OPINION

Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids

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Abstract | The link between chronic psychosocial and metabolic stress and the pathogenesis of disease has been extensively documented. Nevertheless, the cellular mechanisms by which stressful life experiences and their associated primary neuroendocrine mediators cause biological damage and increase disease risk remain poorly understood. The allostatic load model of chronic stress focuses on glucocorticoid dysregulation. In this Perspectives, we expand upon the metabolic aspects of this model—particularly glucose imbalance—and propose that mitochondrial dysfunction constitutes an early, modifiable target of chronic stress and stress-related health behaviours. Central to this process is mitochondrial regulation of energy metabolism and cellular signalling. Chronically elevated glucose levels damage both mitochondria and mitochondrial DNA, generating toxic products that can promote systemic inflammation, alter gene expression and hasten cell ageing. Consequently, the concept of 'mitochondrial allostatic load' defines the deleterious structural and functional changes that mitochondria undergo in response to elevated glucose levels and stress-related pathophysiology.

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Introduction

Chronically elevated circulating levels of glucose and lipids constitute metabolic stress, which increases susceptibility to cardiovascular disease, cancer, neurological disorders, and all-cause mortality.[1] In particular, conditions in which metabolic stress persists, such as diabetes mellitus, lead to oxidative stress, systemic inflammation and telomere shortening that ultimately reduce lifespan by 5–20 years.[2] Metabolic stress also impairs brain structures and cognitive function throughout life,[3,4] underlining its pervasive ability to harm the central nervous system and other organs. Thus, metabolic stress represents a primary pathway of multisystem biological damage that accelerates the cellular ageing process.

Metabolic stress could help explain how chronic psychosocial stress promotes cellular senescence and disease susceptibility. In response to threats—either real or perceived—secreted neuroendocrine factors, such as catecholamines and glucocorticoids, mobilize glucose and lipids into the circulation. Much research has focused on cortisol, the primary mammalian stress hormone belonging to the glucocorticoid family, originally named for their ability to influence glucose homeostasis.[5] Cortisol concentrations can increase up to 10-fold during acute stress responses and reach maximum levels within 20 min after exposure to psychosocial stressors.[6]

This adaptive mechanism is evolutionarily conserved to mobilize energy resources in the form of glucose to fuel 'fight or flight' responses. However, long-term energy mobilization can promote dysglycaemia and insulin resistance, a chronic state of 'metabolic oversupply' (Box 1) similar to diabetes mellitus. Interestingly, the accelerated telomere shortening observed in diabetes mellitus, in which the duration and severity of glucose intolerance are associated with progressively shortened telomeres,[7] is also a feature of individuals under chronic psychosocial stress.[8,9] This observation and other evidence presented below suggest that both psychosocial and metabolic stress could act via a common underlying subcellular mechanism in which the mitochondria are key players.[10] The goal of this Perspectives is, therefore, to integrate current knowledge on mitochondrial function and dynamics with advances in our understanding of glucocorticoid pathophysiology fostered by the 'allostatic load' model (Box 1). This discussion in turn leads us to the concept of mitochondrial allostatic load. By focusing on the 'gluc' (for glucose) in 'glucocorticoids,' which have mainly been studied in the context of stress-induced brain remodelling,[11] we examine the metabolic aspects of stress responses and discuss potential damaging primary effects on mitochondria, cellular dysfunction and senescence.

Competing interests
The authors declare no competing interests.

Stress, health and ageing

Stress constitutes a real or interpreted threat to an individual's physiological and psychological integrity that results in biological and behavioural responses.[12] The social environment and psychological states have broad effects on human health.[13,14] Chronic stress drives physiological dysregulation and hypercortisolaemia, and leads to functional and anatomical remodelling of the brain and impaired cognition.[15] Non-neurological effects of chronic stress predict the occurrence of cardiovascular disease,[16] as well as diabetes mellitus, obesity and the metabolic syndrome.[17] At the cellular level, chronic stress is linked to premature ageing, as shown by telomere shortening in blood cells.[18] Individuals under chronic stress,[8] facing repeated adversity early in life[19] or with low educational attainment[20] have shortened telomeres in their peripheral blood mononuclear cells. Individuals who secrete high levels of cortisol in response to psychosocial stress also have shortened telomeres,[21] suggesting a mechanistic link between the glucocorticoid stress response and cellular ageing, possibly via glucose imbalance and mitochondrial allostatic load. Importantly, non-strenuous exercise and a healthy lifestyle, which enhance mitochondrial content and function, among other effects, could help to buffer the physiological effects of chronic stress and maintain telomere length.[22]

