Stress, Adaptation, and Longevity

Leonardo da Vinci
Changes with Aging in the Hypothalamo-Pituitary-Adrenal Axis

No significant changes in healthy, non-stressed, elderly

The few changes that occur are rapidly compensated for (e.g. decreased secretion of GCs from the adrenal cortex) but also

less rapid metabolism in the liver & less urine excretion

Therefore the circulating levels remain constant

Also, normal ACTH & cortisol responses to CRH administration

Some alterations of the circadian rhythm
STRESS

Cortisol, norepinephrine, and epinephrine
Figure 10.4 Corticosterone titers in young (3-5 mo) and aged (24-28 mo) rats
Stress:
In biology, any change (stressor) in the environment that may tend to alter an existing equilibrium and trigger counteracting responses at molecular, cellular, and systemic levels to preserve/reestableish such an equilibrium and insure adaptation.

Claude Bernard, (1813-1878, Prof. of Physiology at the Collège de France, Paris), suggests that the equilibrium or steady state of the “milieu intérieur” is to remain constant to allow for optimal function and survival.
Types of Stress

• Examples of Physical/Chemical Stress
  – High/low extreme temperatures
    – Physical injury
    – Hemorrhage
    – Hypoglycemia, etc.

• Examples of Psychological/Emotional Stress
  – Fear
    – Cognition of danger
    – Memories
    – Sorrow or joy
    – Hate or love, etc.

From left to right: F. Skelton, R. Guillemin (Nobel Prize 1977), Prof. C. LeBlond, P.S. Timiras
The Nobel Prize was awarded for the identification of the hypothalamic hypophysiotropic hormones.
Homeodynamics

A constant environment obtained through a series of dynamic adjustments

This continual need for adjustment is implicated in the term “allostasis”

(From Greek allo “different” stasis “state”)

Emphasizes the dynamism of adaptive responses to stress

This adaptation to stress is often achieved with a price -- a declining ability to adapt and/or an increased pathology and disease

*Prof. T. Seeman, Geriatrics, UCLA (UCB alumna)
<table>
<thead>
<tr>
<th>Functions Stimulated by Stress:</th>
<th>Functions Inhibited by Stress:</th>
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<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td><strong>All functions not immediately necessary for defense and survival are decreased:</strong></td>
</tr>
<tr>
<td>- Increased cardiac rate</td>
<td>- Decreased growth</td>
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<tr>
<td>- Elevated blood pressure</td>
<td>- Decreased appetite (anorexia)</td>
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<tr>
<td>- Increased blood coagulation</td>
<td>- Decreased reproductive function and sex drive</td>
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<tr>
<td>- Redistribution of blood from peripheral (skin) and internal systems (gastro-intestinal) to heart, skeletal muscles, brain</td>
<td>- Decreased circulation in tissues not involved in stress response</td>
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<tr>
<td><strong>Respiratory</strong></td>
<td>- Decreased response to pain</td>
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<tr>
<td>- Increased respiratory ventilation</td>
<td>- Decreased immune function</td>
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<tr>
<td><strong>Metabolic</strong></td>
<td>- Decreased thymus size</td>
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<tr>
<td>- Increased glycogen mobilization</td>
<td>- Decreased thymic hormones and cytokines</td>
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<tr>
<td>- Increased glycemia</td>
<td>- Increased lipolysis</td>
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<td>- Increased glycemia</td>
<td>- Increased CRH, ACTH, glucocorticoids</td>
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<tr>
<td><strong>Hormonal</strong></td>
<td>- Increased vasopressin, NGF</td>
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<tr>
<td>- Increased CRH, ACTH, glucocorticoids</td>
<td>- Increased catecholamines (E &amp; NE)</td>
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</table>
Table 10.6

Pathophysiologic Responses During Stress

During Stress

Energy storage ceases because:

- ↑ sympathetic activity
  (i.e. increased vigilance/arousal)
- ↓ parasympathetic activity
- ↓ insulin secretion

Access to energy storage is facilitated and energy storage steps are reversed because of:

- ↑ glucocorticoid secretion
- ↑ epinephrine/norepinephrine secretion
- ↑ glucagon secretion
**Pathophysiologic Responses After Stress**

If physiologic responses are insufficient and adaptation is incomplete, symptoms of poor health are registered (e.g., loss of energy when freeing energy from storage and returning to storage).

Examples of consequences:
- Muscle wasting
- Diabetes (Type 2)
- Ulcers, colitis, diarrhea
- Inhibition of growth (in childhood)
- Osteoporosis (in old age)
- ↓ LHRH, ↓ testosterone

**Table 10.6**
Figure 10.10
Some physiologic and pathologic responses to stress in selected organs
Table 10.9
Risk Factors (Allostatic Load)
Endangering Health and Shortening Life Span

**Elevated Physiologic Indices (at risk)**
- Systolic blood pressure: $\geq 148$ mm Hg
- Diastolic blood pressure: $\geq 83$ mm Hg
- Waist-hip ratio: $\geq 0.94$
- Total cholesterol-High Density Lipoprotein ratio: $\geq 5.9$
- Total glycosylated hemoglobin level: $\geq 7.1\%$
- Urinary cortisol level: $\geq 25.7$ mg/g creatinine
- Urinary epinephrine level: $\geq 5$ mg/g creatinine
- Urinary norepinephrine level: $\geq 48$ mg/g creatinine

**Lowered Physiologic Indices (at risk)**
- HDL cholesterol level: $\leq 1.45$ mmol/L
- DHEA (Dehydroepiandrosterone) level: $\leq 2.5$ $\mu$mol/L
Janus is the Roman God of gates and doors, of beginnings and endings and hence, is represented by a double faced head; generally placed on the gates of the city, the menacing face looking towards the outside of the city ready to defend it against any attackers, the benevolent face turned towards the city is a protector and promoter of prosperity and good health.
Moderate stress of short duration leads to moderate stress of short duration. Severe and prolonged stress leads to severe and prolonged stress.

