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Cognition, Attention and Stress

Neuroendocrinology of Stress

Structure, Plasticity and Repair of the Nervous System
UZH: BIO343 / ETH: 376-1305-01 V
2 x 45 min

Prof. Dr. Johannes Bohacek

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Course Description:

Overview of the stress axis. Understanding stress as a whole-organism response. Discuss how stressful experiences shape brain function and behaviour, and how they can lead to disease (psychiatric, metabolic etc.).

Semester: HS2017
Time: Mondays, 10:15 - 12:00
Location: Lecture hall Y15 G40 (Irchel Campus)

Learning Ressources: Purves (5th Edition): Chapter 21; 29

For interested readers, very in-depth, including stress interactions with immune system, metabolic syndrome, sexual function etc.
Tsigos et al (2016) Endotext: Stress, Endocrine Physiology and Pathophysiology https://www.ncbi.nlm.nih.gov/books/NBK278995/

Introduction

Goal

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Group Exercise
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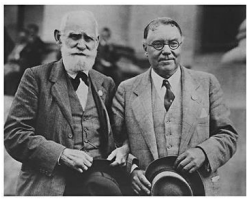
Walter Cannon (1871-1945)



Walter Cannon gave us…

1) The fight or flight response (1915)

2) The concept of homeostasis (1932)

3) Adrenline-mediated effects of acute stress (adrenal medulla, epinephrine)

He described how adrenaline activates the body's energy while inhibiting unnecessary energy-consuming processes such as digestion and reproduction. The ultimate result is to quickly prime an organism for a fight-or-flight response.

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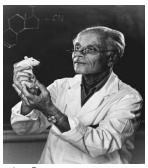
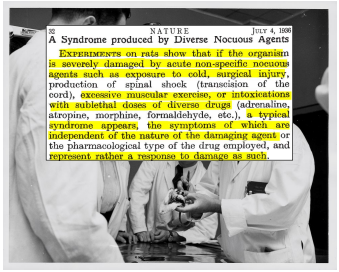
STRESS: "The sum of all forces that act against a resistance" Hans Selye



"Only the dead have no stress" Hans Selye



98 NATURE JULY 4, 1936

A Syndrome produced by Diverse Nocuous Agents

Experimenters on rats show that if the organism is severely damaged by acute non-specific noxious agents such as exposure to cold, surgical injury, production of spinal shock (transection of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.

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Hans Selye (1952) The story of the adaptation syndrome
http://www.endocrus.com/Textbook/Selye1952.pdf

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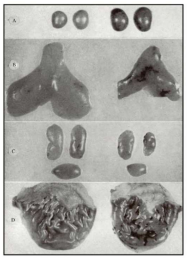
STRESS: "The sum of all forces that act against a resistance" Hans Selye



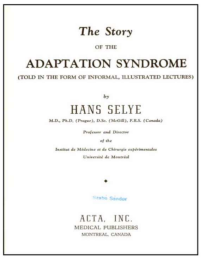


Figure 4. The typical triad of the "general alarm reaction". (A) adrenals, (B) thymus, (C) iliac lymph nodes, and (D). gastric mucosa of a normal rat (left) and one which was exposed to the frustrating mental stress of being immobilized on a metal board for 24 h. Note the marked enlargement of the adrenals (which also showed lipid discharge and hyperemia, and consequently became reddish-brown), the intense atrophy of the thymus and lymph nodes and the numerous blood-covered gastric erosions in the stressed rat (right; modified from Selye 1952).

The syndrome develops in 3 stages:

1) Alarm reaction (6-48hrs): Shrinkage of thymus, spleen, lymph nodes and liver; fat tissue disappears; oedema formation (thymus and retroperitoneal connective tissue); fall of body temperature; acute erosions in the digestive tract (stomach/peptic ulcers); loss of chromaffin from adrenals

2) Resistance (after 48hrs; if treatment not too severe): adreanals are greatly enlarged; animal seems to cope with the situation, all organ functions return to normal

3) Exhaustion (depending on noxious stimulus; >1month): sympotms similar to «alarm reaction»; disease, death

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STRESS DEFINITION: "The sum of all forces that act against a resistance" Hans Selye

All vital physiologic systems of the body are inherently programmed, through rigorous fine-tuning achieved during evolution, to preserve a predefined steady state, *i.e. homeostasis*, which is essential for life and well-being.

Homeostasis is constantly challenged by adverse forces which are intrinsic or extrinsic, real or even perceived, and are described as *stressors*. Thus, *stress* is defined as a state of disharmony, *i.e. allostasis*.

The organism counteracts stress through an intricate repertoire of physiologic and behavioral responses which aim to maintain/reestablish the threatened homeostasis (*adaptive stress response*).

