM of each dNTP, 20 mM Tris-HCl (pH 8.3), 2.5 mM MgCl2, 63 mM KCl, 0.05% Tween 20, 1 mM EGTA, 0.1 mg/mL BSA, and 0.1 µg each of the primers TS (5’-AATCCGTCGAGCAGAGTT-3’) and TSR8 is an oligonucleotide with a sequence identical to the TS primer extended with 8 telomeric repeats being AG(GGTTAG)7. The reaction was performed on ABI PRISM 7900 HT Sequence Detection System for RT-TRAP amplified by Power SYBR Green. The amplification protocol consisted of an initial 10 minute incubation at 95°C for 5 minutes. DNA/complementary DNA was stored at -80°C until further processing.
amplified by using Power SYBR Green in 10 µL total volume. The reaction was performed on ABI PRISM 7900 HT Sequence Detection System with the following conditions: 95°C for 10 minutes, followed by 39 repeats of 95°C for 15 seconds and 60°C for 1 minute, followed by a dissociation stage to monitor amplification specificity. The relative TL was calculated according to the 2^{-ΔΔCt} method, where ΔΔCt = ΔCt_{sample} - ΔCt_{calibrator sample} and ΔCt_{sample} = Ct_{sample} - Ct_{copy proton}. The tested genes and corresponding primer sequence were (written 5’-3’): Tel1: CG GTTTGTTTGGGTGGTTTGGTTGGTGGTT; Tel2: GG CTTGCCTAACCTTACCTTACCTTACCTTACCTTACCT; Rp30 Fw: CA GACGCCAAGATGCCGGG; Rp30 Rv: GCTCCGTTCTGCTTCCGCT

Statistical Analyses

Data in the bar graphs are presented as mean values ± 1 SEM. Normality of the data and the homogeneity of the variance were tested using Shapiro-Wilk and Levene’s tests, respectively. The difference in mean between 2 groups was assessed using 2-tailed Student’s t test. The threshold for statistical significance was set at \( P < .05 \). All analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY).

Results

Shorter Telomeres, Decreased Tert Expression and Telomerase Activity, and Decreased BDNF Expression in the Hippocampus of the Naïve FSL Rats

First, we measured the TL in hippocampi from the FSL and FRL rats. The FSL had shorter TL compared with the FRL (\( P = .038 \)) (Figure 1a). Second, we explored if the shorter telomeres in the FSL could reflect a reduced telomerase activity. Since the expression levels of full-length Tert, in most cases, correlate with telomerase activity (Greenberg et al., 1998; Kaneko et al., 2006), we determined the expression levels of the full-length Tert. Tert levels were reduced in the FSL compared with the FRL rats (\( P = .023 \)) (Figure 1b). Consistent with the downregulation of Tert expression, telomerase activity was lower in the depressed FSL (\( P = .041 \)) (Figure 1c). Finally, BDNF both expression and protein levels were significantly lower in the FSL hippocampi compared with FRL (mRNA: \( P = .023 \) and protein: \( P = .007 \)) (Figure 1b), which was in agreement with the decreased telomerase activity in FSL.

Lithium Treatment Increases Tert and Telomerase Activity and β-Catenin Expression in the Hippocampus of the FSL

Tert expression was increased in the hippocampi from the lithium-treated FSL (FSL-Li) compared with the FSL vehicle-treated group (\( P = .012 \)) (Figure 2a). In line with the Tert upregulation, telomerase activity was also increased in the FSL-Li group (\( P = .015 \)) (Figure 2b). To test the hypothesis that β-catenin mediates lithium’s effect on Tert, we measured the β-catenin levels in FSL-Veh and FSL-Li hippocampi. No baseline differences between naïve FSL and naïve FRL were found (mRNA: \( P = .31 \) and protein: \( P = .83 \)) (Figure 1b). However, lithium significantly increased β-catenin expression in FSL both at mRNA and protein levels (mRNA: \( P = .028 \) and protein: \( P = .036 \)) (Figure 2a). Additionally, we explored if lithium influenced the hippocampal TL in the FSL rats; the point estimate of the TL mean was increased in the FSL-Li group but did not reach the statistical level of significance

Discussion

We provide 2 novel findings on telomere regulation in a well-documented model of depression. First, hippocampal telomeres were shorter in the FSL rats compared with the control rats. In accordance with this finding, the Tert expression and telomerase activity were reduced in the FSL hippocampus, which was in agreement with a decreased BDNF expression in FSL. Second, the aberrant Tert expression and telomerase activity in the FSL hippocampus were reversed after lithium treatment at clinically relevant doses. A possible mediator of this effect was β-catenin, which was upregulated by lithium treatment.