Allostatic load

Many physiological functions are maintained within a strict homeostatic range. Beyond this stability of the internal environment, organisms must also recalibrate basal

Box 1 | Glossary of terms

- **Allostasis.** The process whereby an organism maintains physiological stability (homeostasis) through changing parameters of its internal milieu by matching them appropriately to environmental demands.[23]
- **Allostatic load.** The biological 'wear and tear' that allostatic mechanisms exert on organs and tissues under chronic stress that cumulatively predisposes to the development of disease.[26]
- **Allostatic overload.** An extreme form of allostatic load in which dysregulation of allostatic responses, coupled with health-damaging behaviours (poor sleep, increased caloric intake, lack of exercise, smoking and drinking alcohol), often in response to chronic stressors, lead to disease. Both allostatic load and allostatic overload occur in nature.[119]
- **Glucose allostasis.** The toxic effect of chronically elevated blood glucose levels on cells and tissues as a result of insulin resistance.[24]
- **Metabolic oversupply.** The overabundance of energetic substrates (glucose or lipids) relative to cellular energy demand, which generates metabolic stress and generally results in weight gain and mitochondrial stress and/or damage.[64]

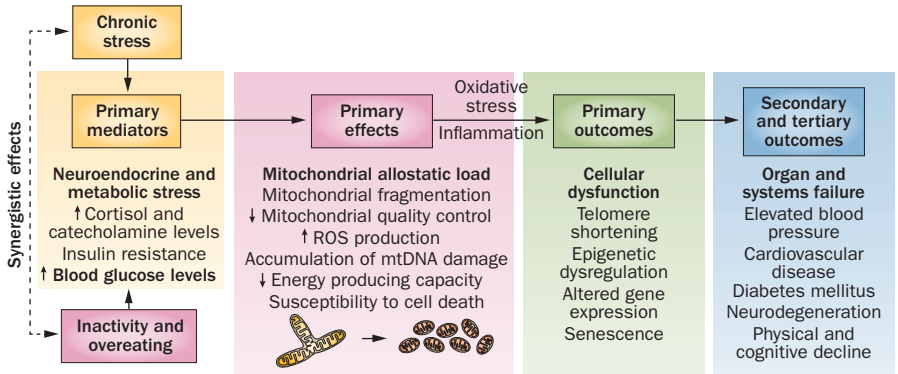

Figure 1 | The stress–disease cascade and mitochondrial allostatic load. Allostatic load is a pathophysiological process in which multisystem biological dysregulation caused by chronic stress synergizes with unhealthy behaviours. Chronic stress perturbs adaptive glucocorticoid signalling and glucose levels (primary mediators) that in turn alter mitochondrial structure and function (primary effects), generating oxidative stress and cellular damage (primary outcomes). This process cumulatively worsens risk factors (secondary outcomes), which consequently leads to disease (tertiary outcomes). In this multilevel cascade, mitochondrial dysfunction is depicted as an early event mediating the relationship between primary mediators of chronic stress and disease trajectories. Abbreviations: mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

functioning to adapt to environmental demands. This process is referred to as 'allostasis'—or biological stability through change (Box 1).[23] For example, rises in postprandial blood glucose levels are usually matched by transient increases in insulin secretion to restore glucose homeostasis. In the context of chronic hyperglycaemia, such as is seen among patients with diabetes mellitus, excess insulin secretion is associated with peripheral insulin resistance, which marks the transition from maintaining glucose homeostasis to the development of deleterious glucose allostasis (Box 1).[24] Similarly, chronic activation of otherwise adaptive neuroendocrine and immune mediators can lead to physiological dysregulation as multiple interconnected systems become recalibrated.[25] Allostatic load (Box 1) refers to the cumulative damage to the body that results from generating allostatic responses under conditions of chronic stress. This situation is further aggravated when an individual engages in maladaptive health-related behaviours.[26]

