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Mitochondria and Early-Life Adversity

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Abstract

Early-life adversity (ELA), which includes maltreatment, neglect, or severe trauma in childhood, increases the life-long risk for negative health outcomes. Mitochondria play a key role in the stress response and may be an important mechanism by which stress is transduced into biological risk for disease. By responding to cues from stress-signaling pathways, mitochondria interact dynamically with physiological stress responses coordinated by the central nervous, endocrine, and immune systems. Preclinical evidence suggests that alterations in mitochondrial function and structure are linked to both early stress and systemic biological dysfunction. Early clinical studies support that increased mitochondrial DNA content and altered cellular energy demands may be present in individuals with a history of ELA. Further research should investigate mitochondria as a potential therapeutic target following ELA.

Keywords

Mitochondria; early-life adversity; stress; trauma; mechanisms

Introduction

Early experiences shape the development of emotional and physiological responses to stress and thereby exert long-term influences on health throughout the lifespan. Childhood is a developmental period in which individuals are especially vulnerable to the harmful consequences of stress as the brain is undergoing extensive experience-dependent growth and plasticity (Heim et al., 2019). Furthermore, because children rely on caregivers to meet their physical and emotional needs, the early environment exerts a profound influence on

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development and behavior (McLaughlin et al., 2017). This need for nurturing in childhood, combined with developmental changes to the nervous system, amplifies the neurobiological vulnerability to stressful environmental factors. Dynamic interactions between neural circuitry, genetics, and environmental stressors produce physiologic changes early in life, and result in downstream impact on health outcomes (Berens et al., 2017; Heim et al., 2019).

Early-life adversity (ELA) includes experiences of abuse, neglect, caregiver death, exposure to stressors associated with low socioeconomic status, and other traumatic events that threaten a child's safety. Epidemiological studies provide robust evidence of associations between ELA and a variety of negative somatic and psychiatric health outcomes throughout the lifespan. A landmark study on adverse childhood experiences found a dose-dependent relationship between adverse childhood experiences and multiple health risk factors such as substance abuse disorders, depression, ischemic lung disease and cancer (Felitti et al., 1998). More recent meta-analyses continue to support that ELA increases risk for obesity, cardiovascular disease, other chronic diseases in adulthood (Danese and Tan, 2014; Gilbert et al., 2015; Li et al., 2019). Immune dysregulation, increased risk for developing cancer, and greater all-cause mortality risk have also been associated with adverse experiences in childhood (Baumeister et al., 2016; Boeck et al., 2016; Fagundes et al., 2013; Hughes et al., 2017; Rod et al., 2020). Finally, it has been well-documented that ELA is associated with many psychiatric disorders including major depressive disorder (MDD), post-traumatic stress disorder (PTSD), anxiety disorders, bipolar disorder, substance abuse, and behavioral problems (Gilbert et al., 2009; Syed and Nemeroff, 2017). Given the substantial evidence supporting the association between early adversity and later chronic health conditions, an understanding of the biological mechanisms transducing psychosocial stress into disease is needed to develop informed intervention and treatment strategies.

Mitochondria have gained attention in recent years for their potential role as targets of the stress response and mediators of stress-related dysregulation downstream (Picard et al., 2014). In response to acute stress exposure, mitochondria respond dynamically to cues from stress-signaling pathways enacted by the CNS, endocrine and immune systems, in order to adjust their activity to meet the current energetic demand (Manoli et al., 2007; Picard et al., 2018c). Evidence from rodent models suggests that mitochondria exhibit structural and functional changes with long-term exposure to stress, such as decreased respiratory enzymatic activity or mitochondrial membrane potential, resulting in an impaired capacity for energy production (Picard and McEwen, 2018a). Throughout this paper, we propose evidence to support the growing hypothesis that the mitochondrial response to stress is a key contributor to the broad range of pathological outcomes observed in individuals with ELA.

Foundations of Stress Physiology

CNS and Neuroendocrine Responses—The CNS and neuroendocrine systems are responsible for coordinating the physiological and behavioral responses to stress exposure. The cortico-limbic brain network, including regions such as the prefrontal cortex (PFC), the amygdala, and the hippocampus, perceives threat and coordinates responses to emotionally charged stimuli. The PFC regulates the amygdala, a region integral to fear and other emotional responses. Under acute stress, inhibition of the amygdala is released (Arnsten,

2015), which in turn activates the sympathetic-adrenal-medullary (SAM) axis and causes the release of catecholamines, such as adrenaline, from the adrenal gland. The hypothalamic-pituitary-adrenal (HPA) axis is also stimulated by the amygdala, driving the release of corticotropin-releasing factor (CRF) from the hypothalamus. CRF acts on the pituitary gland, precipitating the systemic release of adrenocorticotropic hormone (ACTH), which then stimulates the production of the glucocorticoid hormone, cortisol (Godoy et al., 2018).

