General adaptation syndrome - stress

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GAS, stress

- History
- Definitions
- Mechanisms
- Research

- Practical experiment
History

• 14th century- stress as hardship, straits, adversity, affliction

• 17th century - stress in the context of physical sciences
  • Load: external force
  • Stress: ratio of internal force created by the load to the area over which the force acted
  • Strain: deformation or distortion of the object
  • Still used in engineering today

• 19th and 20th century - stress and strain as the cause of „ill health“ and „mental disease“

• 1910 - relationship of stress to angina pectoris

• 1925 - fight of flight reaction
Hans Selye

- János Hugo Bruno "Hans" Selye
- 1907 – 1982
- First scientific paper on stress in 1936
- 1700 papers, 39 books
- Nobel prize nominee first time in 1949
1. Homeostasis

• What should you know?

• Cannon’s 4 features of homeostasis
• Components of a control system
• Function of negative feedback system
Constancy of the internal environment

• 19\textsuperscript{th} century Claude Bernard – central importance of a stable internal environment, which he termed the \textit{milieu intérieur}

• Composition of IE has to be compatible with the survival needs of the individual cells

• \textbf{Body fluids} are the internal environment

• 20\textsuperscript{th} century Walter Cannon evolved this concept to a system of \textbf{physiologic processes} that \textbf{oppose change}

• These processes are \textbf{automatic}

• Resistance to both \textbf{internal} and \textbf{external} disturbances
Homeostasis

- Purposeful maintenance of a stable internal environment maintained by coordinated physiologic processes that oppose change
- Cannon 1932 *Wisdom of the body*
  - When a factor is known to shift homeostasis in one direction, mechanisms exist that have the opposite effect (blood glucose level, body temperature, pH)
  - 4 features of homeostasis
4 features of homeostasis

• Constancy needs mechanisms that maintain it
• Tendency toward change automatically meets with factors that resist change (increase in blood glucose results in thirst)
• Homeostatic system consists of a number of cooperating mechanisms acting simultaneously or successively
• Homeostasis does not occur by chance, but is the result of organized self-government
Control systems

• Processes that oppose change
• Collection of interconnected components that keep the parameter of the body constant
• Operate by negative feedback mechanisms:
  • Sensor – detects a change
  • Integrator/comparator – sums and compares incoming data with a set point
  • Effector – returns the sensed function to values within the range of the set point
• Regulation of cellular function, control of life processes, integration of different organs’ function
Negative feedback

- Present in most systems – **ensures stability**
- Decrease of the monitored value below the set point – feedback mechanisms lead to increase
- Similar to *thermostat* on a heating system
Positive feedback

• Initial stimulus produces more of itself
• Birth – uterine contractions lead to secretion of oxytocin that increases contractions
• Blood clotting – activated platelets activate more platelets
• Lactation – suckling stimulates production of prolactin that stimulated production of milk
• Cytokine storm – release of cytokines leads to further release
Questions

• Cannon’s 4 features of homeostasis
• Components of a control system
• Function of negative feedback system
2. Stress and adaptation

• What should you know?

• Selye’s definition of stress
• Define stressor
• 2 factors that influence the nature of the stress response
• Components of the nervous system in mediating the stress response
• Stress responses of autonomic nervous system, endocrine system, immune system
2. Stress and adaptation

• What should you know?

• Purpose of adaptation

• 6 factors that influence a person’s adaptive capacity

• Experience, previous learning and social support in the process of adaptation
Hans Selye 1930’s

• **Changes** in rats that were exposed to a variety of different stimuli

• These changes are the manifestations of the body’s attempt to adapt to stimuli

• **Stress** – “a state manifested by a specific syndrome of the body developed in response to any stimuli that made an intense systemic demand on it”
Triad of changes in rats

• Adrenal enlargement
• Thymic atrophy
• Gastric ulcer

• Response to many different or non-specific experimental challenges
• Assumed role of hypothalamic-pituitary-adrenal axis
In patients

- Patients with diverse diseases have many signs and symptoms in common – loss of:
  - appetite
  - muscular strength
  - weight
  - ambitions
  - facial expression

