EDITORIAL

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EDITORIAL

When blue turns to grey: Do stress and depression accelerate cell aging?

Biological researchers have explored the ‘biogenic amine’ hypothesis of major depression for several decades, with variable success (Charney 1998; Hindmarch 2002). More recent theories have focused on cell endangerment in the brain, and in the hippocampus in particular. Most recently still, data have emerged suggesting that cells outside the central nervous system may also be endangered and prematurely ‘aged’ in depression and in states of chronic psychological stress. Whether or not such cellular ‘aging’ in the periphery mirrors aging processes in the brain, it may play a role in depression’s co-morbidity with diseases associated with aging, such as cardiovascular disease, osteoporosis and dementia. In this Editorial, we will review the background and possible significance of these findings.

Sapolsky and McEwen and others were among the first to propose that chronically elevated levels of glucocorticoids (as seen in a proportion of patients with major depression) can have neurotoxic or neuroendangering effects on hippocampal neurons (McEwen et al. 1979; Sapolsky et al. 1985). These observations, largely derived from animal studies, led to speculation that such processes may underlie the diminished hippocampal volume seen in some depressed patients (McEwen and Magarinos 2001; Sapolsky 2000a,b; Sheline 1996, 2000). The possibility of cellular dysregulation within the hippocampus was subsequently elaborated upon by Duman and others (Duman et al. 1997; Duman and Monteggia 2006). These investigators observed in animals that stress, as well as excessive exposure to glucocorticoid hormones, led to diminished hippocampal levels of brain-derived neurotrophic factor (BDNF). BDNF plays an important role in facilitating neuronal outgrowth of stem cells in the subventricular zone and the subgranular region of the hippocampus. It may additionally provide a measure of neuroprotection to existing neurons (Groves 2007). Duman and colleagues also observed that antidepressant treatment (regardless of proximal mechanism of action) in animals prevented or reversed these changes in BDNF levels and increased hippocampal neurogenesis. Together, these observations led to a ‘neurotrophic hypothesis’ of depression. It was proposed that stress-associated increases in cortisol can lead to impaired neurogenesis in the hippocampus, which might then (via uncertain mechanisms) result in depressive symptoms. The data in support of this theory, including findings of low serum BDNF levels in untreated depressed patients (Karege et al. 2002), are intriguing but have recently been challenged (Groves 2007).

In 2004, Epel and colleagues discovered a novel aspect of cellular damage that is associated with chronic psychological stress (Epel et al. 2004), though they did not study depression per se. Their studies focused on peripheral blood mononuclear cell (PBMC) telomere length (a putative marker of cell aging) and telomerase activity. Telomeres are the ‘end caps’ of linear DNA strands that serve to protect the ends of DNA from fraying and from end-to-end fusions. In replicating somatic cells, telomeres progressively shorten with each mitotic cycle. Telomeres are also shortened by exposure to various genotoxic stressors, such as oxidative stress (von Zglinicki 2002). When telomeres reach a critically short length, cells undergo apoptosis and die. In fact, telomere length has been proposed as a useful biomarker of ‘biological aging’ (as opposed to ‘chronological aging’) (Aviv 2006; Brouilette et al. 2003). Telomerase, on the other hand, is a reverse transcriptase enzyme that restores telomere length. Telomerase may also have anti-aging and cell survival-promoting effects independent of its effects on telomere length by regulating transcription of growth factors, having intrinsic anti-apoptotic effects, protecting cells from necrosis and stimulating cell growth in adverse conditions (Mattson et al. 2001). Consistent with their utility as ‘biomarkers of aging,’ shortened telomeres are potent risk factors for cardiovascular disease and early death (Cawthon et al. 2003). Epel and colleagues studied a group of middle-aged women who were primary caregivers for chronically ill children, in comparison to a well-matched control group. They found that the chronically stressed caregiving women had shorter PBMC telomere lengths and decreased PBMC telomerase activity, compared to the controls. These between-groups differences were even more apparent when the groups were combined and stress ratings were correlated with the cell aging parameters.
Specifically, women with greater self-rated stress had shorter telomeres and less telomerase activity than women with low levels of self-rated stress. The difference in telomere length between the high- and low-stress women was not trivial; it was the equivalent of approximately 13 years of accelerated aging (based on estimated normal aging-associated yearly telomere attrition rates of 31–63 base pairs per year in adults). Most recently, Simon and colleagues found shortened PBMC telomeres in patients with depression, bipolar disorder and/or co-morbid anxiety disorders, representing as much as 10 years of accelerated aging (Simon et al. 2006). These investigators did not measure telomerase activity. Both of these studies require replication but are consistent with accelerated PBMC ‘aging’ in chronic stress and depression.

