Chronic metabolic stress, central nervous system gene expression and innovator traits: What might we do to manage them?

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ABSTRACT

Modern global markets have made for shorter product cycles. In turn, the importance of innovation to advanced economies has risen and psychological traits associated with innovation and entrepreneurship (as measured, for example, on some subscales of the eSAIL inventory, such as agency and abstract construal) have become recognized as a critically important national resource. Recent work has shown an inverse correlation between chronic stress and scores achieved on such scales. In light of the epidemic levels of metabolic stress observed in advanced economies, this review focuses on pathways and gene products of importance to mitochondrial homeostasis, known to connect metabolic stress with impaired cerebral function, with possible implications for agency and abstraction. Knowledge of these pathways identifies possible interventions, and some of these are also discussed.

Keywords: chronic metabolic stress, innovation, nephrilin, mitochondria, abstraction, agency.

1. Background

1.1. Metabolic stress

An important form of chronic stress experienced in modern industrialized societies is metabolic stress. According to the Center for Disease Control, obesity in the adult population of the United States is increasing at the rate of half a percentage point per year. Not surprisingly, the slope of increase in per capita US prescriptions for anti-hyperlipidemic drugs to adults 45-64 years of age between 1988 and 2012 is almost identical to the rate of increase in obesity, and about ten times the rate of increase of prescriptions for a control group of drugs (bronchodilators, sedatives, analgesics) over the same period of time [1]. Interestingly, the rate of increase for prescriptions associated with metabolic disease and its complications (depression 5.4X, diabetes 2.3X,
hypertension 2.5X, renal failure 2.4X and epilepsy 1.8X; p<0.05 for group) was also increased significantly for this demographic over the same period of study. Depression, dementia and epilepsy have, in fact, been linked to metabolic disease in population studies [2, 3]. It is therefore reasonable to pose the question: does elevated metabolic stress lead to impaired cerebral function in those economies that most need innovation for their continued prosperity?

1.2. Stress and psychometric scales

Three psychometric sub-scales of the eSAIL inventory [4] — agency, independent thinking and abstract construal — were found to correlate with innovation scores in an adult female cohort [5]. In addition, male CEOs scored significantly higher than the population average in independent thinking and restrictive subscales of the eSAIL [6]. In another study, a female cohort that reported elevated stress over the span of a decade was found to score significantly lower on all four of these eSAIL subscales when compared to a control cohort reporting low stress over the same span [7]. Some of these findings are summarized in Figure 1. Remarkably, the geographical distribution of innovation industries in the United States also appears to correlate with higher mean population scores in abstract construal, agency and independent thinking [6].

![Figure 1](image-url)

**Figure 1.** Mean scores for cohorts relative to the population average. Subscales of the eSAIL are shown along the x-axis. See text. (a) white bars = low chronic stress, black bars = high chronic stress; female cohort data adapted from reference 7; (b) white bars = high innovation tertile, gray bars = low innovation tertile; female cohort data adapted from reference 5; (c) white bars = male CEOs, gray bars = control males; * p<0.05, ** p<0.01 for each pairwise comparison.

Although these findings are correlational, the possible connection between chronic stress and traits of critical importance to the economic productivity of modern societies should make us ask questions about how we might successfully intervene in the process if such a link does indeed exist [8]. There is, at any rate, enough circumstantial evidence to raise the alarm. We need a better understanding of the biological connections between chronic metabolic stress and key mental faculties critical to modern economic prosperity.
2. Genes, Pathways and Interventions.

2.1. Mitochondrial dysfunction

One way to frame the question scientifically is to ask which gene products in the central nervous system (CNS) are most affected by chronic stress, how they modulate cerebral circuits that impact agency, independent thinking and abstraction, and how we might influence pathways they control by using appropriate interventions.

In one study cited above [7], scoring on the agency scale was negatively correlated with scores in a scale for clinical apathy, which increased significantly in the high-chronic stress group. Given the close linkage between apathy and depression, and the linkage between chronic metabolic stress and depression [9] it seems reasonable to investigate a possibly connection to agency. Abstract construal (and affective theory of mind, another casualty of chronic stress; [7]) have previously been linked to anorexia nervosa [10], a stress condition characterized by impaired mitochondrial function [11]. This is an intriguing observation because, in a broad sense, most complications of metabolic stress — such as diabetic, cardiorenal and neurological, for example — can be traced to this type of central dysfunction, a loss of mitochondrial homeostasis. Such foundational dysfunction may even be said to underlie most of the morbidity and mortality associated with chronic metabolic stresses of aging, as well as in the aging process itself. Key manifestations of mitochondrial dysfunction include:

- **loss of ATP-generating capacity** leading to organ hypoperfusion and lowered glucose consumption, disproportionately affecting organs such as kidney, heart and brain, which are rich in mitochondria, leading to cognitive dysfunction [12]; within the brain, mitochondria-rich parvalbumin interneurons, essential for the coordination of neuronal synchrony during sensory and cognitive processing, are particularly affected [13];

- **elevated oxidative stress** damages parvalbumin interneurons [14]; and other neurons, in general, depend on the protective effects of astrocytes to combat this devastating insult;

- **elevated insulin resistance** and **chronic inflammation** (which appear to be linked to oxidative stress) are implicated in metabolic diseases, aging and dementia [15, 16].

