The physiology and pathophysiology of stress

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Stress:
A state of threatened (or perceived as threatened) homeostasis
Stress facilitates processes adaptive for survival

ALLOSTASIS – Allostatic load

Behavioral and physical adaptation during acute stress

<table>
<thead>
<tr>
<th>Behavioral adaptation: adaptive redirection of behavior</th>
<th>Physical adaptation: adaptive redirection of energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased arousal and alertness</td>
<td>Oxygen and nutrients directed to the CNS and stressed body site(s)</td>
</tr>
<tr>
<td>Increased cognition, vigilance, and focused attention</td>
<td>Altered cardiovascular tone, increased blood pressure and heart rate</td>
</tr>
<tr>
<td>Euphoria (or dysphoria)</td>
<td>Increased respiratory rate</td>
</tr>
<tr>
<td>Heightened analgesia</td>
<td>Increased gluconeogenesis and lipolysis</td>
</tr>
<tr>
<td>Increased temperature</td>
<td>Detoxification from toxic products</td>
</tr>
<tr>
<td>Suppression of appetite and feeding behavior</td>
<td>Inhibition of growth and reproduction</td>
</tr>
<tr>
<td>Suppression of reproductive axis</td>
<td>Inhibition of digestion-stimulation of colonic motility</td>
</tr>
<tr>
<td>Containment of the stress response</td>
<td>Containment of the inflammatory/immune response</td>
</tr>
</tbody>
</table>

Adapted from Chrousos & Gold (2).
Physiological Stress Systems

In the fight-or-flight response, the hypothalamus sends a neural message through the spinal cord.

The sympathetic division of the autonomic nervous system is activated to stimulate the medulla of the adrenal gland.

The adrenal medulla releases epinephrine into the circulatory system.

Epinephrine activates the body's cells, endocrine glands, and the brain.

Epinephrine = Adrenaline

Figure 7.20 Activating a Stress Response
Kolb and Whishaw: An Introduction to Brain and Behavior, Second Edition
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Figure 5.15 Neurochemistry of the ANS
Kolb and Whishaw: An Introduction to Brain and Behavior, Second Edition
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# The Autonomic Nervous System

<table>
<thead>
<tr>
<th>Structure</th>
<th>Sympathetic Stimulation</th>
<th>Parasympathetic Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iris (eye muscle)</td>
<td>Pupil Dilation</td>
<td>Pupil Constriction</td>
</tr>
<tr>
<td>Salivary Glands</td>
<td>Saliva production reduced</td>
<td>Saliva production increased</td>
</tr>
<tr>
<td>Oral/Nasal Mucosa</td>
<td>Mucus production reduced</td>
<td>Mucus production increased</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart rate and force increased</td>
<td>Heart rate and force decreased</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchial muscle relaxed</td>
<td>Bronchial muscle contracted</td>
</tr>
<tr>
<td>Stomach</td>
<td>Peristalsis reduced</td>
<td>Gastric juice secreted; motility increased</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>Motility reduced</td>
<td>Digestion increased</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>Motility reduced</td>
<td>Secretions and motility increased</td>
</tr>
<tr>
<td>Liver</td>
<td>Increased conversion of glycogen to glucose</td>
<td>Increased urine secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>Decreased urine secretion</td>
<td></td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>Noradrenaline and adrenaline secreted</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>Wall relaxed</td>
<td>Wall contracted</td>
</tr>
<tr>
<td></td>
<td>Sphincter closed</td>
<td>Sphincter relaxed</td>
</tr>
</tbody>
</table>

## Physiological Effects of Adrenal Medullary Hormones

- **Increased rate and force of contraction of the heart muscle**: this is predominantly an effect of adrenaline acting through beta receptors.

- **Constriction of blood vessels**: noradrenaline, in particular, causes widespread vasoconstriction, resulting in arterial blood pressure.

- **Dilation of bronchioles**: assists in pulmonary ventilation.

- **Stimulation of lipolysis in fat cells**: this provides fatty acids for energy production in many tissues and aids in conservation of reducing reserves of blood glucose.

- **Increased metabolic rate**: oxygen consumption and heat production increase throughout the body in response to adrenaline. Medullary hormones also promote breakdown of glycogen in skeletal muscle to provide glucose for energy production.

- **Dilation of the pupils**: particularly important in dangerous situations under conditions of low ambient light.

- **Inhibition of certain “non-essential” processes**: as examples, the inhibition of gastrointestinal secretion and motor activity.
**Hypothalamus-Pituitary-Adrenal (HPA) axis**

In response to sensory stimuli and cognitive activity, the hypothalamus produces neurotransmitters that enter the anterior pituitary through axons and the posterior pituitary through axons.

On instructions from these releasing hormones, the pituitary sends hormones into the bloodstream to target endocrine glands.

In response to pituitary hormones, the endocrine glands release their own hormones that stimulate target organs, including the brain. In response, the hypothalamus and the pituitary decrease hormone production.