Incidence of Cardiovascular Diseases

Allostatic Load weak or absent

Moderate stress of short duration stimulates vigilance, attention, and memory storage. Excessive stress of long duration reduces the number of neurons, neurotransmitter balance, and memory storage.

Cognitive Alterations

Figure IV: Protection contre Pathologie: fonction cérébrale et mémoire
Moderate & Regular Physical Exercise

Allostatic Load weak or absent

Cardiovascular function
Energy mobilization
Immune efficacy
Cognition & vigilance
Mass & strength of muscle & bone

Excessive & prolonged physical exercise or lack of regular exercise

Allostatic Load Progressive & increasing

Atherosclerosis
Obesity
Incidence of cardiovascular diseases
Immunosuppression
Depression, anxiety, memory loss
Bone fragility
Muscle atrophy & weakness
Beneficial effects of Hormesis may be due to:

- DNA repair
- Immune competence
- Neurologic acuity
- Neuromuscular activity
- Better memory
- Resistance/ adaptation to stress
Among invertebrates, the most used models have been the fly (*Drosophila melanogaster*) and the nematode (*C. elegans*).

Suppression of the receptor for insulin/IGF hormone will produce a mutant nematode that will live 6x longer than corresponding controls and be more resistant to all stress, but they will not grow, undergo development, or reproduce.
**IN FLIES** (Drosophila melanogaster):

- Genetic Manipulation
  - Inactivation of IGF-1 receptor analog

- Shift of metabolism from aerobic to anaerobic
  - Greater resistance to stress

- Increased longevity
  - Decreased mortality

- Decreased growth
  - Delayed maturation

- Greater resistance to stress
  - Increased longevity
  - Decreased mortality
IN WORMS (Caenorhabditis elegans):

- Genetic Manipulation
- Inactivation of IGF-1 receptor analog

- Shift of metabolism from aerobic to anaerobic
- Decreased free radical accumulation
- Greater resistance to stress

- Increased longevity 6X
- Mortality

- Decreased growth
- Delayed maturation
IN MAMMALS (Rodents):

Genetic Manipulation
Inactivation of IGF-1, I, GH, PL, & TSH receptor analog

Increased longevity 18-40%
Delayed aging & mortality

Shift of metabolism from aerobic to anaerobic
Decreased free radical accumulation
Greater resistance to stress

Decreased growth
Delayed maturation
Most functions normal
LEVELS OF PROTEIN ORGANIZATION

PRIMARY PROTEIN STRUCTURE
is the sequence of amino acids.

SECONDARY PROTEIN STRUCTURE
occurs when the sequence of amino acids are linked by hydrogen bonds; it is defined as the local conformation of the structure’s backbone.

TERTIARY PROTEIN STRUCTURE
is the protein’s three-dimensional shape, incorporating the pleats and helices along with the spatial disposition of its side chains.

QUARTERNARY PROTEIN STRUCTURE
is a protein consisting of more than one amino acid chain.

Taken from P.H. Hunter, Protein Folding: Theory Meets Disease, The Scientist, volume 17, number 17, pg. 24-27, 2003
CHAPERONES

Intracellular peptides that help other proteins to fold

Prevent production of
- Inactive protein
- Protein fragments
- Protein aggregates

WITHOUT CHAPERONES

Miss a fold, prompt a disease

Amyloidosis
- Lung, blood, liver diseases
- Diabetes, cancer, infections

Severe stress?
Stress Proteins or Heat Shock Proteins (HSP)

They are synthesized in response to a sudden rise in temperature or other types of stress.
ON FLIES, WORMS, RODENTS:

LONGEVITY is associated
With stimulation (up-regulation)
Of genes involved in response to
stress including those of HSP

HSPs act as chaperones and
promote greater tolerance/resistance
to stress (thermic and others)

Hence, increased longevity and hormesis may depend on
Increased HSPs and their actions as chaperones
### Interventions to prevent or treat deleterious effects of stress

<table>
<thead>
<tr>
<th>According Grandmother</th>
<th>Pharmacologic/Genetic</th>
<th>Psychotherapy</th>
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<tbody>
<tr>
<td>Good nutrition</td>
<td>Hypnotics &amp; sedatives</td>
<td>Psychiatric counseling</td>
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<tr>
<td>Regular exercise</td>
<td>Tranquilizers &amp; Anti-anxiety drugs</td>
<td>Meditation</td>
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<tr>
<td>Good habits</td>
<td>Hormones</td>
<td>Yoga</td>
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<tr>
<td>Regular medical visits</td>
<td>others</td>
<td>Continuing interaction with family &amp; community</td>
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<tr>
<td>Good education in youth and continuing into old age</td>
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<tr>
<td>Avoiding isolation, living with family and in community</td>
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Coping Skills to Withstand Stress

Inner Resources
- e.g. beliefs, assumptions

Knowledge
- e.g. years of education

Spirituality
- e.g. religious beliefs

Social support
- e.g. interpersonal relations