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Review article

The potential impact of biochemical mediators on telomere attrition in major depressive disorder and implications for future study designs: A narrative review

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ABSTRACT

Background: Major depressive disorder (MDD) has been proposed to represent a "disease of premature aging", which is associated with certain biomarkers of cellular ageing and numerous other age-related diseases. Over the last decade, telomere length (TL) arose as a surrogate for cellular aging. Recent data suggests that TL might be reduced in patients with MDD, however, results are still inconclusive. This might be explained by the lack of assessment of potential biochemical mediators that are directly associated with telomere shortening and frequently observed in patients with MDD.

Methods: A narrative review was performed. The PubMed database was searched for relevant studies.

Results: We identified four major mediators, which are recurrently reported in patients with MDD and are associated with reduced TL: inflammation/oxidative stress, dysregulation of the hypothalamic-pituitary-adrenal axis, metabolic dysbalance including insulin resistance, and decreased brain-derived neurotrophic factor. These mediators are also mutually associated and were not systematically assessed in current studies investigating TL and MDD, which might explain inconclusive findings across current literature. Finally, we discuss possible ways to assess those mediators and potential implications of such approaches for future research.

Limitations: The majority of identified studies had cross-sectional designs and used heterogeneous methods to assess TL and associated relevant biochemical mediators.

Conclusions: A better understanding of the complex interactions between biochemical mediators, somatic comorbidities and shortened telomeres in patients with MDD might further specify the pathophysiology-based conceptualization and, based on that, personalized treatment of MDD.

1. Introduction

Major depressive disorder (MDD) is characterized by alterations of affective, cognitive and somatic functions and is associated with relevant functional disability and mortality (Ebmeier et al., 2006). With a life time prevalence of 16% and a point prevalence of 4.4% (Ferrari et al., 2013), MDD represents the third leading cause of global disease burden as well as the leading cause of disability (Ustün et al., 2004). The annual economic costs of depression in the United States were calculated at 83 billion dollars in 2000, and in Europe at 118 billion euro in 2004 (Donohue and Pincus, 2007; Sobocki et al., 2006). Overall, MDD has not only a tremendous impact on patients' quality of life but causes also great societal and economical costs (Ferrari et al., 2013).

Although remarkable efforts have been made in order to elucidate the causes of MDD on a biological level and to infer on potential molecular targets for treatment, the neurobiological basis of MDD remains incompletely understood (Pryce and Seifritz, 2011). Recently, it has been suggested that MDD might represent a syndrome of "premature aging" (Wolkowitz et al., 2010). One biomarker for cellular aging is telomere length (TL), which can be measured in leukocytes (LTL) or peripheral mononuclear blood cells (PMBCs) (Aubert et al., 2012). Telomeres protect chromosomes from taking damage by capping the chromosomal DNA ends. They can be shortened by incomplete replication of the telomere ends during mitosis and exposure to inflammation, cytotoxins, oxidative stress as well as stress hormones such as cortisol and catecholamines (Lindqvist et al., 2015). In case telomeres reach a critical length, cell functioning becomes unstable due to replicative senescence or genomic instability. Therefore, TL is proposed to be a valuable biomarker of aging, which is related to declining physiological integrity and consecutive functional impairment and

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susceptibility to death (Lin et al., 2016).

Over the past decade, clinical investigations have tried to elucidate a potential relationship between shortened telomeres and MDD (Darrow et al., 2016; Lin et al., 2016; Ridout et al., 2016; Schutte and Malouff, 2015). Although most studies found significantly shortened telomeres in patients with MDD (Garcia-Rizo et al., 2013; Hartmann et al., 2010; Karabatsiakis et al., 2014; Lung et al., 2007; Wikgren et al., 2012), some conflicting findings were also discovered (Schaakxs et al., 2015; Simon et al., 2006, 2015). Presumably, some inconsistencies might be explained by differences in study populations, diagnostic assessments of mental disorders, methods in measuring TL and general study designs. The clear heterogeneity across studies strongly suggests that in addition to aforementioned factors, potential biological confounders might play a crucial role regarding a potential modulation of TL in MDD (Darrow et al., 2016; Lin et al., 2016; Lindqvist et al., 2015). More specifically, attrition of telomeres in patients with MDD could be considered as expected concomitant, and/or consequence of those confounders (Price et al., 2013).

In addition to findings in MDD, short telomeres in humans have also been associated with several medical conditions, including cardiovascular disease (Hoen et al., 2011), diabetes (Liu et al., 2014), and cancer (Lin et al., 2015). There are some studies linking shorter telomeres in leukocytes (LTL) with pre-mature mortality (Weischer et al., 2013) and a reduction in years of healthy living (Njajou et al., 2009). Furthermore, reduced LTL has been associated with specific pathophysiological alterations and biochemical mediators, such as increased inflammation (Wolkowitz et al., 2011a), increased activity of the hypothalamus-adrenal-pituitary (HPA) axis (Wikgren et al., 2012), aberrant metabolic regulation (Garcia-Rizo et al., 2013) and decreased neurotrophic factors, such as Brain-derived neurotrophic factor (BDNF) (Niu and Yip, 2011). Interestingly, all of those pathological conditions are more frequent in patients with MDD. In addition, patients with MDD also have an increased risk of smoking, eating poorly and being less physically active (van Gool et al., 2007), which has also been linked to shortened telomeres (Latifovic et al., 2016). Given this observation, it can be assumed that the heterogeneity in the literature regarding TL in patients with MDD can be at least partially explained by a mixture of various pathophysiological conditions and somatic conditions. However, since MDD is diagnosed based on nosological classifications, i.e. where MDD is defined as an entity characterized by specific psychiatric symptoms and co-occurring somatic conditions are seldom accounted for, only few studies investigating TL in MDD considered depression-associated somatic conditions as potential confounders (Mayberg, 2007). Nevertheless, such studies could significantly improve our current understating of possible disease-specific mechanisms induced by shorter telomeres, particularly since it is still unclear, whether telomere attrition represents a risk factor for developing certain age-related diseases, appears as trans-diagnostic biological abnormality common to age-related diseases or reflects a dose-dependent marker of pathological conditions or behavioral phenotypes (Lindqvist et al., 2015; Wolkowitz et al., 2010).