Glucocorticoids serve a number of important functions in the stress response, including upregulating metabolic pathways, such as gluconeogenesis, lipolysis and proteolysis, to meet increased energy demands (Karatsoreos et al., 2010). Additionally, glucocorticoids facilitate the timely suppression of the physiological stress response and a return to basal conditions through negative feedback. Repetitive or excessive activation of the neuroendocrine system, especially during development, impairs negative feedback control and results in long-term dysregulation (Ceruso et al., 2020; van Bodegom et al., 2017). Both hypo- and hyper-reactive ACTH and cortisol levels have been observed in individuals with ELA at baseline and in response to acute stressors (Carpenter et al., 2007; Cicchetti et al., 2010; Cicchetti and Rogosch, 2001; Elzinga et al., 2008; Trickett et al., 2010; Tyrka et al., 2008; Young et al., 2020); the pattern of dysregulation may be determined by type and developmental timing of ELA (Carpenter et al., 2011; Miller et al., 2007; Tyrka et al., 2008), current age (Bunea et al., 2017), genetics (Trickett et al., 2010) and psychopathology (Berens et al., 2017). HPA axis dysregulation has clinical implications and has been linked with psychiatric disorders, including major depression and PTSD, and treatment response (Nikkheslat et al., 2020). Alterations in HPA axis functioning may provide the link between early stress, psychopathology, and metabolic outcomes such as obesity and metabolic syndrome (García-Eguren et al., 2019; Yu et al., 2014).

Impact of Stress on the Immune and Metabolic Systems—Glucocorticoids regulate immune and metabolic functioning in order to signal the possibility of injury or infection and increased systemic energy need when under threat. Individuals with chronic stress exposure in childhood demonstrate significant and graded elevations in inflammatory proteins and pro-inflammatory cytokines in adolescence and adulthood, an association not explained by mediators such as adult stressors or unhealthy behaviors (Baumeister et al., 2016; Danese and Lewis, 2017; do Prado et al., 2017). One study found that women with a history of childhood maltreatment exhibited greater pro-inflammatory cytokine release from peripheral blood mononuclear cells as compared to healthy controls in one small sample (Boeck et al., 2016). These pro-inflammatory responses were also associated with increased oxidative stress and altered mitochondrial function in immune cells, which will be discussed further below. Another study in women with childhood abuse-related post-traumatic stress disorder found that immune dysfunction following childhood maltreatment may be mediated by increased NF-κB pathway activity (Pace et al., 2012), which controls the expression of multiple pro-inflammatory cytokines (Liang et al., 2004). In rodent models, prolonged glucocorticoid activation has been shown to produce metabolic abnormalities which approximate metabolic syndrome (García-Eguren et al., 2019; Karatsoreos et al., 2010). Therefore, the association between ELA and cardiometabolic risk factors, such as obesity and unfavorable lipid profiles, may be driven by metabolic stress processes, which may be

further exacerbated by additional exposures and health behaviors such as smoking, drug use, diet, and exercise (Duffy et al., 2018; Li et al., 2019). Discussed in more depth below, mitochondria may function as one avenue by which stress influences the immune and metabolic systems, as mitochondrial function is responsive to glucocorticoid signaling, inflammatory molecules, and availability of metabolic substrates (Boeck et al., 2016).

Stress throughout the lifespan also accelerates physiological aging of cells and the associated functional decline of organs within the body. Telomeres, the DNA-protein complexes that cap the ends of chromosomes, provide a buffer so that critical DNA segments are protected during replication (Epel and Prather, 2018). Telomeres are identified as an indicator of biological age, as telomeres shorten with aging and cellular stress (Han et al., 2019). Telomere shortening beyond a critical threshold leads to arrest of the cell cycle, cellular senescence, DNA damage and cell death. Over the past decade, a growing body of evidence has demonstrated a robust inverse relationship between telomere length and early adversity (Hanssen et al., 2017; Li et al., 2017; Ridout et al., 2018). Telomere attrition is also associated with chronic medical disorders, psychosocial stress and psychiatric disease; it may serve as one mechanism by which early-stress produces risk for multiple disease outcomes (Epel and Prather, 2018). While mitochondrial DNA does not contain telomeres, DNA damage and telomere shortening on nuclear chromosomes have been mechanistically linked with a decline in mitochondrial function, as both processes may be co-regulated within cells (Billard and Poncet, 2019; Sahin and DePinho, 2012). In human studies, telomere attrition and increased mitochondrial DNA copy number have been linked in the context of early stress (Cai et al., 2015; Tyrka et al., 2016).