The allostatic load model proposes a specific three-stage temporal and causal sequence of biological damage linked to health outcomes.[12] First, overactivation or underactivation of primary mediators, such as glucocorticoids, induces direct effects and outcomes on cellular processes. Next, secondary outcomes (metabolic, cardiovascular, neural and second-order immune biomarkers) become dysregulated as indicated by their abnormal patterns, including lack of adaptation, prolonged response or blunted response.[25] Finally, this process culminates in tertiary outcomes or clinical end points (Figure 1).[27]

The allostatic load model postulates that by measuring multisystem biomarkers, individuals at a high risk of severe disease outcomes or 'allostatic overload' (Box 1) can be identified.[28] A substantial body of empirical evidence demonstrates that allostatic load algorithms incorporating multiple primary mediators (for example, levels of cortisol or cytokines) and secondary outcomes (for example, levels of HbA_{1c}, insulin or blood pressure) are predictive of cumulative biological damage, clinical risk and age-related pathology.[28,29] However, the primary effects, or the mechanisms that link primary mediators to secondary and tertiary outcomes, have remained unclear (Figure 1).

Glucocorticoids and glucose

Glucocorticoids trigger physiological processes that ultimately increase circulating levels of glucose and lipids. This response in turn promotes the development of hypertension, central obesity and glucose intolerance, collectively recapitulating the key features of the metabolic syndrome.[30] Glucocorticoids drive these effects by acting to increase hepatic glucose production and decrease peripheral glucose uptake by skeletal muscles.[31] Experimental elevation of cortisol levels increases postprandial blood glucose and lipid levels in healthy individuals,[31] similar to the situation in type 2 diabetes mellitus.[32] In cross-sectional samples, individuals with high cortisol levels exhibit elevated glucose and triglyceride levels, along with decreased insulin sensitivity.[33] Likewise, chronic glucocorticoid administration in rodents leads to hyperglycaemia and insulin resistance,[34] whereas adrenalectomy sensitizes the rodent brain to insulin action.[35] Thus, glucocorticoids play a pivotal role in the regulation of systemic glucose metabolism, by promoting postprandial hyperglycaemic excursions and chronic metabolic oversupply.

Studies that have evaluated responses to psychosocial stress (stress reactivity) in humans also demonstrate the natural metabolic effects of glucocorticoids. For example, in 1929, stress physiologist Walter Cannon found that college rowers anticipatorily experienced elevated blood glucose concentrations the night before a competition.[36] Since then, studies of psychological stress reactivity have demonstrated that acute perceived stress alters glucose control and leads to postprandial hyperglycaemia.[37,38] High glucose intake might also increase the amount of cortisol that is released in response to controlled psychosocial stressors,[39] producing a vicious cycle whereby stress and metabolic oversupply enhance each other's effects. Interestingly, psychological therapy aimed at reducing

psychosomatic distress among individuals with type 2 diabetes mellitus improves long-term glycaemic control,[40] an observation that supports links between psychological states, glucocorticoids and glucose regulation.

Additional biological effects of glucocorticoids contribute to metabolic stress. In rodents and humans, catecholamines and glucocorticoids can directly inhibit insulin release by pancreatic β cells.[41] Impaired insulin secretion, as occurs in type 1 diabetes mellitus, further prevents the removal of circulating glucose and promotes glucose toxicity. Likewise, sleep disturbances[42] and disruption of diurnal patterns[43] alter cortisol levels, which then cause insulin resistance and impair glucose regulation. Chronic activation of glucocorticoid-induced energy-mobilizing processes in the allostatic load cascade might, therefore, potentiate metabolic stress that in turn exerts deleterious effects on susceptible cellular elements. Of paramount importance in this regard are alterations in the structure and function of the mitochondria.