How might stress-induced telomere shortening occur? Shortening of telomeres with stress and depression could be explainable by referencing two other bodies of research: the first relating stress and depression to changes in certain biological mediators, and the second relating changes in the same biological mediators to telomere shortening. For example, chronically stressed and depressed individuals (especially females) have increased levels of circulating oxidative stress markers (e.g., increased F2-isoprostanes, 8-hydroxy-deoxyguanosine (8-OHdG)), along with decreases in anti-oxidant enzymes, and the concentration of oxidative stress markers is directly correlated with the severity of depression (Forlenza and Miller 2006; Irie et al. 2002, 2003; Tsuboi et al. 2004). Additionally, depression may be associated with increased levels of pro-inflammatory cytokines (Leonard 2000; O’Brien et al. 2004), although not all studies support this. Both oxidative stress and pro-inflammatory cytokines influence telomere dynamics: oxidative stress directly damages telomeric DNA (von Zglinicki 2002) and increases intra-nuclear activity of telomerase (Haendeler et al. 2004), and pro-inflammatory cytokines may either decrease or increase telomerase activity (Akiyama et al. 2002, 2004). Finally, depression is often (but not always) associated with hypercortisolemia, which in turn may exacerbate oxidative stress and pro-inflammatory cytokine release (McIntosh and Sapolsky 1996; Sorrells and Sapolsky 2007). Glucocorticoids can also lead to downregulation of telomerase activity (Akiyama et al. 2002) and to shortened telomeres (Ichiyoshi et al. 2003). Consistent with a role of these biological mediators in telomere dynamics in chronic stress, Epel and colleagues found that oxidative stress was inversely related to PBMC telomere length and telomerase activity (Epel et al. 2004), and nocturnal urinary cortisol levels were inversely correlated with PBMC telomere length in chronically stressed caregivers (Epel et al. 2006).

The importance of these possible mediators in the pathophysiology of depression and in promoting cell aging remains largely speculative, and much research remains to be done. If the finding of shortened PBMC telomeres in depression is replicated, this might provide a new window into the pathophysiology of depression and its co-morbid medical illnesses. If PBMC telomere dynamics directly mirror CNS ones (especially in mitotic cells such as hippocampal stem cells), this could help us understand cell-level pathology in the brain in depressed patients. Even if PBMC telomere length bears no relationship to hippocampal cell telomere length, shortened PBMC telomeres could still be significant in depression: (1) if shortened telomeres in peripheral immune cells eventuate in premature aging of those cells, this could result in impaired immune responsiveness and in hypersecretion of pro-inflammatory cytokines (Effros 2007; Leonard 2000); (2) as noted above, shortened telomeres have been associated with a variety of human medical illnesses, such as cardiovascular disease (Cawthon et al. 2003) and dementia (von Zglinicki et al. 2000; Franco et al. 2006; Honig et al. 2006; Martin-Ruiz et al. 2006). If in depression, shortened telomeres and heightened risk for medical illness bear causal relationships with each other, then telomere shortening could provide a ‘missing link’ to explain the higher-than-expected medical morbidity seen in depression (Musselman 1998; Brown 2004). Also, to the extent that telomere pathology is important in the pathophysiology of various illnesses, discovering the biochemical mediators leading to telomere shortening could lead to new classes of medications (Effros 2007). It is still not known if depression leads to accelerated ‘aging’ of mitotic cells. However, as our understanding of depression grows ever more complex, new models should lead to additional targets for therapeutic intervention.

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