For interested readers, lots of detail:
https://www.ncbi.nlm.nih.gov/books/NBK278995/
Tsigos et al (2016) Endotext: Stress, Endocrine Physiology and Pathophysiology

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Central Nervous System

Autonomic nervous system = visceral motor system (formerly «vegetative nervous system»)

Viszera (Eingeweide)

Parasympathetic division | Sympathetic division

1) Controls involuntary functions: smooth muscle fibers, cardiac muscle fibers, glands
2) Noradrenaline = Norepinephrine (sympathetic); Acetylcholine (parasympathetic); co-neurotransmitters; neuropeptides (many varied effects on visceral muscles) → **homeostasis**
3) Hypothalamus
4) Cell bodies of lower motor neurons are located outside the central nervous system in **autonomic ganglia**
5) Contacts between visceral motor neurons and the viscera are not highly branched and structurally variable. Neurotransmitters often diffuse over hundreds of microns before binding postsynatpic receptors.

Somatic nervous system

1) Controls skeletal muscles
2) Acetylcholine

3) Primary motor cortex; Premotor cortex
4) Cell bodies of lower motor neurons are located in the ventral horn of the spinal cord gray matter and in the motor nuclei of the cranial nerves in the brainstem

Unteres (oder 2.) Motoneuron

5) Neuromuscular junctions of the somatic motor system (motor endplate) are highly differentiated (lots of branches), and have a highly ordered structure (30nm synaptic cleft)

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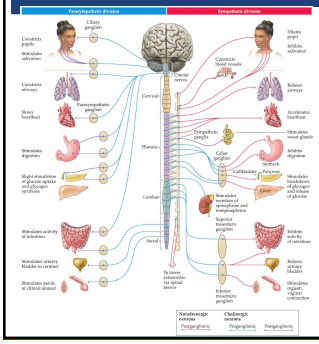


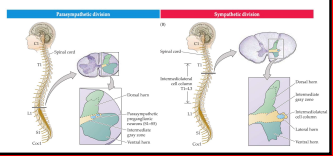
Sympathetic vs Parasympathetic Division

Preganglionic neurons are located in…

Thorakal- und Lumbalmark

- the thoracic-lumbar segments of the spinal cord (sympathetic) -
- the brainstem and sacral part of spinal cord (parasympathetic)

Cell bodies of lower motor neurons are located outside the central nervous system in **autonomic ganglia** either close to the spinal cord (sympathetic) or embedded in neural plexus (network of intersecting nerves) near or inside the target organ (parasympathetic and enteric divisions).



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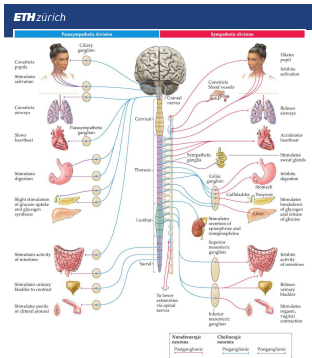

High levels of sympathetic activity: FIGHT or FLIGHT

1. pupils dilate and the eyelids retract (allowing more light to reach the retina and the eyes to move more efficiently)
2. blood vessels of the skin and gut constrict (rerouting blood to muscles, thus allowing them to extract a maximum of available energy)
3. hairs stand on end (making our hairier ancestors look more fearsome)
4. bronchi dilate (increasing oxygenation)
5. heart rate accelerates and the force of cardiac contraction is enhanced (maximally perfusing skeletal muscles and the brain
6. the adrenal medulla releases epinephrine and norepinephrine into the bloodstream and mediates the release of glucagon from the pancreas, further enhancing energy-mobilizing (catabolic) functions.
7. Digestive and other vegetative functions become quiescent (thus diminishing activities that are temporarily unnecessary)

lec: study this slide in detail

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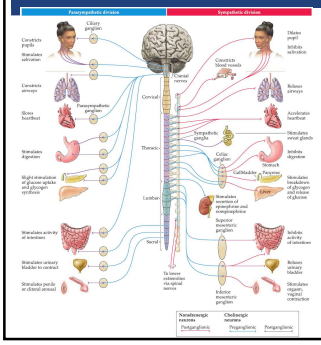
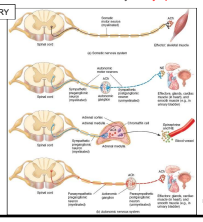


High levels of parasympathetic activity: REST & DIGEST

1. Pupils constrict
2. Heartrate slows down
3. Peristaltic activity of the gut increases
4. Voiding of the bladder is promoted

Most organs are innervated by both branches, BUT:
sweat glands, adrenal medulla, piloerector muscles of the skin and most arterial blood vessels are ONLY innervated by the sympathetic division