Mitochondrial allostatic load

Mitochondria and mitochondrial DNA

Mammalian cells each contain within their cytoplasm hundreds to thousands of mitochondria. This organelle is best known for conducting oxidative phosphorylation, which comprises a series of biochemical reactions that occur within the mitochondria whereby breathed oxygen and ingested calories are combined to synthesize ATP.[44] This conversion ultimately provides energy for most cellular processes within the body. Other critical mitochondrial functions include uptake of Ca^{2+}, biosynthesis of lipids and nucleic acids, and production of reactive oxygen species (ROS). Owing to their involvement in several critical aspects of cell function, mitochondria are key participants in intracellular signalling and influence cell function in several interrelated ways.[45]

Consistent with an evolutionary origin as bacteria, mitochondria contain their own genome, a circular molecule referred to as mitochondrial DNA (mtDNA) that is inherited from the mother.[44] Although it does not contain telomeres, mtDNA is organized into analogous DNA–protein complexes called nucleoids, and encodes two ribosomal RNAs and 22 transfer RNAs that are essential for the translation of its 13 protein-coding genes.[46] Although mitochondria contain approximately 1,500 unique proteins, mostly derived from the nuclear genome, those encoded by the mtDNA are all essential

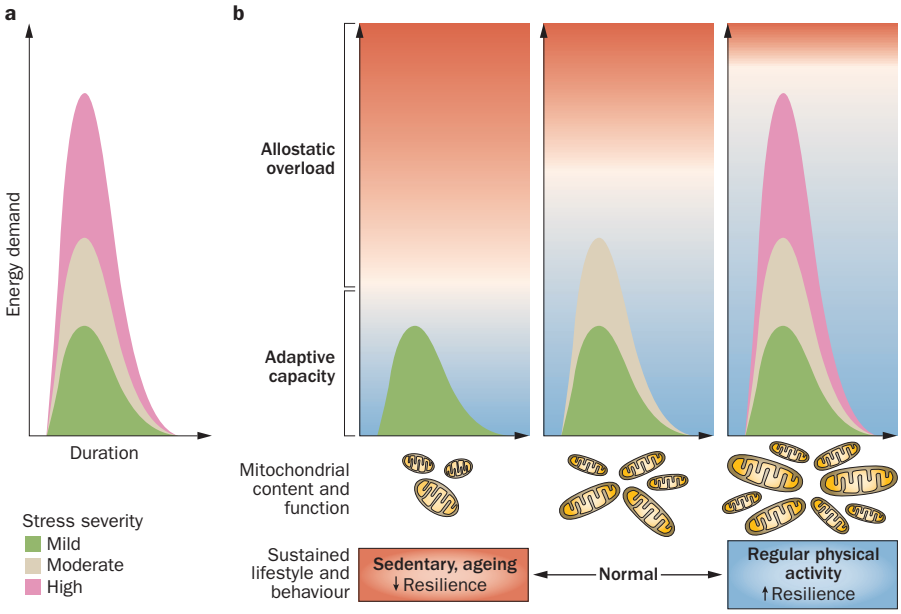

Figure 2 | Hypothetical model demonstrating how sustained lifestyle and behaviour modulate adaptive capacity. **a** | Relationship between stress severity and energy demand. Stressors of mild, moderate and high intensity incur increasing energy demands for successful adaptation, determined by their duration and intensity. **b** | Relationship between lifestyle, mitochondria and adaptive capacity. Lifestyle and behavioural factors that decrease mitochondrial content and function reduce cellular energy capacity and the adaptive range. This process expands the window for allostatic overload to occur in response to stresses of moderate and high severity. Conversely, factors promoting mitochondrial proliferation result in increased dynamic range of adaptive capacity and minimize windows of susceptibility for allostatic overload.

subunits of the electron transport chain involved in oxidative phosphorylation; mutations in the mtDNA genes cause severe and often lethal multisystem diseases.[47] Non-pathological evolutionarily conserved groups of single-nucleotide polymorphisms in mtDNA (termed haplogroups) that vary with geographic origin and ethnicity, might also influence mitochondrial bioenergetics and have been linked to susceptibility to age-related diseases, including neurodegenerative diseases, psychopathological disorders, cancer and diabetes mellitus.[46,48]

Mitochondria in health and disease

As mtDNA encodes a small number of genes essential for mitochondrial energy production, damage to mtDNA impairs mitochondrial function and results in signs consistent with accelerated ageing.[49,50] Oxidative damage and defects (for instance, mutations or deletions) in mtDNA accumulate with age in numerous tissues.[51,52] Similar to shortening of telomeres, cumulative damage to mitochondria could act as a cellular 'ageing clock' by eroding bioenergetic capacity.[53] Individuals with inherited mutations of mtDNA develop progressive multisystem degenerative diseases that affect the same organ systems as those involved in ageing, with the brain being particularly vulnerable.[47,50] Mitochondria are, therefore, likely to play an important part in age-related accumulation of metabolic damage and associated decline in physiological function.