Intersectional Role of Mitochondria—A great deal of research on stress physiology has focused on the effect of primary neuroendocrine mediators such as glucocorticoids, and secondary effects on metabolism, immune function, and telomere shortening. However, recent evidence suggests that mitochondria occupy a central and overlapping role in these processes. Mitochondria respond to signals from established stress-pathways, and alterations in mitochondrial function further modify the activity of these physiological systems (Figure 1). The intersectional role of mitochondria in multiple stress-related systems has important clinical implications. Individuals with psychiatric illness often have medical comorbidities, suggesting that stress may produce psychiatric and somatic disease via parallel mechanisms in different organ systems (Epel and Prather, 2018). As a highly energy-dependent organ, the brain is densely populated with mitochondria (Magistretti and Allaman, 2015). Genetic and functional abnormalities in mitochondria have been linked with anxiety behavior in rodents, as well as numerous psychiatric, neurodegenerative and somatic medical disorders in humans (Filiou and Sandi, 2019; Pei and Wallace, 2018; Picard et al., 2016). The mechanisms by which extreme or prolonged exposure to adversity and stress mediators alter mitochondrial DNA and function is described in depth in the following section.

Mitochondria and Mitochondrial Function

Mitochondria play a critical role in a broad range of functions within the cell and throughout the body, from energetics, epigenetics and inflammation, to hormone synthesis and metabolism (Juster et al., 2016; Picard et al., 2018c; Shaughnessy et al., 2014). Originating

1.5 billion years ago through the engulfment of a bacterial cell, mitochondria are the only non-nuclear organelle to contain their own genome-- the maternally-inherited, circular, double-stranded mitochondrial DNA (mtDNA; Hoffmann and Spengler, 2018; Sagan, 1967). The amount of mitochondrial DNA per cell, or the mitochondrial DNA copy number (mtDNAcn), varies between tissue types and individuals, and is subject to complex regulation (Lee and Wei, 2005; Moraes, 2001)). Although mtDNAcn is often used as a proxy measure of mitochondrial biogenesis (Picard et al., 2014; Wu et al., 1999), mtDNAcn is also influenced by the number of mtDNA copies per mitochondrion and the rate of mitophagy, or normal control process removing damaged mitochondria (Clay Montier et al., 2009; Frank et al., 2012). Importantly, mitochondria sense, integrate and signal information about cellular environments by responding to metabolites and neuroendocrine factors, driving inflammatory processes, and regulating the cell cycle (Picard and McEwen, 2018b).

Mitochondrial dysfunction is associated with many neuropsychiatric disorders as well as normal aging (Sun et al., 2016; Wang et al., 2019). Individuals with genetically inherited defects in mtDNA or mitochondrial proteins present with a variety of clinical symptoms indicative of CNS deficits, including neurological manifestations, atrophy of brain matter, or affective changes (Gorman et al., 2016; Kasahara and Kato, 2018). Additionally, mitochondrial abnormalities have been documented with psychiatric, neurodevelopmental, and neurodegenerative diseases such as schizophrenia (Bertolin et al., 2011; Gonçalves et al., 2018; Ichikawa et al., 2012; Martorell et al., 2006; Suárez-Méndez et al., 2020), mood disorders (Kato et al., 2018; Lindqvist et al., 2018; Scifo et al., 2018), Autism Spectrum Disorder (Chauhan et al., 2011; Chen et al., 2015; Singh et al., 2020), Alzheimer's disease (AD; Huang et al., 2020; Lin et al., 2002; Smith et al., 1996; Trushina et al., 2012), and Parkinson's disease (Gautier et al., 2016; Narendra et al., 2008), even in patients without inherited mitochondrial mutations. Work in animal models supports a causal association between mitochondrial dysfunction and changes representative of psychopathology, such as anxiety or depressive-like behaviors (Hollis et al., 2015; Kasahara et al., 2016), or neurodegeneration (Di Maio et al., 2016; Pickrell et al., 2015). For example, a pivotal recent study utilizing *Caenorhabditis elegans* and mouse models of AD found that stimulation of mitophagy could reverse memory impairment (Fang et al., 2019). New research showing that lifelong psychosocial factors influence cognitive-reserve and risk for dementia highlights the importance of further exploring the impact of early-life adversity on mitochondrial function and downstream disease-burden (H.-X. Wang et al., 2017).

