Systems Biology and the Stress Response: From Pythagoras and the Epicureans to Modern Medicine

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Physical and Emotional Stress

- Stress Concepts
- Stress Mechanisms
- Effects of Stress on the Organism
- Coping with Stress

Complex Systems Theory

<table>
<thead>
<tr>
<th>Disturbing Forces</th>
<th>Harmony</th>
<th>Counteracting Reestablishing Forces</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Equilibrium</td>
<td>II Adaptive Response</td>
</tr>
</tbody>
</table>

Stressors (Physical, Emotional)

Pythagoras: Harmony
Alcmaeon: Iso-nomia
Walter Cannon: Homeostasis

Stress is the State of Threatened (or Perceived as Threatened) Homeostasis

Homeostasis over Time

Healthy Baseline Homeostasis

Improved Homeostasis / Hyperstasis

Constitutional Mood

Deteriorated Homeostasis / Cacostasis

Suppressed Mood

Homeostasis over Time

Improved Homeostasis + Hyperstasis

Eustress Mood

Constitutional Mood

Deteriorated Homeostasis + Cacostasis

Suppressed Mood

STRESS CONCEPTS

- Pythagoras: Harmony
- Alcmaeon: Iso-nomia
- Walter Cannon: Homeostasis

Homeostasis over Time

Healthy Baseline Homeostasis

Stress Excess

Constitutional Mood

Deteriorated Homeostasis

Suppressed Mood

Homeostasis over Time

Improved Homeostasis + Hyperstasis

Eustress Mood

Constitutional Mood

Deteriorated Homeostasis + Cacostasis

Suppressed Mood
Human Stressors

Daily hassles
Work stress (Effort Reward Imbalance, ERI)
Life transitions
Natural and unnatural catastrophes
Starvation, Excessive nutrition, Deficient exercise, Excessive exercise, Obesity
Socioeconomic status, Minority status (Oligmny)
Job loss, Downsizing, Loss of control
Bereavement
Caring/taking: Pathologic empathy/Unprincipled compassion
Addictions/Toxic substances
Inflammations (Traumatic, Infectious, Autoimmune, Allergic)
Anxiety, Depression, Personality disorder
Sleep deficiency

CRITICAL* PERIODS OF LIFE

Prenatal, Early Childhood, Puberty
(Human brain ontogeny complete at 25-27 y)

Organizational Effects of Hormones
(CRH, glucocorticoids, sex steroids, cytokines)

From the child of five to myself is but a step. But from the newborn baby to the child of five is an appalling distance."
Leon Tolstoy 19th century

"The past is never dead. It's not even past."
William Faulkner 20th century

The brain loses the nervous circuits that are not used!
Prefrontal/Frontal Lobe
“Higher Functions”

- Interpretation of the environment, social cues
- Problem solving
- Planning
- Proper control of impulses

Cognitive and Language Development

Synaptic Development

Homeostatic Systems

Physical and Emotional Stress

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- Stress Mechanisms
- Effects of Stress on the Organism
- Coping with Stress

What Mediates the Adaptive Response?

The Stress System

a. CNS
   1. CRH system
   2. Locus coeruleus (LC)-norepinephrine (NE) (autonomic (sympathetic) systems)

b. Periphery
   1. HPA axis
   2. Autonomic (sympathetic) systems

Stress System

- CRH
- NE
- LC-NE

- ANS

- CRH

- NE

- LC-NE
**SICKNESS SYNDROME**

**Manifestations**
- Anorexia/Nausea
- Fatigue and/or depressed affect
- Fatigue
- Pain/Neural Afferent Program
- Somnolence
- Hyperalgesia
- ± Headache
- Elevated temperature/fever
- Increased metabolic rate

**Molecular Effectors**
- Inflammatory Cytokines/Mediators
  - TNF-α
  - IL-1
  - IL-6
- Cytokines
- Glucocorticoids
- Immune Function
- TRH
- ACTH
- Glucocorticoids
- TSH/T3
- T4
- GHRH/GH
- LH/FSH
- SmC
- STS
- LH
- FSH
- G.P. Chrousos