Disturbed Hippocampal TL and Telomerase Activity in a Rat Model of Depression

Shorter blood LTL has been associated with depression and post-traumatic stress disorder in several studies (Lung et al., 2007;


In contrast, fluoxetine and intrahippocampal injection of an adenovirus vector expressing Tert reversed these effects, leading the authors to suggest that hippocampal telomerase plays a role in depression-like behaviors, possibly by regulating neurogenesis (Zhou et al., 2011). We investigated the full-length Tert transcript that encodes functional telomerase (Kaneko et al., 2006) in the hippocampus of depressed FSL rats and found that it was decreased. Correspondingly, telomerase activity was also reduced in FSL, which was in line with the work by Zhou et al (2011). BDNF was reported to modulate telomerase activity in embryonic hippocampal neurons (Fu et al., 2002); thus, the decreased BDNF levels we observed in the naïve FSL may in part underlie its reduced telomerase activity. On the other hand, the Tert expression difference between naïve FSL and FRL may also be related to genetic variation between these strains in telomere regulating genes, or genes implicated in metabolic stress, inflammation, or oxidative stress. For example, we previously found that the FSL harbors a functional 1-base genetic variant in the promoter of the neuropeptide Y (Npy) gene, which modulates Npy’s transcriptional activity (Melas et al., 2013). In humans, a number of single nucleotide polymorphisms in telomere-regulating genes have been associated with LTL (Cawthon et al., 2013; Oddsson et al., 2014). Cortisol levels were suggested to influence telomerase activity (Choi et al., 2008; Gotlib et al., 2014); however, serum corticosterone levels were not different between FSL and FRL rats (Owens et al., 1991; Ayenju et al., 1995). The telomerase deficiency in the FSL hippocampus implicated potential disturbance in cell survival and proliferation; this warrants future investigation.

**Lithium Treatment Increases Hippocampal Telomerase Activity**

In addition to the documented efficacy in treatment and prophylaxis of mood disorders (Johnson et al., 2001; Husum and Mathé, 2002; Angelucci et al., 2003; Miller et al., 2007), therapeutic effects of lithium have been explored in several degenerative CNS disorders, notably Alzheimer’s disease, amyotrophic lateral sclerosis, and stroke (Chiu and Chuang, 2011). On the cellular level, lithium exerts a variety of facilitatory and inhibitory effects on enzymes and signaling systems; for instance, it enhances neuroprotective pathways, for example, Bcl-2 and Wnt signaling, and inhibits phosphatidylinositol phosphatases and GSK-3. Importantly, lithium’s modification of hippocampal telomeres is proposed to be a core mediating event of neuroprotective and neurotrophic effects of lithium (Pasquali et al., 2010). Importantly, β-catenin, an established marker for GSK-3β inhibition (Gould et al., 2004), was shown to be involved in activation of hTERT transcription in cancer cell lines (Zhang et al., 2012). However, molecular mediators of lithium’s effect on telomerase have not been clarified. Our results show that lithium rescued the reduced Tert expression and telomerase activity in the FSL hippocampus. In line with these results, lithium significantly increased β-catenin expression. This is the first report on the possible mechanism of lithium’s modification of hippocampal TL. Lithium was previously reported to upregulate BDNF levels in hippocampus and temporal cortex (Fukumoto et al., 2001; Hashimoto et al., 2002). However, we found no BDNF increase in hippocampi from lithium-treated FSL rats measured by Western blot, which is consistent with our previous results measured by ELISA (Angelucci et al., 2003). This discrepancy in effect on BDNF might be explained by differences in the duration of lithium treatment. In the study of Fukumoto et al. (2001), an increase in BDNF was found after 14 days, but not 21 days, while the treatment duration in our study was 42 days. In this study, lithium did not increase hippocampal TL, that is, the TL did not follow the

![Figure 2. Expression levels of Tert, brain-derived neurotrophic factor (BDNF), β-catenin, telomerase activity, and telomere length (TL) measured in the hippocampus of vehicle-treated Flinders Sensitive Line (FSL) and lithium-treated FSL.](image-url)
change in telomerase activity. A similar lack of TL change despite telomerase upregulation was reported by Wolkowitz et al. (2012). TL changes much slower than telomerase activity (Epel et al., 2009; Epel et al., 2010), and our previous study found that long-term lithium treatment (≥30 months) in patients diagnosed with bipolar disorder correlated positively with LTL (Martinsson et al., 2013). Species and tissue differences, that is human vs rodent and brain vs leukocytes, are possible explanations for these discrepancies.

Limitations of our study are that we did not perform behavioral tests comparing the FSL-vehicle and FSL-Li treated groups and therefore cannot provide direct evidence that enhanced telomerase activity by lithium is associated with an antidepressant-like effect. Moreover, due to the insufficient number of available FRL rats, we did not compare possible differential effects of lithium on FSL and FRL rats. On the other hand, the primary aim of the lithium treatment was to verify our hypothesis that lithium protects against TL shortening and to explore the possible molecular mechanisms. Another limitation is that our results were derived from hippocampus homogenates; thus, cell type-specific expression should be addressed in follow-up studies. For example, telomerase activity was recently reported to be expressed not only in neural stem cells but also in astrocytes and oligodendrocytes in white matter of the adult brain (Szebeni et al., 2014). The strength of this project is that we demonstrated, for the first time, that 1) telomeres are shorter, 2) Tert expression is reduced, 3) telomerase activity is decreased in hippocampus of a rat genetic model of depression, and 4) lithium treatment increases expression of β-catenin and Tert and telomerase activity in the FSL rat hippocampus.

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