Besides this diagnostic perspective, first studies suggest that TL measurements might be a valuable prognostic marker, predicting both disease progression and mortality in patients with bladder cancer (Lin et al., 2015) as well as treatment response to selective serotonin reuptake inhibitors (SSRI) in patients with MDD (Hough et al., 2016; Wolkowitz et al., 2012).

Therefore, a better understanding of pathological mediators in MDD could not only help to identify new targets for treating depression and its comorbid medical conditions, but could also help to reclassify MDD as a multisystem disorder in contrast to the current nosological conceptions based on psychopathology.

Here, we present a narrative review covering the latest advances throughout the relevant literature. We (1) discuss the major four mediators of shortened telomeres which are frequently associated with MDD; (2) summarize the literature on telomere attrition in patients with MDD with respect to those mediators; (3) present a potential approach for future studies investigating the relationship between shortened telomeres and MDD that takes those mediators systematically into account. We will propose how to improve future studies with respect to telomeres and to allow for a better inter-study comparability.

2. Potential mediators of shortened telomeres in patients with MDD

2.1. Inflammation and oxidative/nitrosative stress

Inflammation and oxidative stress are frequently associated with MDD and have an impact on telomere shortening (Lindqvist et al., 2015; Wolkowitz et al., 2010, 2011a; Pariante, 2017). On a cellular level, it has been shown that inflammation and oxidative stress can induce senescent properties in mature neurons (Jurk et al., 2012). In general, oxidative and nitrosative stress refers to the cellular inability to neutralize reactive oxidative (ROS) or nitrosative species (RNS) via antioxidative mechanisms (Miller and Sadeh, 2014). Aerobic cells produce ROS/RNS as a by-product during numerous metabolic processes; in particular, around 1–5% of the oxygen consumed by mitochondria is converted to ROS/RNS (Maurya et al., 2016). In case of a mismatch between the amount of ROS/RNS and the cellular capacity of available antioxidative mechanisms, ROS/RNS can induce oxidative damage to various molecules, including DNA (Maes et al., 2011). Noteworthy, the cellular anti-oxidative capacity decreases over the lifespan, resulting in an increased rate of oxidative damage during the aging process as well as in the presence of severe somatic disorders (Inal et al., 2001). Telomeric DNA is particularly sensitive to oxidative damage (von Zglinicki, 2002; Wolkowitz et al., 2011a) and repair of oxidative damage is relatively inefficient in telomeres, suggesting that LTL might be a surrogate for a life time measure of cumulative oxidative damage (Lindqvist et al., 2015; von Zglinicki, 2002). Furthermore, the impact of inflammation on LTL is most likely mediated by the induction of immune cell replication as well as by several pathways inducing oxidative stress (Rawdin et al., 2013). These notions are supported by findings that otherwise healthy individuals with high level of the C-reactive protein (CRP) and elevated cumulative inflammation parameters showed shorted LTL (Révész et al., 2014). Furthermore, in healthy pre-menopausal female individuals, shortened leukocyte telomeres have been demonstrated to yield a negative correlation with oxidative stress markers (Epel et al., 2004).

In general, MDD is associated with prominently increased concentrations of inflammatory cytokines (Wolkowitz et al., 2011a). More specifically, significantly increased concentrations of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 have been consistently found in patients with MDD (Dowlati et al., 2010). Furthermore, Goldsmith et al. (2016) found in a recent meta-analysis increased levels of interleukines (including IL-6, IL-10, IL-12, sIL-2R and sIL-6R) and TNF-α in patients with MDD, while interferon gamma (IFN-γ) and IL-4 were significantly decreased. After successful treatment of acute depression, levels of IL-6, IL-10 and IL-12 decreased while IL-4 levels increased, suggesting a normalization of the immune response. Interestingly, in patients with treatment-resistant MDD, IL-6 remained significantly increased during treatment (Goldsmith et al., 2016).

In patients with MDD, Wolkowitz et al. (2011a) measured IL-6 as peripheral marker of inflammation and F2-isoprostane/vitamin C ratio as peripheral marker of oxidative stress and found that IL-6 was significantly correlated with shorter telomeres in patients with MDD, while F2-isoprostane/vitamin C ratio was associated with shorter telomeres in both patients with MDD and healthy controls, providing further evidence that inflammatory processes might explain reported shortening of telomeres in patients with MDD. Furthermore, Garcia-Rizo et al. (2013) found that lymphocyte count was lower in patients with MDD; however, no correlation could be demonstrated between