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Stres a všeobecný adaptační syndrom

Embryolog – seminář – 9. 12. 2024

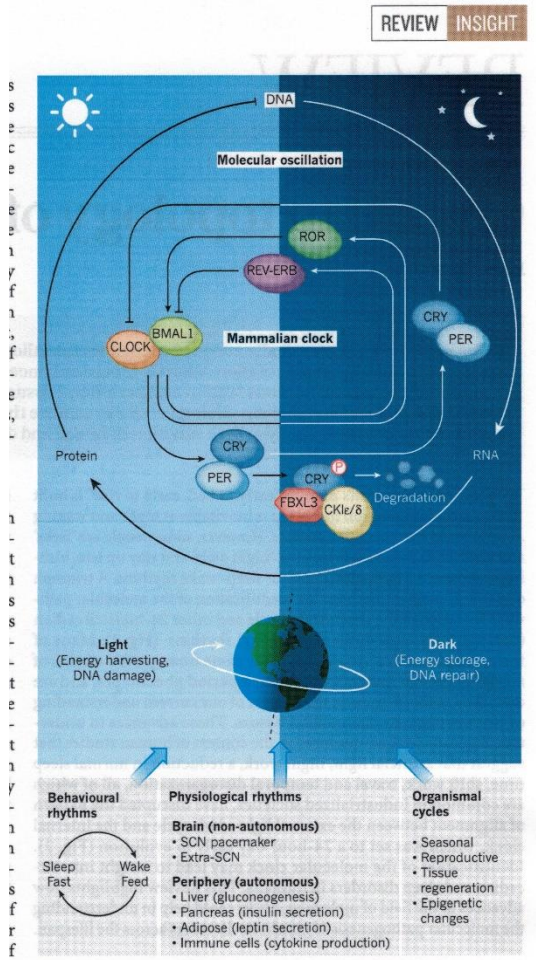
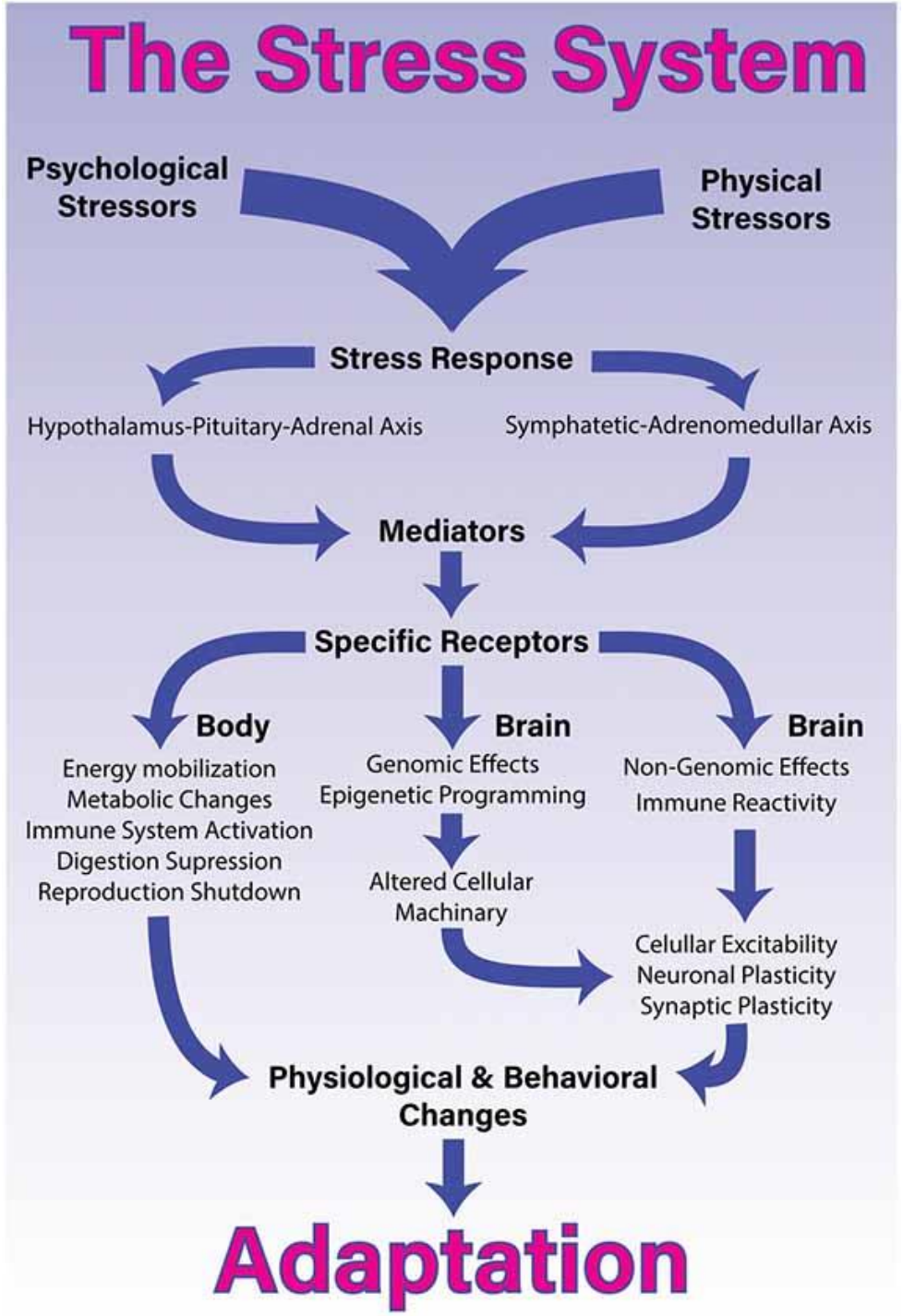


