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The Cellular Sequelae of Early Stress: Focus on Aging and Mitochondria

That stress and trauma impact physiologic systems and promote psychiatric and other medical illness is now well accepted. Biologic aging is driven by molecular alterations at the cellular level, including telomere decline and mitochondrial DNA (mtDNA) mutations, promoting DNA damage, and mitochondrial dysfunction. These changes contribute to cellular senescence, apoptosis and cancer risk, signal increased inflammation, and ultimately contribute to organ dysfunction and risk for age-related conditions including diabetes and cardiovascular disease. Early or severe stress is associated with reductions in telomere length and maintenance, suggesting these exposures might accelerate the aging process (Ridout *et al*, 2015). New research supports the intriguing hypothesis that early stress may also affect mitochondrial function, further linking early stress and accelerated aging.

Mitochondria provide the main source of cellular energy through aerobic respiration and are integral to cellular signaling. Reactive oxygen species are a by-product of mitochondrial respiration that are not simply mediators of cellular damage but have vital roles in cellular signaling pathways (Picard *et al*, 2014). Aging is characterized by increased mitochondrial ROS production, declines in mitochondrial function, mtDNA mutation accumulation, and mitochondrial replication alterations. These changes contribute to metabolic and inflammatory system dysregulation and the development of age-related disorders, including diabetes, Alzheimer's disease, and cardiovascular disease (Picard *et al*, 2014).

New data suggests that stress and psychopathology are associated with mitochondrial changes similar to those seen with aging. Our group recently reported increased leukocyte mtDNA copy number in adults with a history of early life stress and with depressive, anxiety, and substance use disorders (Tyrka *et al*, 2015b). In the same subjects, telomere length was reduced and mtDNA and telomere length were correlated (Tyrka *et al*, 2015a). Similar findings were reported in saliva of subjects with early stress and depression (Cai *et al*, 2015) and, in animals exposed to chronic stress or depression models, mitochondrial activity is impaired in the hippocampus, thalamus, and cortex (Picard *et al*, 2014). mtDNA copy number is a gross measure of mitochondrial activity; increases may occur as a compensatory response to impaired mitochondrial function (Picard *et al*, 2014). These results suggest that early stress may contribute to mechanisms triggering such compensatory responses and that psychiatric disorders may represent a form of chronic stress.

New findings identify mechanistic pathways linking stress, glucocorticoid signaling, telomere dynamics, and mitochondrial proliferation and function. Telomerase, an enzyme that maintains telomere length and modulates cell signaling, gene expression, and DNA damage responses, also influences mitochondrial proliferation and function (Sahin and DePinho, 2012). Telomerase activity changes with stress and other conditions altering neuroendocrine function (Ridout *et al*, 2015). Glucocorticoid exposure, and associated inflammatory and oxidative stress pathway activation, is linked with telomere shortening and may be a mechanism through which early stress contributes to telomere decline (Ridout *et al*, 2015). Glucocorticoid signaling is also involved in mitochondrial replication (Cai *et al*, 2015) and can damage mitochondria via elevating glucose levels, promoting systemic inflammation, altering gene expression in proapoptotic pathways, and hastening cellular aging (Picard *et al*, 2014). Increased demands on mitochondria in brain regions impacted by early stress such as the hippocampus may increase ROS production and mtDNA damage, contributing to reduced energy production and proapoptotic signaling in these brain regions, which may result in changes in neurotransmitter signaling, neuronal cell function, and viability (Picard *et al*, 2014). Such potential mechanisms warrant further exploration and may constitute intervention targets to prevent stress-related aging and disease.

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