Mitochondria are also key components of the stress response owing to their role in energy production and the capacity to generate signals that promote cellular adaptation.[54] Individuals with genetic defects in mitochondrial function seem to have exaggerated allostatic responses to mild aerobic exercise.[55,56] In theory, mitochondrial energy production determines the limits of an organism's adaptive capacity.[57] Whereas reduced mitochondrial content and impaired mitochondrial function limit adaptive capacity, upregulation of both of these parameters is related to increased adaptability and biological resilience (Figure 2).

Mitochondria also influence cell function and adaptation through dynamic changes in their morphology via fusion and fission.[58] Mitochondrial fusion results in elongated and interconnected structures, whereas fission results in fragmented and isolated mitochondria. Such mitochondrial 'shape-shifting' is linked to changes within both the mitochondria and the cell cytoplasm that affect cell function, particularly in the

context of adaptation to metabolic perturbations.[59,60] For example, mitochondria respond acutely to cellular stress signals by undergoing networked fusion to promote survival. By contrast, long-term and/or severe stress leads to widespread mitochondrial fragmentation and dismantlement of the mitochondrial network, which sensitizes cells to death via apoptosis.[61]

From a functional standpoint, excessive and long-term mitochondrial fragmentation is associated with accumulation of mtDNA damage and increased oxidative stress.[62,63] Within the context of diabetes mellitus and other sources of chronic metabolic oversupply, the adverse health effects of metabolic stress might be mediated by chronic perturbations in mitochondrial dynamics and consequent accumulation of mtDNA damage.[64] Mitochondria can thus be regarded as a cellular 'portal' on the metabolic environment. As organisms must adapt to environmental fluctuations in energy demands to sustain normal function, it is unsurprising that mitochondria exhibit sensitivity to hormones and metabolic perturbations arising under conditions of stress.

Primary stress mediators

Mitochondria participate in the stress response in part by sensing levels of glucocorticoids.[54] Receptors for glucocorticoids and other stress hormones naturally exist within mitochondria, or translocate from the cytoplasm into the mitochondria in the presence of their ligand,[65] endowing these organelles with the ability to sense and readily respond during acute stress. Although the effects of glucocorticoids on mitochondrial function are not yet fully defined, molecular actions of these hormones seem to increase acute binding of the glucocorticoid receptor to mtDNA, enhancing mitochondrial gene expression.[66] Increased mtDNA gene expression augments the energy production capacity of individual mitochondria. Glucocorticoids also increase the expression of key autosomal genes (in the cell nucleus) that are required to produce new mitochondria.[66] This process of mitochondrial biogenesis increases the total number of mitochondria per cell, and thus total cellular energy capacity. However, as expected from an evolutionarily conserved physiological response, in which an anticipated rise in energy demand is required for successful adaptation (for example, fighting or running away from a real threat), acute cell stimulation with glucocorticoids increases the capacity of mitochondria to generate energy.

Conversely, sustained actions of glucocorticoids on mitochondria can have maladaptive effects.[67] For example, glucocorticoids modulate mitochondrial function and apoptotic sensitivity in nerve cells in a biphasic (inverted U-shaped) manner.[68] Consistent with the allostatic load model, administration of physiological doses of glucocorticoids acutely increases mitochondrial membrane potential, Ca^{2+}-buffering capacity and resistance to apoptotic signalling (the 'up' phase of the inverted U); whereas chronic exposure to high doses depresses mitochondrial membrane potential and sensitizes cells to apoptosis (the 'down' phase of the inverted U).[68] Cell exposure to high-dose glucocorticoids also increases the production of ROS, leading to oxidative stress and molecular damage, which are associated with depressed mitochondrial respiratory chain activity.[69] Similarly, in mouse and rat models, exposure to chronic stress leads to mitochondrial damage and dysfunction in different regions of the brain, including the hippocampus, cortex and thalamus.[70–72] Chronic administration of corticosterone also contributes to dampen mitochondrial function in the context of partial dysfunction.[73] Other experimental evidence indicates that glucocorticoids can directly cause mitochondrial fragmentation in hepatocytes by inducing proteins that promote mitochondrial fission.[74] Direct modulation of mitochondrial structure and function by primary mediators may, therefore, contribute to both short-term adaptation and long-term damage associated with chronic stress.