- “Syndrome of being sick”
General adaptation syndrome

• **General** – systemic reaction
• **Adaptation** – response is in reaction to a stressor
• **Syndrome** – physical manifestations are coordinated and dependent on each other

• 3 stages:
  • Alarm
  • Resistance
  • Exhaustion
Alarm stage

- Generalized stimulation of the **sympathetic nervous system** and **HPA axis**
- Release of **catecholamines** and **cortisol**
- **Fight-or-flight**
- Resistance to physical damage drops for a short time, so that organism can rearrange its priorities to cope with stressor
- If the stressor no longer exists, the body returns to its normal level of resistance
Fight or flight

- **Sympathetic nervous system manifestations**
- Basic survival response – redirecting the energy to essential life processes
- Increased attention and arousal – intensifies memory
- Heart rate increases
- Respiratory rate increases
- Hands and feet become moist
- Pupils dilate
- Mouth becomes dry
- Activity of the GIT decreases
Resistance stage

- The **stressor persists**
- Level of **resistance increases** beyond normal
- The body selects the most effective and economic channels of defense
- Increased energy demands – **catabolism**
- **Increased blood pressure**, Na+ retension
- **Allostasis** – achieving stability through change
Exhaustion stage

- If the **stressor is prolonged** or overwhelms the ability of the body to defend
- **Resources are depleted**
- **Signs of systemic damage** appear
- Extreme catabolism, immunodeficiency, cardiovascular consequences
Stressor

• The events or environmental agents responsible for initiating the stress response

• Endogenous
• Exogenous

• Somatic
• Psychic
Nature of the stress response

- Defined by:
  - Properties of the stressor
  - **Conditioning** of the person being stressed

- Eustress
- Distress

- Selye: „Mild, brief and controllable periods of stress could be perceived as positive stimuli to emotional and intellectual growth and development“
Conditioning factors

• Determine different responses to the same stressor in different persons
• Pool of CF - adaptive capacity of the person

• Internal factors – genetic predisposition, age, sex
• External factors – exposure to environmental agents, life experience, dietary factors, social support
Neuroendocrine responses

• Communication along neuronal pathways
• Cerebral cortex – vigilance, cognition, attention
• Limbic system – emotional components
• Thalamus – receiving, sorting, distributing sensory input
• Hypothalamus – coordinates endocrine system and autonomic nervous system
• Pituitary gland
• Reticular activating system – mental alertness, ANS, skeletal muscle tone
Neuroendocrine responses

- **Locus ceruleus** in brain stem
- Central integrating site for the ANS response to stressful stimuli
- Neurons producing noradrenaline
# Neuroendocrine Interactions

**TABLE 9-1**  
Hormones Involved in the Neuroendocrine Response to Stress

<table>
<thead>
<tr>
<th>Hormones Associated With the Stress Response</th>
<th>Source of the Hormone</th>
<th>Physiologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines (norepinephrine, epinephrine)</td>
<td>Locus ceruleus, adrenal medulla</td>
<td>Produces a decrease in insulin release and an increase in glucagon release resulting in increased glycogenolysis, gluconeogenesis, lipolysis, proteolysis, and decreased glucose uptake by the peripheral tissues; an increase in heart rate, cardiac contractility, and vascular smooth muscle contraction; and relaxation of bronchial smooth muscle</td>
</tr>
<tr>
<td>Corticotropin-releasing factor (CRF)</td>
<td>Hypothalamus</td>
<td>Stimulates ACTH release from anterior pituitary and increased activity of neurons in locus ceruleus</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Anterior pituitary</td>
<td>Stimulates the synthesis and release of cortisol</td>
</tr>
<tr>
<td>Glucocorticoid hormones (e.g., cortisol)</td>
<td>Adrenal cortex</td>
<td>Potentiates the actions of epinephrine and glucagon; inhibits the release and/or actions of the reproductive hormones and thyroid-stimulating hormone; and produces a decrease in immune cells and inflammatory mediators</td>
</tr>
<tr>
<td>Mineralocorticoid hormones (e.g., aldosterone)</td>
<td>Adrenal cortex</td>
<td>Increases sodium absorption by the kidney</td>
</tr>
<tr>
<td>Antidiuretic hormone (ADH, vasopressin)</td>
<td>Hypothalamus, posterior pituitary</td>
<td>Increases water absorption by the kidney; produces vasoconstriction of blood vessels; and stimulates the release of ACTH</td>
</tr>
</tbody>
</table>
Corticotropin-releasing hormone

