Energetic and Mitochondrial Drivers of Stress responses
BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS
PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

RESILIENCE
**ENERGY STORED AS CHEMISTRY**

Oils and fats, proteins, carbohydrates

\[ \text{CO}_2 + \text{H}_2\text{O} = \text{C}_{17}\text{H}_{33}\text{COOH} + \text{O}_2 \]

**EATING and BREATHING**

Food

\[ \text{CO}_2 \quad \text{H}_2\text{O} \]

‘Waste’ products

**ENERGY STORED AS CHEMISTRY**

**BIOLOGY, PHYSIOLOGY, COGNITION, CONSCIOUSNESS**

PSYCHOBIOLOGICAL ALLOSTATIC PROCESSES

**RESILIENCE**

Biochemistry 2022
How much energy do stress responses cost?
Life-sustaining processes driving homeostatic regulation

Acute response patterns and predictive recalibrations within the range of adaptive capabilities

Chronic, energetically-demanding recalibrations towards new regulatory set-points

Breakdown of physiological network leading to symptoms, accelerated aging, disease, and death

ACUTE STRESS

CHRONIC STRESS

ALLOSTATIC RESPONSES

ALLOSTATIC STATES

Disrupted communication (e.g., blunted hormonal response)

System dysfunction (e.g., high HbA1c)

System breakdown (e.g., heart failure)

Hyperactive system (e.g., inflammation)

Hypoactive system (e.g., ANS, low HRV)

Energy expenditure

Organismal network

Bobba-Alves, Juster, Picard. Psychoneuroendocrinol 2022
Cellular allostatic load is linked to increased energy expenditure and accelerated biological aging.

Glucocorticoid signaling increases energy expenditure by 60% and accelerates cellular aging by 10-40%.

Bobba-Alves et al. PNEC 2023
How much energy do stress responses cost?
How do energetics and mitochondria influence physiological responses?
Animal models of impaired mitochondrial OxPhos and redox

Picard et al. PNAS 2015
Mitochondrial functions influence stress-induced HPA axis activity

**mtDNA**

- **Stress**
- **Recovery**

- **WT**
- **ND6**
- **COI**

**Corticosterone (ng/dL)**

- **Time (min)**
  - 0
  - 30
  - 60
  - 90
  - 120

**Glucose levels during stress and recovery**

- **WT**
- **ND6**
- **COI**
- **nDNA**

**Plasma concentration of alanine in unstressed and after 60 min stress**

- **Ratio CORT/ACTH**
  - 60 minutes (n = 7-10, one-way ANOVA P = 0.054 (mtDNA) and < 0.001 (nDNA), Holm-Sidak's multiple comparisons).

**Picard et al. PNAS 2015**
Sympathetic Adrenal-Medullary (SAM) Axis

Norepinephrine

Epinephrine

Picard et al. PNAS 2015
Mitochondria drive unique stress response “signatures

Mice with different mitochondria

- **WT**: Normal function
- **ND6**: ↓ Respiration
- **COI**: ↓ Respiration
- **ANT1**: ↓ Energy Exchange
- **NNT**: ↑ Oxidative Stress

Stress response measures (n=74)

**WT**

**Component 1 (48.5%)**

**Component 2 (25.2%)**

**STRESS RESPONSE SIGNATURES**

Picard et al. *PNAS* 2015
How do energetics and mitochondria influence physiological responses?
Do mitochondria regulate the stress response in humans?
Mitochondrial Stress, Brain Imaging, and Epigenetics — MiSBIE
Mitochondrial Stress, Brain Imaging, and Epigenetics — MiSBIE

Brain structure and function
Neuropsychological function

Disease biomarkers
Stress reactivity
Energy expenditure
e.g., Cortisol, NE, GDF15, Lactate, etc.

mtDNA heteroplasmacy
Mitochondrial OxPhos
Lymphocytes, Monocytes, Neutrophils, Platelets

Total N = 110

- Healthy controls (n = 70)
- mtDNA defects
  - 3243A>G (group A) (n = 20)
  - 3243A>G (group B) (n = 5)
  - Single deletion (n = 15)
How do metabolites shape stress responses?
Picard and Shirihai. Cell Metab 2022
Gut-derived metabolite short-chain fatty acids

Placebo  Low dose  High dose

[Graph showing cortisol levels over time for placebo and different doses of intervention]
How do metabolites shape stress responses?
How does information about mitochondrial health reach the brain?

GDF15
What does GDF15 mean to the organism?

- Expressed in >90% of somatic tissues
- Triggered by cellular stressors (ISR)
- Activates canonical stress axes
  - Hypothalamic-pituitary adrenal (HPA) axis (CORTISOL)
  - Sympathetic activation (Catecholamines (NE))

Signals on the brainstem

Lockhart et al. *Endocr Rev* 2020
What does GDF15 mean to the organism?

Expressed in >50% somatic tissues

Triggered by cellular stressors (ISR)

Signals on the brainstem

Activates canonical stress axes

Organismal body-brain signaling

Psychological stress transiently increases GDF15 in humans

Monzel et al. *Life Metab* 2024
Knowledge Gaps

• What proportion of interindividual differences in the magnitude and nature of stress responses in humans is driven by interindividual differences in mitochondria? MiSBIE

• How variable is mitochondrial biology, within a person, over time? Likely variable

• Can we study mitochondrial stress regulation in vitro, in simple cellular systems? Complexity of stressors, feedback

• Are the health benefits of interventions like exercise on physiological systems, mental health, and aging driven by mitochondrial adaptations?
Research Opportunities

• Studies among individuals across a wide spectrum of mitochondrial energy transformation capacity/health (genetic mitochondrial defects — MiSBIE)

• Exogenous metabolite supplementation (SCFAs)

• Understanding the basis of health and resilience, in exceptionally healthy individuals

• Psychobiological studies of resilience beyond biology and physiology
Precious collaborators

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