SUMMARY



summary: important

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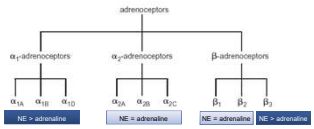
One neurotransmitter – multiple effects on target tissues

The effects of (nor)epinephrine are dependent on the receptors expressed in the target tissue



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One neurotransmitter – multiple effects on target tissues

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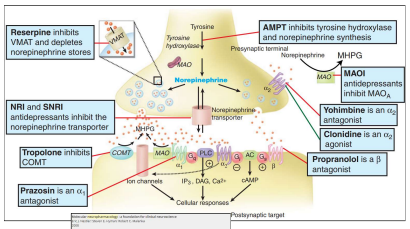

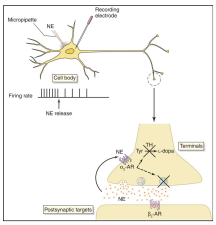

...and on where they are expressed (within the circuit)

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the details of this slide are not important

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One neurotransmitter – multiple effects on target tissues

The effects of NE are dependent on the receptors expressed in the target tissue

Group Exercise
(hidden)

see purves table 21.2

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Group Exercise
(hidden)

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15 min break

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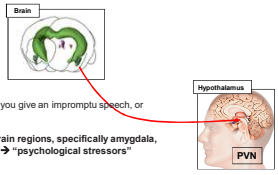
Understanding the stress response

Sympathetic nervous system to a large degree **controlled by reflex arcs between brainstem, medulla and preganglionic sympathetic neurons** (monitoring and responding to blood loss, respiratory distress, pain, inflammation)

→ This does not explain why you start sweating and get cold hands when you give an impromptu speech, or when someone stops you at gunpoint

The sympathetic nervous system can also be activated from higher brain regions, specifically amygdala, which excites the paraventricular nucleus (PVN) of the hypothalamus → "psychological stressors"



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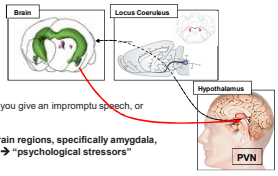
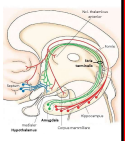


Stress perception: Amygdala → Stria terminalis → Hypothalamus (PVN)
Bed nucleus of the stria terminalis → key «limbic» hub that activates the PVN

1)PVN activates CRH-containing neurons → Locus Coeruleus (release of brain noradrenaline)

2)PVN triggers sympathetic nervous system (release of Adrenaline/Epinephrine)

3)PVN triggers HPA axis (release of Cortisol/corticosterone)



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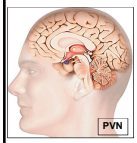
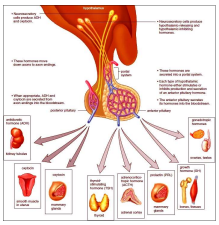
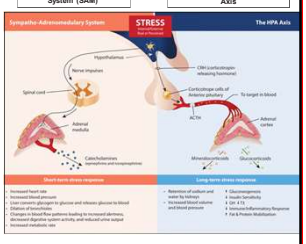
Understanding the stress response – PVN, SAM and HPA-Axis





Sympatho-Adrenomedullary System (SAM)

Hypothalamus-Pituitary-Adrenal Axis



2)PVN triggers sympathetic nervous system (release of Adrenaline/Epinephrine)

3)PVN triggers HPA axis (release of Cortisol/corticosterone)

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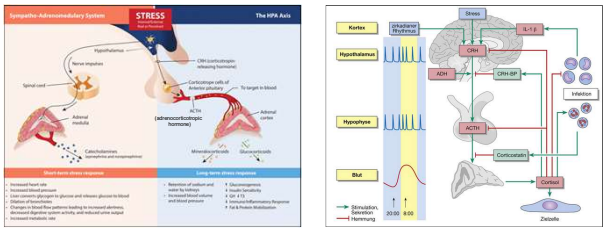
HPA Axis



HPA axis activation results in release of coritsol (corticosterone in rodents). However, many stimuli trigger corticosterone release, like sex.
CORTISOL ≠ STRESS

circadian rhythm: before waking up (naturally), corticosterone/cortisol goes up to prime the body for activity

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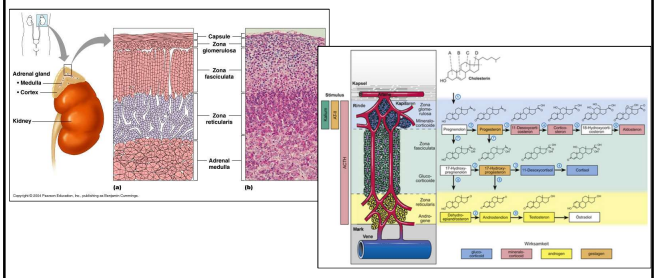
Steroidogenesis in the Adrenal Gland