**Stress System**
- CRH
- ACTH
- Glucocorticoids
- TSH/T4
- T3
- Growth and Thyroid Function
- CRH
- LH
- FSH
- Reproduction
- β-endorphin
- Testosterone, Estradiol

**Acute Stress**
- Behavioral adaptation
- Physical adaptation

**The Reward System**
- Structures related to emotional regulation
- Stress System
- Sickness Syndrome

**Fatigue**
- Mercurial
- Ejection Fraction
- Peripheral Immune Activation and Cytokine Secretion
- Central Secretion of Cytokines
- Intracerebral Infections
- Intraperitoneal Infections
- Postpartum Period
- Stress Autoimmune Disease
- Neurodegenerative Disease
- Stroke, Trauma

**Sickness Syndrome**
- Inflammatory (Sickness) Syndrome
- Stress Syndrome
- Fatigue Polyneuropathy Afferent Program
- Stress Syndrome
- Acute Phase Reaction

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Physical and Emotional Stress

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- Effects Stress on the Organism
- Coping with Stress

THE STRESS SYSTEM

Pathophysiology

Acuity vs. Chronicity of Stress System Activation

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THE STRESS SYSTEM

Pathophysiology

Acute effects of stress system activation

- Asthma, eczema, urticaria
- Migraine and tension headache
- Gastrointestinal pain
- Hypertensive episodes, CVA, death (compromised host)
- Panic attack
- Cardiac ischemia, MI, arrhythmia, death (compromised host)
- Psychotic episodes

Chronic effects of stress system malfunction

- Behavioral
  - Logos & Self-regulation (early effects)
  - Fear/Anger
  - Reward/Punishment
- Cardiovascular
- Metabolic
- Immune
- Pain and Fatigue
- Sleep

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HYPERCYTOKINEMIA

TRAUMA BURNS
INFECTION/IllNESSES
AUTOIMMUNE INFLAMMATORY DISEASES
ALLERGIC INFLAMMATIONS
CNS INFLAMMATIONS
NONINFLAMMATORY STRESS
OBESITY/VISCERAL OBESITY
AGING

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Both IL-4 and TNFα correlate with BMI

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Cellular Stress

**Nutritional** → **Inflammatory**

**Oxidative**

**Cellular Stress**

**Nutritional** → **Inflammatory**

**Oxidative**

Muscular System

Keap1 (SH sensor)-Nrf2-ARE

"Grief and fear when lingering provokes melancholia"

Hippocrates 460-479 BCE

**STRESS SYSTEM**

**HYPERACTIVITY AND PARADOXIC OBESITY IN DEPRESSION**
**Pearson’s correlations between mean 0800-2300 h plasma IL-6 levels and MVAS scores.**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Controls</th>
<th>Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>-0.61</td>
<td>0.07</td>
</tr>
<tr>
<td>Concentration</td>
<td>-0.64</td>
<td>0.05</td>
</tr>
<tr>
<td>Craving</td>
<td>-0.45</td>
<td>0.19</td>
</tr>
<tr>
<td>Guilt</td>
<td>-0.82</td>
<td>0.004*</td>
</tr>
<tr>
<td>Physical discomfort</td>
<td>-0.35</td>
<td>0.32</td>
</tr>
<tr>
<td>Sadness</td>
<td>-0.72</td>
<td>0.02</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>-0.86</td>
<td>0.002*</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>-0.88</td>
<td>0.0007*</td>
</tr>
<tr>
<td>Tiredness</td>
<td>-0.75</td>
<td>0.02</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>-0.21</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Note: For each measure, a higher VAS score denoted better feelings.

*Correlations of IL-6 with guilt, self-esteem and suicidal thoughts remained significant after Bonferroni correction.

**Antidepressants Sickness Behavior, Depression Equates an Inflammatory Condition?**

Peripheral Infections
- Post Partum
- Stress
- Autoimmune Disease
- Neurodegenerative Disease
- Stroke, Trauma
- Intracerebral Infections

Peripheral Immune Activation and Cytokine Secretion
- Central Secretion of Cytokines (TNFα, IL-1, IL-6, etc.)
- Alterations in Neurochemical Systems (NE, 5-HT, CRH, etc.)