Mitochondria in the Stress Response—Accumulating evidence supports a key role for mitochondria in stress-associated physiological systems. Energy demands increase with stress because the "fight or flight" behavioral response and allostatic biological systems are fueled by energy in the form of ATP. As a result, mitochondria respond to glucocorticoid signaling by increasing production cellular energy, generating signals to promote cellular adaptation, and undergoing biogenesis (Manoli et al., 2007; Picard et al., 2014). Furthermore, steroid hormones, including glucocorticoids, are both synthesized and metabolized by mitochondria (Bose et al., 2002; Lin et al., 1995). Indeed, preclinical evidence supports that mitochondrial dysfunction, induced by mutations in key

mitochondrial genes, produces alterations in glucocorticoid production and the HPA response to stress (Meimaridou et al., 2012; Picard et al., 2015).

Excessive stress is associated with changes to mitochondrial structure and function. In conditions of severe or prolonged exposure to stress, circulating levels of glucocorticoids and associated metabolic substrates are chronically elevated. Research in cell culture and animal models shows that this promotes mitochondrial fragmentation, or the breakdown of networks of communicating mitochondria within cells, which is associated with mtDNA damage, oxidative stress, and increased risk of cell death (Hoffmann and Spengler, 2018; Lee et al., 2004; Picard et al., 2014; Shutt and McBride, 2013). Similarly, preclinical evidence demonstrates that excessive or chronic elevations in glucocorticoids decrease mitochondrial function by dampening the mitochondrial membrane potential, decreasing respiratory chain enzymatic activity, lowering the threshold for apoptosis, and increasing the production of ROS (Du et al., 2009; Manoli et al., 2007; Picard et al., 2014; Yu et al., 2014). Overall, severe stress and associated alterations in glucocorticoid signaling promote mitochondrial dysfunction through altering mitochondrial dynamics.

Mitochondrial and immune function are closely intertwined, a relationship that may further link the physiological response to early adversity with systemic biological changes and health outcomes. Due to the evolutionary origin of mitochondria from bacteria, circulating cell-free mtDNA (ccf-mtDNA) and other mitochondrial components act as damage associated molecular patterns (DAMPs) when outside the cell, and activate the innate immune system via Toll-Like Receptors (West et al., 2011; Zhang et al., 2010). Inflammation is also associated with increased production of mitochondrial ROS, which has a detrimental impact on genetic stability and cellular functions (Boeck et al., 2016). Additionally, mitochondrial dysfunction promotes inflammasome activation, or the maturation of pro-inflammatory cytokines in response to innate immune danger signals (Zhou et al., 2011). In this feedforward cycle of dysfunction, inflammation promotes ROS generation and mitochondrial dysfunction, which in turn stimulates further inflammation by engaging a pro-inflammatory cytokine response. One recent study in human leukocytes has identified an association between mitochondrial respiratory chain activity with lipopolysaccharide-induced IL-6 production, finding that mitochondrial respiratory capacity may contribute to the inter-individual variability in pro-inflammatory responses (Karan et al., 2020). Neuroendocrine, metabolic and immune responses to stress are highly integrated, with mitochondria playing a critical role as shared actor in these converging pathways.

Animal Studies on Early Stress and Mitochondrial Alterations

Several studies using rodent models have confirmed that both chronic and acute environmental stressors, such as physical restraint or unpredictable habitat changes, impair mitochondrial function. Chronic unpredictable stress procedures in adult rodents have been shown to decrease oxygen consumption, respiratory chain enzymatic activity, and membrane potential, as well increase ROS production in both brain and peripheral tissues (Cai et al., 2015; Liu and Zhou, 2012; Picard and McEwen, 2018a). A study of 8-week-old male mice subjected to 6 weeks of mild unpredictable stressors exhibited depressive-like behaviors, which were associated with decreased rates of mitochondrial respiration in three brain

regions as well as swollen, damaged mitochondrial structure (Gong et al., 2011). This study and others provide strong evidence that chronic stress produces mitochondrial abnormalities, with phenotypic consequences (Picard and McEwen 2018).

Most work on mitochondrial changes in response to stress has been done in adult animals, and the relationship between environmental stress exposure during the post-natal period and long-term mitochondrial function has been less extensively studied. While early stress likely activates the same adaptive processes as stressors occurring later in life, the particular alterations may be unique. For example, the severity and duration of dysregulation from early stress may be more severe. The plasticity of the brain in early-life, as well as the potential for intervention before adulthood pathology presents, necessitates research focused specifically on the effects of early-stress on mitochondrial function.