Mitochondrial dysfunction can also arise from the hyperglycaemic effect of glucocorticoids. In the presence of high concentrations of glucose, mitochondria undergo excessive fragmentation, causing increased production of ROS,[63] which compromise the integrity of mtDNA[75] and lead to the accumulation of mtDNA damage.[76,77] Furthermore, mitochondrial fragmentation activates proapoptotic pathways that sensitize cells to undergo programmed cell death,[78] whereas mitochondrial fusion can promote cell survival.[79] Indeed hyperglycaemia-induced mitochondrial and cellular oxidative stress are prevented by genetically (with RNA interference or mutagenesis) or pharmacologically blocking mitochondrial fragmentation (reviewed elsewhere[59]). This finding indicates that fragmentation of the mitochondrial network is an early event in the mitochondrial response to chronic metabolic stress that could potentially be exploited as a target for preventative interventions.

Collectively, these data demonstrate that mitochondria readily sense both glucocorticoids and glucose as primary stress mediators. In response, mitochondria undergo dynamic morphological and functional changes associated with deleterious effects on cell function and senescence.

Cell function and senescence

Mitochondrial dysfunction can directly cause many of the adverse cellular outcomes related to chronic stress, including oxidative stress, inflammation, telomere shortening, epigenetic dysregulation, altered gene expression and cell senescence (Figure 3).

Mitochondria are the principal cellular source of ROS, including superoxide anions, hydroxyl radicals and hydrogen peroxide.[80] Oxidative stress and oxidative damage to biomolecules (proteins, DNA and RNA) occurs when mitochondrial production of ROS exceeds the antioxidant capacity of a cell. The mtDNA is more vulnerable to oxidative damage than is the nuclear DNA.[81] For instance, oxidative damage to mtDNA leads to the production of 8-hydroxy-2'-deoxyguanosine and 8-oxoguanine, and to deletions of mtDNA,[82] which also accumulate in tissues with ageing.[51,83] Oxidative DNA damage is increased among patients with diabetes mellitus[84] and individuals experiencing chronic psychosocial stress.[85] Consequently, it seems plausible that increased mitochondrial ROS production during chronic stress might contribute to oxidative stress, leading to neurodegeneration, telomere shortening and other ageing effects.[86]

Collectively, mtDNA damage, mitochondria-derived ROS and oxidative stress lead to telomere shortening[87] and cell senescence.[88] Evidence suggests that primary mtDNA defects that impair mitochondrial energy production capacity cause telomere shortening,[89] and that mitochondrial function and telomere maintenance are mechanistically linked.[90] Acquired mitochondrial dysfunction might promote telomere shortening, which in turn contributes to loss of mtDNA and mitochondrial function by inhibiting mitochondrial biogenesis.[90] As a result, the number of mtDNA molecules per cell (mtDNA copy number) is emerging as a potential biomarker of mitochondrial dysfunction.[91] Together, these processes involve a vicious cycle that impairs cellular bioenergetics and promotes senescence.

Mitochondria also induce programmed cell death.[92] Furthermore, mitochondrial signals regulate the cell cycle,[93] and disruption of mitochondrial fusion–fission dynamics can cause replicative senescence,[94] revealing the existence of multiple interrelated pathways linking mitochondrial dysfunction to cell ageing.