2.2. Gene functions and possible interventions

Some of the genes known to be involved in the above phenomena offer points for possible interventions. These are illustrated by solid arrows in Figure 2. Statistical surveys of genetic markers significantly associated with depression or dementia that simultaneously perturb the biochemical pathways shown can provide clues to hypothesis-building. One experimental approach can be to study changes in CNS gene expression after a variety of stress insults (such as diabetes) in rodent models, and then explore the normalization of those functions with targeted interventions.
Figure 2. Genes associated with mitochondrial dysfunction. Genes are grouped by functional area (see text). Interventions currently under investigation are shown with fat arrows.

Mitochondrial biomass and quality are governed by a number of master gene products such as PGC-1a, the sirtuins and TFAM (biogenesis; [17-19]), PINK1 (mitophagy; [20]), BOK, FIS1 and MFN2 (mitochondrial fission and fusion; [21, 22]). Key regulators such as MTCH2, UCP2, HIF1a and P66SHC influence oxidative synthesis and lipid metabolism [23-26], while NRF2, OXR1, STEAP4, ALDH2 and SESN3 can act as protective factors against oxidative stress [27-30]. Generally speaking, any intervention that modulates the mitochondrial impact of the above genes in a positive direction is worthy of investigation.

A major control point for oxidative metabolism is a cascade of post-translation phosphorylation events that begins with Rictor complex, a sensor of cellular stress and activator of AGC kinases such as Akt and protein kinase C (PKC) isoforms [31]. Nephritin peptide, a designed inhibitor of Rictor complex that controls excess activation of PKC isoforms alpha, beta and delta, has been successfully used to inhibit the effects of stress in a variety of rodent models [32-34], and appears to control downstream effectors RAC1, P66SHC and NADPH oxidases via epigenetically modulated transcriptional and post-transcriptional mechanisms [35]. NADPH oxidases (NOX) play a central role in systemic oxidative stress. Of the five known NOX isoforms, NOX1, NOX2 and NOX3 are controlled by activated RAC1 [36]. NOX2, in particular, may be of particular interest in the CNS, because it appears to be a major isoform in astrocytes which are known to play an essential role in the brain’s response to oxidative stress [37]. NOX4, another important
isoform associated with oxidative stress [38], is not controlled by RAC1 and may therefore be part of a stress-sensitive regulon that is not responsive to inhibitors such as nephrilin peptide. A small-molecule inhibitor of NOX4 is under investigation [39].

A more global approach to reduced mitochondrial function is to increase overall mitochondrial capacity by nutritional supplementation with nicotinamide riboside (NR). In recent work in a variety of rodent models of metabolic and neurological disease, NAD+ levels were successfully manipulated by NR supplementation, with beneficial outcomes [40, 41].

In recent years, much excitement has surrounded the “immunological theory” of depression, in which inflammation up-regulates the kynurenine pathway (KP), the major tryptophan-degrading pathway in the CNS [42]. Major gatekeepers to this pathway, such as IDO1 and TDO2, are genes whose products are being targeted by several small-molecule interventions already in clinical trials [43]. A particularly interesting aspect of the KP degradation cascade is the generation of quinolinic acid, a precursor to NAD that also happens to be a neurotoxic glutamate receptor agonist. The branchpoint enzyme encoded by ACMSD can divert the synthesis of quinolinic acid to picolinic acid, a neuroprotective molecule [44], and is thus a gene of interest for controlling the effects of a dysregulated KP. Quinolinic acid can generate elevated glutamatergic activity in the hippocampus and consequent upregulation of classical astrocyte markers such as GFAP and GLUL (which specifies an ammonia-degrading enzyme, important for scavenging metabolites generated by dysregulated glutamate signaling).

3. Conclusion

The intriguing connection between dysregulated mitochondrial function and abstraction in anorexia as well as apathy (an inverse readout of agency) in depressive disorders suggests a possible link between chronic metabolic stress and psychometric traits associated with innovation and entrepreneurship. By unpacking the pathways and gene products that play central roles in mitochondrial homeostasis we can identify points for possible intervention. Interestingly, some of the pathways are also dysregulated in cancer, especially in metastasis. Indeed, some of the interventions listed above were, in fact, initially developed for use in cancer. Regardless of purpose, as such new drugs receive regulatory approval and become available for use in human populations, we stand to learn much about how they may also affect cerebral function.

4. References