Post-natal maternal separation (MS), during which pups are separated from their mothers for several hours per day beginning shortly after birth, is a frequently tested model of ELA. Several studies have observed mitochondrial dysfunction in the rodent CNS following MS. For example, adult rodents who underwent MS had increased ROS, decreased ATP production, decreased and antioxidant levels in the hippocampus as compared to control animals (AminiKhoei et al., 2017; Fattahi Masrour et al., 2018). In these two studies, treatment with oxytocin, a neuromodulator with potential anti-inflammatory and anti-depressant properties (Matsushita et al., 2019; Matsuura et al., 2016), the antidepressant fluoxetine, or exercise in adulthood improved indicators of mitochondrial dysfunction after MS (Amini-Khoei et al., 2017; Fattahi Masrour et al., 2018). Similar alternations in mitochondrial function have been observed following MS in peripheral tissues, such as cardiac tissue and bowel fibroblasts, which were also mitigated with adult exercise (Khorjahani et al., 2020; Sahafi et al., 2018). Together, these studies provide early evidence that post-natal stress promotes later mitochondrial dysfunction, and that interventions which reduce inflammation and enhance antioxidant properties may attenuate the negative effects of early stress on mitochondrial function in rodents.

Importantly, most studies on the effects of stress on mitochondria occur in male animals, and information on sex differences in stress-responses and mitochondrial function is lacking (Picard and McEwen, 2018a; Ventura-Clapier et al., 2017). Both mitochondria and neuroendocrine pathways are sensitive to sex hormones, suggesting that ELA may have differential effects on mitochondrial function based on sex (Bekhbat and Neigh, 2018; Torrens-Mas et al., 2020). One recent study investigated the sex-specific effects of MS in rodent CNS (González-Pardo et al., 2020). While both sexes exhibited a decrease in mitochondrial oxidative capacity in cortico-limbic regions of the brain including the PFC, nucleus accumbens, and hippocampus, females exhibited a greater reduction in metabolic capacity after MS than males (González-Pardo et al., 2020). These findings highlight the importance of using both sexes for future animal research in the field, particularly when designing studies to test interventions that may mitigate the harmful effects of MS on mitochondrial function.

Although not a direct measure of mitochondrial function, mtDNAcn is a mitochondrial measure that can be readily studied in both animal models and humans. Chronic

unpredictable stress (CUS) in adult mice increased mtDNAcn in blood and saliva (Cai et al., 2015). Increased mtDNAcn was associated with decreased oxidative phosphorylation capacity in stressed mice, suggesting that the elevation in mtDNAcn is indicative of either inefficient mitochondrial function or increased reliance on glycolysis for energy production (Cai et al., 2015). Furthermore, 8 weeks of glucocorticoid administration to adult female mice replicated the increase in mtDNAcn observed with CUS, suggesting that glucocorticoid signaling mediates stress-induced changes in mtDNAcn. After four weeks in a favorable environment, the mtDNAcn of stressed mice returned to normal levels. However, because this study utilized adult mice, it is unclear if changes to mtDNAcn induced by early stressors are also reversible. In contrast, a study utilizing a MS protocol found that early stress decreased mtDNAcn in muscle tissue of stressed adult mice (Ghosh et al., 2016). These discrepancies highlight that both timing of stressors and tissue location may influence stress-related changes to mtDNAcn, and additional research is needed to further elucidate these relationships.

Clinical Research on Early-life Adversity and Mitochondria

In the last decade, interest in mitochondrial dysfunction as a pathogenic mechanism in neuropsychiatric disease, as well as in medicine more broadly, has steadily increased (Picard et al., 2016). As such, there have been several clinical studies on the impact of ELA on mitochondrial function or mtDNAcn. One small study of 30 post-partum women found that a history of maltreatment was associated with an increase in mitochondrial respiratory activity in cryogenically-preserved peripheral blood mononuclear cells (PMBCs), which were both associated with increased spontaneous release of inflammatory cytokines (Boeck et al., 2016). Maltreatment was also associated with increased ROS production and decreased antioxidant levels in this sample. These findings suggest that PBMCs from individuals with a history of maltreatment have greater energy requirements than cells from controls and provide a possible link between abnormal mitochondrial function and increased inflammation in those with early stress. The sample size was small, and changes to mitochondrial function are likely tissue specific (Cai et al., 2015) and may be altered with cryogenic preservation, so further research that addresses these issues is needed.

Recently, this group also investigated whether observed changes in mitochondrial bioenergetics are transmitted intergenerationally from mothers to neonates (Gumpp et al., 2020). Gumpp et al. found that mitochondrial respiratory activity in cryopreserved PMBCs was increased in postpartum women with a history of childhood maltreatment, as compared to controls, which supports previous findings (Boeck et al., 2016; Gumpp et al., 2020). Additionally, the maltreated group had increased mitochondrial density in PMBCs, as measured by citrate synthase activity, suggesting that increased respiratory activity may be due to a higher number of mitochondria per cell. However, maternal childhood maltreatment was not significantly associated with neonatal mitochondrial bioenergetics measured from umbilical cord blood mononuclear cells (Gumpp et al., 2020).