**Acute Stress**

MCLS
- Amygdala
- CRH
- PVN
- CRH/AVP
- LC/NE

+ - +

HIPPO - CAMPUS
- Cortisol
- Catecholamines + IL-6

**Melancholic Depression**

MCLS
- Amygdala
- CRH
- PVN
- CRH/AVP
- LC/NE

- +

HIPPO - CAMPUS
- Cortisol
- Catecholamines + IL-6

**Somatic consequences**
- Metabolic syndrome X
- Cardiovascular disease
- Osteoporosis

**Behavioral consequences**
- Anhedonia, Fatigue, Insomnia, Anorexia, Loss of libido

**Sickness syndrome**

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**24 H SAMPLING OVERNIGHT DEXAMETHASONE TEST**

<table>
<thead>
<tr>
<th>A.</th>
<th>B.</th>
<th>C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLASMA CORTISOL</td>
<td>8 am</td>
<td>8 pm</td>
</tr>
<tr>
<td>TARGET TISSUE SENSITIVITY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGET TISSUE RESPONSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORTISOL CONCENTRATION</td>
<td>HS</td>
<td>N</td>
</tr>
<tr>
<td>THRESHOLD FOR HARMFULNESS</td>
<td>D</td>
<td>+D</td>
</tr>
<tr>
<td>D</td>
<td>-</td>
<td>D</td>
</tr>
<tr>
<td>+D</td>
<td>NS</td>
<td>CS</td>
</tr>
</tbody>
</table>

**Chrousos JCEM 1998**
Uncoupling between Circadian Rhythm of Circulating Cortisol and Tissue Glucocorticoid Sensitivity

Cytokines and old age

THE STRESS SYSTEM AND THE METABOLIC SYNDROME

Disease and Disadvantage in the United States and in England

James Banks, PhD; Michael Marmot, MD; Zoe Oldfield, MSc; James P. Smith, PhD
JAMA. 2006;295:2037-2045.

Americans:
CRP 20% higher
HDL 14% lower

Disease and Disadvantage in the United States and in England

James Banks, PhD; Michael Marmot, MD; Zoe Oldfield, MSc; James P. Smith, PhD
JAMA. 2006;295:2037-2045.
America’s Sick Society
Paul Krugman
Editorial, Herald Tribune, 6 May 2006
― Being American seems to damage your health regardless of race and class.
― The richest third of Americans is in worse health than the poorest third of the English.
― Bad habits do not explain the difference.

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Excess Deaths Associated with Underweight, Overweight, and Obesity
Flegal KM, Graubard BI, Williamson DF, Gail MH
Risk of mortality is improving from NHANES I to NHANES II to NHANES III.

Anti-stress and nutritional and other potential life extenders

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Exhausting genetic and epigenetic networks participating in functions important for human survival and species preservation

G.P. Chrousos, Amer J Med 2004

'The shape of things to come'

ENVIRONMENTAL STRESSORS
Species (Genetics) vs. Individual (Epigenetics)

THE STRESS SYSTEM
Chronic Pathophysiology

Chronic intermittent exercise bouts as a chronic stressor
Moderate vs. Excessive
Physical and Emotional Stress

- Stress Concepts
- Stress Mechanisms
- Effects of Stress on the Organism
- Coping with Stress

Dealing with Stress:
- Alleviate/Eliminate Stressors
- Improve Coping

Stress Coping-Management

What can we do about stress?
- Social prerequisites
- Nutrition
- Exercise
- Sleep
- Timing regularity
- Experiencing “Flow”

Basic Social Prerequisites
- Safety, Security
- Social Integration
- Competence
- Authenticity
- Autonomy
The Epicurian Tetrapharmacon Prescription

- We are not threatened by divine power
- There is no life after death
- It is easy to acquire what we need to be happy
- It is easy to endure what makes us suffer

Marcus Aurelius (Meditations) 167 CE

"If you are distressed by anything external or internal, the pain is not due to the thing itself, but to your estimate of it: and this you have the power to revoke at any moment."