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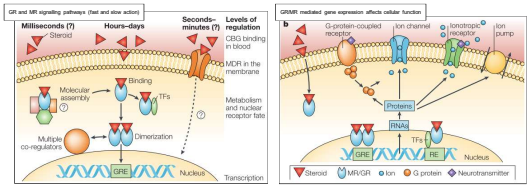
Effect of Corticosterone on target tissues



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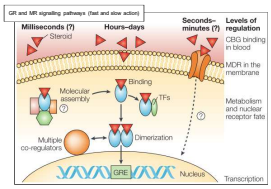
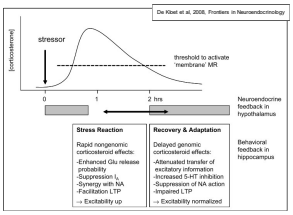
Effect of Corticosterone on target tissues





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Effects of cortisol / corticosterone (chronic stress = bad)

Metabolism: Provide energy for sustained activity

- Stimulates gluconeogenesis (liver)
- Inhibits glucose uptake in fat and muscle cells, increasing blood sugar levels
- Inhibits lipogenesis
  - Simultaneously, catecholamines stimulate lipolysis → increase in free fatty acids → production of ATP for gluconeogenesis

→ The katabolic effects of cortisol have unwanted consequences if Cort-levels stay high for long, e.g. muscle atrophy

Blood: Cort facilitates thrombosis and blood clotting

Immune system: Cort suppresses both adaptive and innate immunity

- Suppresses monocytes, lymphocytes, and production of antibodies
- Blocks cytokines, inhibits pro-inflammatory signaling in target organs/tissues, inhibits prostaglandin synthesis (immunusuppresive and antinflammatory effects)
  - → That's why Cort is used in the clinic to treat allergic reactions, autoimmune diseases, or to suppress the immune response after organ transplants

Psychische Effekte: Chronically elevated Cort levels increase the risk of depressive disorders (Cushing-syndrom, typically results from tumor in the ACTH-producing cells of the pituitary gland, morbus cushing)

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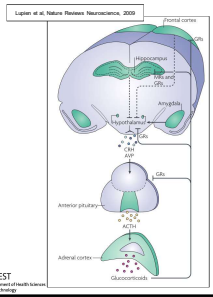
Feedback inhibition of the HPA-axis



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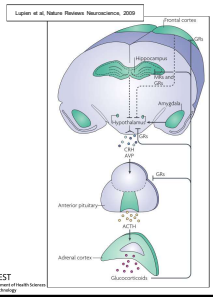
Feedback inhibition – shutting down the stress response

Lupien et al, Nature Reviews Neuroscience, 2009



Weaver et al, Nature Neuroscience 2004

High Licking/Grooming → HIGH maternal care

Low Licking/Grooming → LOW maternal care

Weaver et al, Nature Neuroscience 2004

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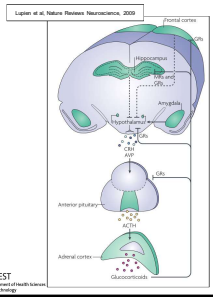
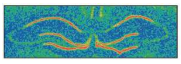
Negative Feedback – shutting down the stress response

Lupien et al, Nature Reviews Neuroscience, 2009

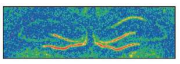


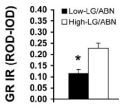
Weaver et al, Nature Neuroscience 2004

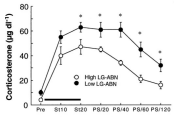
HIGH maternal care



LOW maternal care







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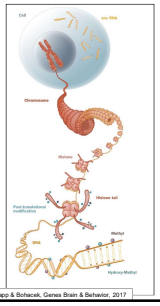
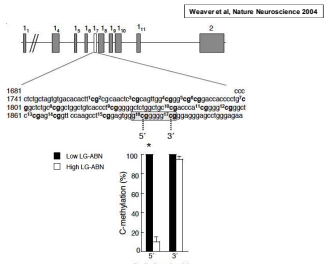
Negative Feedback – shutting down the stress response



Gapp & Bohacek, Genes Brain & Behavior, 2017

Weaver et al, Nature Neuroscience 2004



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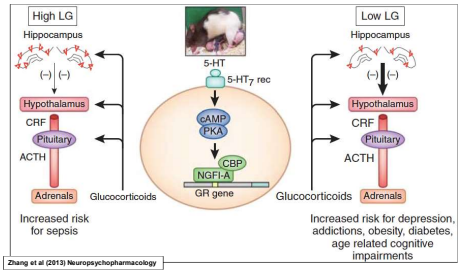
Negative Feedback – shutting down the stress response



Zhang et al (2013) Neuropsychopharmacology

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The End.