Increased mtDNAcn has been reported in both adults and children with ELA. Our group examined mtDNAcn from whole blood leukocytes of 290 healthy unmedicated adults with and without a history of ELA, including childhood maltreatment and parental loss, as well as

with and without a lifetime history of depressive, anxiety, and substance-use disorders. We observed that both ELA and lifetime psychopathology were independently associated with elevations of leukocyte mtDNAcn (Tyrka et al., 2016). The effect of ELA on mtDNAcn was not accounted for by measures of subclinical psychiatric symptoms, recent stressors, or resilience. Adults with both ELA and lifetime psychopathology had the highest mtDNAcn on average, though the burden of early adversity was also greatest in this group. We also found that the association between ELA and mtDNAcn was statistically accounted for by decreased promoter methylation of the glucocorticoid receptor gene NR3C1 (Ridout et al., 2020). This relationship between glucocorticoid signaling and ELA-associated mtDNAcn alterations is consistent with the Cai et al. findings in rodents that suggest a mechanistic role of glucocorticoids in the effects of early stress on mtDNAcn (Cai et al., 2015).

In the largest study to date, Cai and colleagues studied 11,670 Chinese women with and without recurrent MDD, and found that higher salivary mtDNAcn was associated with a history of childhood sexual abuse (Cai et al., 2015). However, MDD moderated the relationship between ELA and mtDNAcn in this sample, as there was no association between sexual abuse and mtDNAcn in women without MDD. Conversely, MDD had associations with higher mtDNAcn that were independent of the early stress measures. Our group recently found that ELA-induced elevations in salivary mtDNAcn may begin in childhood (Ridout et al., 2019). In a sample of n=256 low-income preschool aged children, those with a confirmed case of maltreatment within the previous six months had significantly higher salivary mtDNAcn than non-maltreated children.

Together, these studies provide early evidence that forms of ELA such as maltreatment are associated with increased mtDNAcn, as measured from blood or saliva, presenting as early as in childhood. There is evidence that increases in mtDNAcn, as have been observed with ELA, can be a compensatory response to a decrease in mitochondrial function (Picard et al., 2014), that can serve to increase mitochondrial biogenesis and energy production (Clay Montier et al., 2009). However, because regulation of mtDNAcn is complex, it is also possible that alterations in mtDNAcn occur independently to changes in mitochondrial function.

Elevations in mtDNAcn have also been associated with lifetime mood and substance use disorders (Cai et al., 2015; Tsujii et al., 2019; Tyrka et al., 2016; X. Wang et al., 2017), Parkinson’s disease (Bury et al., 2017), and Autism Spectrum Disorder (Chen et al., 2015; Yoo et al., 2017). Nonetheless, there are important limitations with the use of mtDNAcn as a biomarker of mitochondrial function. First, while consistent elevations in mtDNAcn have been noted following ELA, the direction of change observed in mtDNAcn with psychiatric disorders, including MDD, PTSD, and bipolar disorder, has been less clear (Daniels et al., 2020). Variability in these findings could be due to differences in the nature of the samples (i.e., comorbidities, medications, history of trauma), or differing cell or tissue sources of mtDNAcn (Daniels et al., 2020). Furthermore, clinical studies measure mtDNAcn from tissue with mixed cell populations, such as blood and saliva, which may confound the measurement (Han et al., 2019; Picard et al., 2019). For example, one study has shown that mtDNAcn measured from whole blood overestimates the mtDNA contribution of leukocytes due to the presence of platelets, which possess mtDNA but not nDNA (Hurtado-Roca et al.,

2016). Finally, clinical measurement of mtDNAcn does not distinguish intracellular mtDNA from extracellular ccf-mtDNA, or the cell type origin. While mtDNAcn can be reliably measured as it does not require the preservation of live cells, mtDNAcn is not a direct measure of mitochondrial function and thus findings should be interpreted with caution.

The Mitochondrial Health Index (MHI), developed by Picard and colleagues (Picard et al., 2018d), aims to overcome these challenges through integration of measures of both mitochondrial content (such as mtDNAcn) and mitochondrial enzymatic activity (reflecting mitochondrial function). In a study of 91 mothers, approximately half of whom were experiencing chronic stress in the form of caring for a child with autism, both stress exposure and mood were related to MHI, with lower MHI in individuals with more perceived stress, and higher MHI associated with positive mood. Interestingly, there was no significant relationship between the individual components of the MHI and caregiving status, indicating the MHI may be a valuable composite measure of mitochondrial functional capacity. These findings in a sample of adults with chronic stress warrant investigation of MHI as it relates to ELA.