MC/ML System Tone
- + acute
- - chronic

Stress System Tone

Placebo, Positive thinking, "Flow"
- Nocceo, Negative thinking

MC/ML System Tone
- + acute - chronic

Stress System Tone

Placebo, Positive thinking, "Flow"
- Nocceo, Negative thinking

MC/ML System Tone
- + acute - chronic

Stress System Tone

Stress-related Component of Disease

Patient-doctor Relationship = A Strong Predictor of Response to any Therapy

Maintaining a Young Mind: A Prerequisite for Eulongevity

Young Mind = Exploration ??

Eulongevity = Good and long living

Increasing level of happiness: (+MC/ML System Tone)
- Exploration
- "Flow", Noopaedia
"You ask, how can we know the Infinite? I answer, not by reason. It is the office of reason to distinguish and define. The Infinite, therefore, cannot be ranked among its objects. You can only apprehend the Infinite by a faculty superior to reason, by entering into a state in which you are your finite self no longer—in which the divine essence is communicated to you. This is ecstasy. It is the liberation of your mind from its finite consciousness. Like only can apprehend like; when you thus cease to be finite, you become one with the Infinite. In the reduction of your soul to its simplest self, its divine essence, you realize this union—this identity."

Ancient Greek sage Plotinos (ca. CE 204/5 – 270) in a letter to Flaccus.

"...έδειξε με τις πράξεις του και την μέθοδο της λογικής του ότι για να είναι κάποιος ευτυχής πρέπει να είναι καλός....."

"....he showed with his deeds and the method of his logic that for somebody to be happy one has to be good..."

Aristotle, Eulogy to Plato 4cent BCE

"Aristotelian Eudaimonia"

4 Qualities of Mind that Alleviate Suffering

- Metta = loving kindness
- Karuna = compassion
- Mudita = feeling the joy of others
- Upekkha = ataraxia, equanimity

Upekkha=Ataraxia

An equanimous mind holds all things in an ease-filled balance. From this place of equanimity, when we see people going about their everyday lives, friendliness (metta) is our natural response. When we see someone suffering, compassion (karuna) is our natural response. When we see someone who's happy, joy in their joy (mudita) is our natural response.

Sylvia Boorstein, It is easier than you think, 1995

"ΑΤΥΧΟΥΝΤΙ  ΣΥΝΑΧΘΟΝ"

Show compassion to the unfortunate.

Those only are happy, who have their minds fixed on some object other than their own happiness; on the happiness of others, on the improvement of mankind, even on some art or pursuit, followed not as a means, but as itself an end. Aiming thus at something else, they find happiness by the way...

J. Mill 19th C CE

Fredrickson BL et al. PNAS 2013; 110 (33): 13684-13689

Fredrickson BL et al. PNAS 2013; 110 (32): 13684-13689

Fredrickson BL et al. PNAS 2013; 110 (33): 13684-13689
What can we do about stress?

- Social prerequisites
- Nutrition
- Exercise
- Sleep
- Timing regularity
- Experiencing "Flow"
- Be good-do good
- Have a sustained purpose beyond one's self ("transcendence")

"I decided to be happy because this improves my health"  
Voltaire 1694-1778

Συμπάσχει η ψυχή τω σώματι νοσούντι και τεμνομένω, το δε σώμα τη ψυχή  
Aristotle

"Be equanimous and remember not to believe easily"  
G.P. Chrousos

Cellular Stress

- Nutritional
- Inflammatory
- Oxidative

Nutritional IR
Inflammatory NF-kB

Stress → Depression
Metabolic Syndrome
FAT MASS
VISCERAL FAT = ABDOMINAL ADIPOSE TISSUE
LEAN BODY MASS= SKELETAL MUSCLE MAss + BONE MASS
SYSTEMIC INFLAMMATION= EXTRACELLULAR WATER
BRAIN OEDEMA= EXTRACELLULAR WATER BRAIN

ENVIRONMENTAL STRESSORS
Phylogeny
Long-term
Evolution
Genetics
CNS complexity
Ontogeny
Short-term
Epigenetics
CNS plasticity

The Reward System