• 41-amino acid peptide
• Catecholamines activate paraventricular nucleus of the hypothalamus
• Endocrine regulator of pituitary and adrenal activity
• Induces secretion of ACTH from anterior pituitary
• Secretion of glucocorticoids from adrenal cortex
Glucocorticoids

- Cortisol
- Number of direct and indirect physiologic effects to:
  - Mediate stress response
  - Enhance the action of other hormones
  - Suppress other components of the stress system
- Both, mediator and inhibitor of stress response
- Maintains blood glucose levels
- Enhances the effects of catecholamines in cardiovascular system
- Suppresses osteoblast, hematopoiesis, protein synthesis and immune responses
Other hormones

• CRH increases somatostatin, which inhibits growth hormone

• Decrease in thyroid stimulating hormone

• Inhibition of T4 – T3 conversion

• The effects of stress on failure to thrive in children?

• Increased ADH – water retention

• Decreased reproductive hormones on hypophyseal, gonadal and target tissue level
Stress pathway

- Stressor – afferent neural pathways – amygdala – hypothalamus – ANS – fight or flight
- Prolonged duration od stressor – drop in catecholamines + activation of HPA axis – integrated response of CNS and endocrine systems
Immune responses

• Neuroendocrine – immune interactions
• Causal role of stress in immune-related diseases
• Exact mechanisms unknown
• Receptors for CNS-controlled hormones and neuromediators found on lymphocytes
• Lymph nodes, thymus, spleen are supplied with ANS nerves

• The two systems are interconnected
Purpose of the stress response

• To protect the person against acute threats to homeostasis
• Normally is **time limited**

• If the stress is hyperactive or becomes habituated the psysiologic and behavioral changes induced by stress can become threats
Coping and adaptation to stress

- Ability to respond to challenges of physical or psychological homeostasis and to return to a balanced state
- Influenced by:
  - Previous learning
  - Physiologic reserve
  - Time – how fast is the change
  - Genetics
  - Age
  - Health status and nutrition
  - Sleep-wake cycles
  - Psychosocial factors
Questions

• Selye’s definition of stress
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Questions

• Purpose of adaptation
• 6 factors that influence a person’s adaptive capacity
• Experience, previous learning and social support in the process of adaptation
3. Disorders of stress response

• What should you know?

• Describe the effects of chronic stress response

• Describe 3 states characteristic for post-traumatic stress disorder

• List 5 nonpharmacologic methods of treating stress
3. Disorders of stress response

• Time-limited nature of stress is usually beneficial
• Chronicity is disruptive to health
Acute stress

- Fight-or-flight
- Results from psychologically or physiologically threatening events
- In case of life-threatening trauma – these acute responses can be **life-saving**
- **BUT:** in persons with limited coping abilities, acute stress can be detrimental (pre-existing heart disease, high age, no experience, rapid change, no sleep...)

Chronic stress

• Chronicity or excessive activation of stress response
• Acute necrotizing gingivitis – normal bacterial flora of the mouth becomes invasive
• HSV1 infection (cold sores)

• Persons with great amount of premorbid stress report the most intense symptoms – flu, delayed wound healing...
PTSD

- Chronic activation of stress response as a result of experiencing a life-threatening event
- Battle fatigue or shell shock
- Major catastrophic events
- 35% of those who were exposed to 9/11 attacks
PTSD