Future research on ELA, mitochondrial dysfunction, inflammation, and negative health outcomes should include examinations of ccf-mtDNA concentrations in populations with ELA. Ccf-mtDNA is a mitokine, or a systemic signaling molecule originating from mitochondria, recently identified as a peripheral indicator of mitochondrial health and inflammation. It is present in low levels in healthy individuals, abundant in inflammatory disease, and significantly increased in critically ill hospitalized patients (Nakahira et al., 2013). Several recent small studies suggest a role for ccf-mtDNA in stress-related psychological states. Baseline concentrations of ccf-mtDNA were shown to be elevated in non-medicated suicide attempters and patients with MDD (Lindqvist et al., 2018, 2016). Furthermore, ccf-mtDNA was shown to increase in response to acute psychosocial stress in two samples of healthy adults (Hummel et al., 2018; Trumpff et al., 2019). Research on concentrations of ccf-mtDNA in adults who experienced ELA will further elucidate the role of this signaling molecule in psychiatric disease and stress responses.

Synthesis of Findings and Clinical Implications

Synthesizing findings from animal models and clinical research, we wish to highlight three important themes. First, ELA has been shown to impair mitochondrial function and increase salivary and leukocyte mtDNAcn in recent preclinical and clinical research (Amini-Khoei et al., 2017; Boeck et al., 2016; Cai et al., 2015; Fattahi Masrour et al., 2018; Ghosh et al., 2016; González-Pardo et al., 2020; Khorjahani et al., 2020; Ridout et al., 2019; Sahafi et al., 2018; Tyrka et al., 2016). While the existing findings in regards to ELA have been quite consistent, current research, especially in humans and even more so in children, is limited and thus conclusions should be interpreted cautiously. The second finding spanning research in both animals and humans is that glucocorticoid signaling may mediate the increase in mtDNAcn, as measured in human leukocytes and saliva, following ELA. This finding is in accordance with previous evidence that mitochondria are responsive to neuroendocrine signaling. Thus, changes in mtDNAcn may be a novel marker indicating that established stress signals impact cellular energetics through mitochondrial changes. Finally, limited

research with animal models suggests that ELA-induced mitochondrial dysfunction is potentially reversible with timely intervention. Further investigation, both preclinical and clinical, is needed to determine if mitochondrial dysfunction is an appropriate target for intervention following ELA.

We hypothesize that mitochondrial alterations, such as increased oxidative stress and decreased respiratory capacity, may accelerate biological aging and thereby explain the increased prevalence of disease in adults with a history of ELA. For example, mitochondrial oxidative stress can propagate a wide range of disease outcomes, which are also associated with ELA, from metabolic syndrome to neurodegeneration and cancer (Franco-Iborra et al., 2018; Rani et al., 2016; Yang et al., 2016). Furthermore, recent studies have implicated mitochondrial dysfunction in the pathogenesis of mood and trauma-related disorders (Filiou and Sandi, 2019; Pei and Wallace, 2018; Preston et al., 2018; Srivastava et al., 2018). The density of mitochondria in the brain, as well as the organelle's importance in other physiological systems, may explain why early adversity exerts such a profound influence on risk for both psychiatric and somatic disease.

There are multiple limitations to current research that limit our understanding of the effect of ELA on mitochondria and their role in health outcomes. First, most animal studies on chronic stress utilize fully matured animals. As adverse experiences in childhood are consistently associated with worse long-term health outcomes as compared to stressors occurring later in life, the developmental period of exposure is an important target for stress research. Furthermore, very limited research has considered the sex effects of stress on mitochondrial function, and future experimentation should utilize both male and female animals. It is also important to note that while rodent paradigms allow precise control of experimental conditions, they serve as imperfect models for the early adversities experienced by humans, which encompass a diverse range of socially complex experiences. There have been few studies in humans, and conclusions are limited due to variability in study design, such as definitions of ELA, type of mitochondrial measure and tissue of origin, and presence of comorbidities in the sample. Though several studies have examined mtDNAcn in clinical populations, there is a need for further work directly measuring mitochondrial function, especially utilizing prospective and longitudinal study designs.

While current evidence is still very limited, the potential to reverse ELA-induced mitochondrial dysfunction is promising and worthy of further investigation. Early stress is an especially deserving target for research due to the potential to intervene therapeutically prior to the conclusion of brain development and emergence of clinical pathology. Further work in this field, especially with an emphasis on clinical translations, has the potential to minimize the life-long health burden in a large population of individuals with ELA.