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**HPA axis - Negative Feedback**

Hypothalamus

CRF, AVP (↑)

Pituitary gland

ACTH (↑)

Adrenal glands

Glucocorticoids (cortisol, corticosterone)

Kidney

CRF: Corticotropin Releasing Factor/Hormone

AVP: Vasopressin

ACTH: Adrenocorticotropin Hormone
Physiological Effects of Glucocorticoids

- **Energy mobilization**: glycogenolysis (breakdown of glycogen stores to produce glucose; liver); inhibition of glucose uptake in muscle and adipose tissue.

- **Suppression of innate immunity in immune organs**: Potent anti-inflammatory and immunosuppressive properties (use as drugs).

- Inhibition of bone and muscle growth.

- Potentiation of sympathetic nervous system-mediated vasoconstriction.

- Proteolysis and lipolysis.

- Suppression of reproductive function (H-P-Gonadal axis)

- Behavioral alterations.

In the brain, MR and GR are located in regions essential for the processing of emotion and cognition:

- **MR expression**: hippocampus, septum and amygdala
- **GR expression**: widely distributed throughout the brain
- **Hippocampus**: highest density of MR and GR (co-localised in same cells)
- **Glucocorticoids** (cortisol/corticosterone): 10-times higher affinity for MR than GR
- **Functions**: MRs and GRs exert differential effects in neural excitability
Glucocorticoids act through intracellular receptors: Mineralocorticoid receptor (MR) and Glucocorticoid receptor (GR). They exert genomic mechanisms. There are also membrane receptors that exert rapid non-genomic effects.

Hormone Response Element – HRE
Glucocorticoid RE - GRE

Time course of cellular responses to stress hormones

Nature Reviews | Neuroscience
de Kloet, Joëls & Holsboer, 2005
Receptors for ‘stress’ molecules cluster in ‘hot spots’ in the brain

Marian Joëls & Tallie Z. Baram
Nature Reviews Neuroscience 10, 459-466

Individual differences in stress responsiveness

Gene-expression changes

At least 3 weeks later:
MR/GR downregulation;
CA3 dendritic tree atrophy;
DG cell turnover slowed down;
Reduced expression and function of 5-HT_{1A}/5-HT_{2C};
LTP reduced;
Cognitive impairment;

Vulnerability state to disease
The gene x environment complexity

Stress and Psychopathology

Stress → Adaptation

Stress → Psychopathology
Stress is a risk factor for depression

Hyperdrive of hypothalamic CRH/AVP neurons and HPA hyperactivity: observed after chronic stress and depression

As observed in depression, hypercortisolemia leads to:
- alterations in anxiety, aggression, cognition
- disturbs monoaminergic systems
- causes volume reductions in limbic structures

... these symptoms are modulated by gene mutations in the GR and CRHR1


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Stress is a risk factor for depression

Early life stress can lead to enhanced HPA axis reactivity, increasing vulnerability to depression

HPA activity is a predictor for the relapse and remission of depression

ICV administration of CRH induces anxiety and depression symptoms

Antidepressants modulate MR expression

MR antagonists worsen antidepressant outcome

CRHR1 antagonists ameliorate signs and symptoms of depression

...

Chronic stress can trigger or exacerbate depression

**Stress**

**Chronic Stress**

- DEPRESSION-LIKE BEHAVIORS:
  - Anhedonia
  - Helplessness
  - Low social motivation

ANXIETY
Depression Duration But Not Age Predicts Hippocampal Volume Loss in Medically Healthy Women with Recurrent Major Depression

Yvette I. Sheline,1,2,9 Milan Sanghavi,1 Mark A. Mintun,1,3,9 and Mokhtar H. Gado1,2

Departments of 1Psychiatry and 2Radiology and the 3Walter Reed Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri 63110

![Depression Duration But Not Age Predicts Hippocampal Volume Loss in Medically Healthy Women with Recurrent Major Depression](image-url)
Opposite effects of chronic stress in hippocampus and amygdala

Hippocampus
CA3 (pyramidal neurons):
Atrophy of apical dendrites
Reduced synaptic density
DG:
Inhibited neurogenesis

Amygdala
Basolateral nucleus (pyramidal and stellate neurons):
Hypertrophy of dendrites
Increased spine density

Brain regions with functional and/or structural alterations in depression

Prefrontal cortex
Nucleus accumbens
Hippocampus
Amygdala
The vulnerable phenotype

Stress \[\rightarrow\] Psychopathology
Depression

Can personality traits *predict* stress-associated depression?

VULNERABILITY
Trait

PSYCHOPATHOLOGY
DEPRESSION

STRESS INTENSITY
Chronic Unpredictable Stress

Personality traits, chronic stress, and psychopathology

Personality Characterization

Behavioral Alterations

Brain function

Amygdala

Hippocampal

Behavioral Alterations

Brain function

Amygdala

Hippocampal

High anxiety trait is a risk factor to develop stress-induced depression-like behaviors and altered neurobiological mechanisms

High Anxiety Trait

Chronic Unpredictable Stress
High anxiety trait is a risk factor to develop stress-induced depression-like behaviors and altered neurobiological mechanisms.

(Sandi and Richter-Levin, TINS, 2009)
The vulnerable phenotype

Early life stress \rightarrow Stress \rightarrow Psychopathology

Depression

Different psychopathological vulnerabilities induced by early life stress

Early life stress

Impulsivity & Aggression
Anxiety-like behaviors
Depression-like behaviors

[Image of mice]