1. Intrusion – occurrence of flashbacks during waking hours or nightmares where the event is relived
2. Avoidance – emotional numbing, disruption of personal relationships, depression, survivor guilt
3. Hyperarousal – increased irritability, difficulty in concentration, exaggerated startle reflex, increased vigilance and concern over safety
4. Memory problems, sleep disturbances, anxiety
PTSD

• The 3 types of symptoms must be present for at least 1 month + clinical distress or social / occupational impairment

• Increased reactivity of amygdala and hippocampus

• Decreased activity of anteriocingulate and orbitofrontal areas

• Decreased cortisol levels, increased sensitivity to cortisol receptors, enhanced negative feedback inhibition of cortisol – specific markers of PTSD
Acute stress disorder

- Acute stress reaction / psychological shock / mental shock / shock
- Condition arising in response to terrifying or traumatic event or witnessing such event
- Symptoms: numbing, emotional detachment, muteness, derealization, depersonalization, psychogenic amnesia, re-experiencing the event via thoughts, dreams, and flashbacks, avoidance of any stimulation that reminds of the event
Acute stress disorder

• Diagnosis: symptoms of anxiety + significant impairment in at least one essential area of functioning within 4 weeks of the event. Duration at least 2 days, maximum 4 weeks

• Onset of symptoms usually within minutes or days

• Mixed and changing picture, no type of symptom predominates for long

• If more than 4 weeks - PTSD
Acute stress disorder

• Sympathetic nervous system activation
• Stimulus is relayed from sensory cortex through the thalamus to the brain stem
• Increase in noradrenergic activity in locus ceruleus, activation of sympathetic nervous system – release of noradrenaline from nerve endings
• Activation of hypothalamic-pituitary-adrenal axis
Acute stress disorder

• 2 subtypes:
  • sympathetic – fight or flight
  • parasympathetic – rest and digest
• Week and queasy feeling that some people get in response to seeing blood or injuries
• Rapid vasodilation – drop in blood pressure – lack of perfusion to the brain
Treatment of stress disorders

• Avoiding stressors / changing reaction to stressors / relieving stress
• Purposeful priority setting and problem solving
• Relaxation – decrease in sympathicus and muscle tension
• Guided imagery – all 5 senses
• Music therapy – rhythm, melody, harmony
• Massage
• Biofeedback – control of physiologic functioning
How to measure stress

• ECG
• Blood pressure
• Skin resistance
• Hormone levels – urinary and plasma catecholamines, salivary cortisol
• Immune cell counts, antibody levels
Questions

• Describe the effects of chronic stress response
• Describe 3 states characteristic for post-traumatic stress disorder
• List 5 nonpharmacologic methods of treating stress
Animal models of stress

• Immobilization stress – restrain
• Hypoglycemic stress – insulin
• Pain stress – formalin, capsaicin
• Cold stress
• Hemorrhagic stress
• Forced swim stress
• Dominance stress
• Separation stress
How stress gets „under the skin“?

Accelerated telomere shortening in response to life stress

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Contributed by Elizabeth H. Blackburn, September 28, 2004

Here we provide evidence that psychological stress—both perceived stress and chronicity of stress—is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity, in peripheral blood mononuclear cells from healthy premenopausal women.
The influence of war on the oral health of professional soldiers

M Suman, S Spalj, D Plancak, W Dukic and H Juric
Zagreb, Croatia

Professional soldiers in the Croatian Army
336 soldiers in active service during the war in Croatia
304 soldiers in peacetime service

Decayed, missing and filled teeth index (DMFT)
Community periodontal index (CPI)

War conditions have a significant influence on the increased prevalence and severity of oral diseases for professional soldiers.
Final questions

• Are stress hormones being produced (expressed) or secreted upon stress response?
• What is stress good for?
• Why immune suppression is beneficial?
• How chronic stress can promote diabetes?
• How high cortisol leads to hypertension?
• Why we should cope with stress?
• How antihypertensive drugs target stress?
Practical part

• Mental stress

• Physical stress

• Outcomes: heart rate, blood pressure
• Compare individual and group responses to mental and physical stress
Experiment

• Oxidative stress in plasma, urine and saliva
• Reference values in people from different parts of world

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