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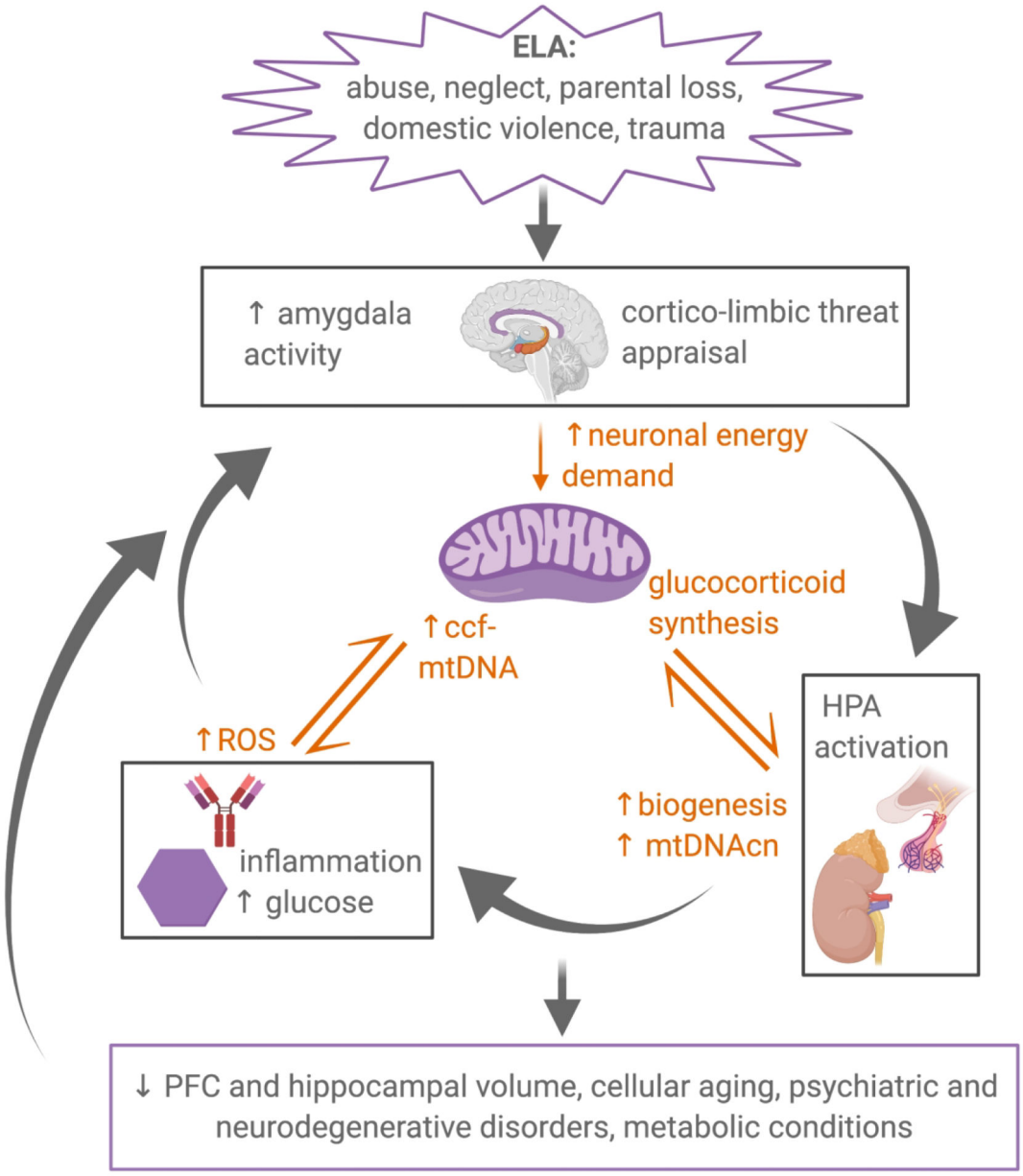

Figure 1.

Mitochondria occupy an intersecting role in stress responses. Early-life adversity (ELA) chronically activates physiological stress responses, coordinated by the cortico-limbic brain network, the HPA axis, the immune system and the metabolic system. Mitochondrial function and structure are altered by stress responses, which in turn exacerbates initial alterations in stress-related physiological systems. This feedforward cycle of dysfunction produces pathology across a variety of biological outcomes. ELA, early-life adversity; HPA, hypothalamic-pituitary-adrenal; mtDNA, mitochondrial DNA; mtDNAcn, mtDNA copy number; ccf-mtDNA, circulating cell-free mtDNA; PFC, prefrontal cortex.