Stressed mitochondria also induce inflammatory processes. Oxidized mtDNA, alarmins (molecules, usually of bacterial origin, that are sensed by the cell as 'foreign') and other damage-associated factors released from impaired mitochondria act as proinflammatory molecules that engage immune and inflammatory processes.[95] Oxidized mtDNA activates canonical pro-inflammatory pathways (for example, the inflammasome) both intracellularly[96] and systemically.[97,98] Free circulating mtDNA induces inflammation that can trigger heart failure in mice,[99] and represents a putative cause of neurodegenerative disorders, such as Alzheimer disease, in humans.[100] Mitochondrial stress and the resultant oxidative stress can, therefore, lead to systemic inflammation via a direct mechanism involving the release of proinflammatory molecules that activate gene expression characteristic of inflammation.

A central determinant of cell structure and function lies in the control of gene expression.[101] Regulation of gene expression occurs by two major processes. The first involves intracellular signals that exert direct effects on the ability of transcription factors to bind DNA. The second mechanism is indirect and involves epigenetic changes (for example, post-translational histone modification, DNA methylation and chromatin remodelling) that regulate specific genes and gene expression programmes.

Under stressful conditions, changes in gene expression and in the epigenome occur in the brain[102] that can be reversed by molecules that influence mitochondrial energy metabolism.[103] Several broad-acting intracellular signal transduction pathways and transcription factors—such as AMPK, p53 and NF-κB—as well as epigenetic silencing complexes, respond to the cellular energy state and to mitochondrial signals, including mitochondria-derived ROS.[104–107] These changes provide a mechanistic basis for rapid and stable regulation of gene expression by mitochondria.

Furthermore, molecules naturally produced and released by mitochondria include all of the major substrates for epigenetic modifications (acetyl coenzyme A for acetylation; ATP for phosphorylation; and α-ketoglutarate and S-adenosylmethionine for demethylation and methylation),[108] highlighting an evolutionary conservation of mechanisms linking bioenergetics to epigenetic control of gene expression. Indeed, genetic defects of mtDNA that affect mitochondrial function cause broad changes in the transcriptome (the sum of all expressed gene products).[109] Likewise, chronic psychosocial stressors can have broad effects on the transcriptome of peripheral blood cells,[110,111] possibly involving transcriptional events that might be regulated by mitochondrial signals.

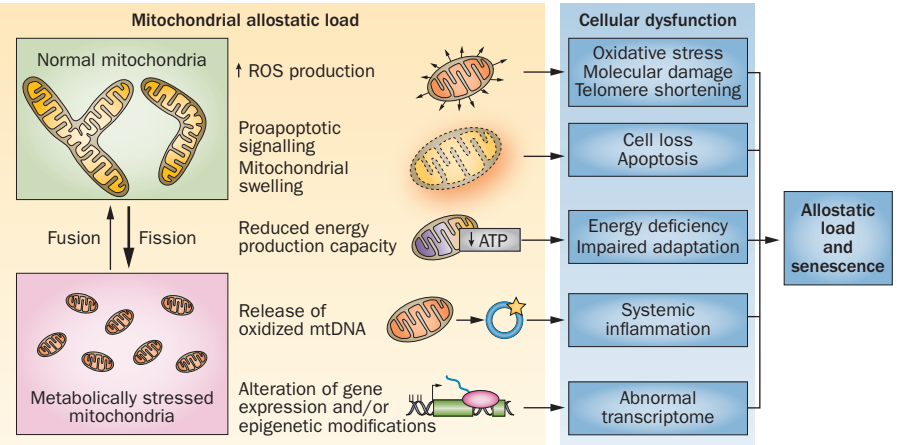

Figure 3 | Mitochondrial allostatic load and downstream biological effects. Mitochondrial morphology is dynamically regulated in response to stress, and mitochondrial fragmentation precedes increased release of ROS and proapoptotic signalling. Accumulation of mitochondrial damage, long-term fragmentation and mtDNA damage erode energy production capacity. Oxidized mtDNA and other immunogenic molecules can also be released from damaged mitochondria promoting inflammation. Finally, mitochondrial signals might modulate gene expression through specific transcription factors and epigenetic mechanisms. Collectively these alterations of mitochondrial structure and function in response to chronic stress constitute mitochondrial allostatic load, which ultimately precipitates the cellular ageing process. Abbreviations: mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

Box 2 | Unresolved questions

Three major concepts are outlined in the mitochondrial allostatic load model:

- Chronic stress responses mediated by neuroendocrine and immune-system mediators produce metabolic effects including elevated glucose mobilization and insulin resistance that are further exacerbated by sedentary and unhealthy lifestyle behaviours
- These metabolic effects lead to metabolic stress, which is damaging to mitochondria in various tissues of the body, causing mitochondrial allostatic load
- Accumulation of mitochondrial damage erodes the cell's bioenergetic capacity and activates pathophysiological mechanisms (for example, oxidative stress or inflammation), which can lead to cellular dysfunction and senescence culminating in allostatic load and overload

Several questions remain to further test the model, including:

- Do neuroendocrine stress mediators (glucocorticoids, catecholamines and cytokines) directly affect mitochondrial dynamics and the integrity of mitochondrial DNA (mtDNA)? What are the effects of these mediators on mtDNA gene expression?
- Are chronic stress-induced changes in gene expression secondary causes of mitochondrial dysfunction, and can resilience be increased by therapies that target the mitochondria?
- Are proinflammatory oxidized mtDNA or other mitochondrial alarmins released into the circulation during stress?
- Does chronic psychosocial and metabolic stress synergistically interact at the level of the mitochondria, augmenting each other when combined (for example, stress exacerbating the effect of poor diet) and cancelling each other when opposed (for example, exercise nullifying the deleterious effects of chronic psychosocial stress)?
- To what extent do acquired age-related mtDNA damage and copy number changes influence telomere maintenance and cellular senescence in humans?

Conclusions

The physiological response to psychosocial stress entails substantial metabolic perturbations and recalibrations linked through the direct biological action and hyperglycaemic effects of glucocorticoids.

These hormones promote metabolic stress through multisystem actions affecting glucose production, peripheral insulin resistance and appetite control.[30] Both metabolic and psychosocial stressors can occur concurrently and so might have synergistic effects,[112] resulting in downstream cellular dysfunction via various mechanisms including telomere shortening and accelerated cellular senescence.[113]

Perhaps as a result of their central role in the evolution of biological complexity, mitochondria contain the molecular machinery and exhibit functional sensitivity to primary stress mediators and glucose levels, enabling tight matching of bioenergetics with the stress response. As an extension of the allostatic load model, chronic activation of allostatic mechanisms at the level of mitochondria (excessive mitochondrial fragmentation; ROS production leading to mtDNA damage and respiratory deficiency; and the release of proinflammatory molecules) constitutes mitochondrial allostatic load. Impaired mitochondrial quality control arising from deficient removal of damaged mitochondria via autophagy during metabolic oversupply might further contribute to mitochondrial allostatic load.[60] Importantly, these structural and functional features of mitochondrial allostatic load cause known downstream primary, secondary and tertiary health outcomes contributing to poor ageing trajectories (Figure 3).

If the mitochondrial allostatic load hypothesis were further supported, interventions targeting mitochondria—pharmacological,[114] behavioural or other—could be effective at preventing the cellular 'wear-and-tear' of chronic stress and allostatic load. Of note, it is encouraging to find that physical activity and exercise, which stimulate mitochondrial biogenesis, function and interactions,[115] confer protection against metabolic stress in diabetes mellitus,[116] against telomere shortening associated with psychosocial stress,[22] and might even reverse age-related atrophy in glucocorticoid-sensitive regions of the brain, such as the hippocampus.[117] Similarly, mitochondria-targeted antioxidants prevent neurodegeneration in animal models.[118] Promoting biological resilience by targeting mitochondrial function and endogenous antioxidant defences, yet without altering their adaptive functions, represents an attractive possibility to counteract the damaging effects of chronic stress. Elements of the mitochondrial allostatic load model that require further investigation are outlined in Box 2.

In conclusion, defining cellular mechanisms underpinning the detrimental effects of chronic stress on health will help to establish the basis of mind–body interactions, expand the biomedical model, and hopefully lead to the design of higher-level health-promoting interventions that are based on the principles of allostasis and bioenergetics.

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Author contributions

M.P. researched the data for the article. All authors provided a substantial contribution to discussions of the content, contributed to writing the article and reviewed and/or edited the manuscript before submission.