Figure 1 | Circadian adaptation as a unifying model that integrates behaviour and physiology. The circadian clock allows light-sensitive organisms to synchronize their daily molecular oscillations, behavioural rhythms, physiological rhythms and organismal cycles with the rotation of Earth on its axis. Core molecular pathways dictate behavioural and physiological cycles. This core molecular clock in mammals, expressed both in brain and peripheral metabolic tissues, comprises a series of transcription–translation feedback loops that include opposing transcriptional activators (CLOCK–BMAL1) and repressors (PER–CRY)[1]. The non-phosphorylated PER–CRY complex represses CLOCK–BMAL1; phosphorylation, in turn, results in the degradation of PER–CRY and the turnover of these repressors. In addition, CLOCK–BMAL1 induces transcription of REV-ERB and of ROR, which regulate BMAL1 expression. During the night, PER–CRY is degraded through the ubiquitylation of CRY by FBXL3. The circadian clock coordinates anabolic and catabolic processes in peripheral tissues with the daily behavioural cycles of sleep–wake and fasting–feeding. SCN, suprachiasmatic nucleus.

Hans Selye

- ***A syndrome produced by diverse nocous agents, Nature 138, 32, 1936***

„General adaptation syndrome-stress reaction of organism:
Experiments with animals showed that different toxic substances applied into the organisms led to stereotyped response explicable by suprarenal gland activation“.


The Stress System
Psychological Stressors
Physical Stressors
Stress Response
Hypothalamus-Pituitary-Adrenal Axis
Symphatetic-Adrenomedullar Axis
Mediators
Specific Receptors
Body
Energy mobilization
Metabolic Changes
Immune System Activation
Digestion Supression
Reproduction Shutdown
Brain
Genomic Effects
Epigenetic Programming
Altered Cellular Machinary
Brain
Non-Genomic Effects
Immune Reactivity
Celullar Excitability
Neuronal Plasticity
Synaptic Plasticity
Physiological & Behavioral Changes
Adaptation

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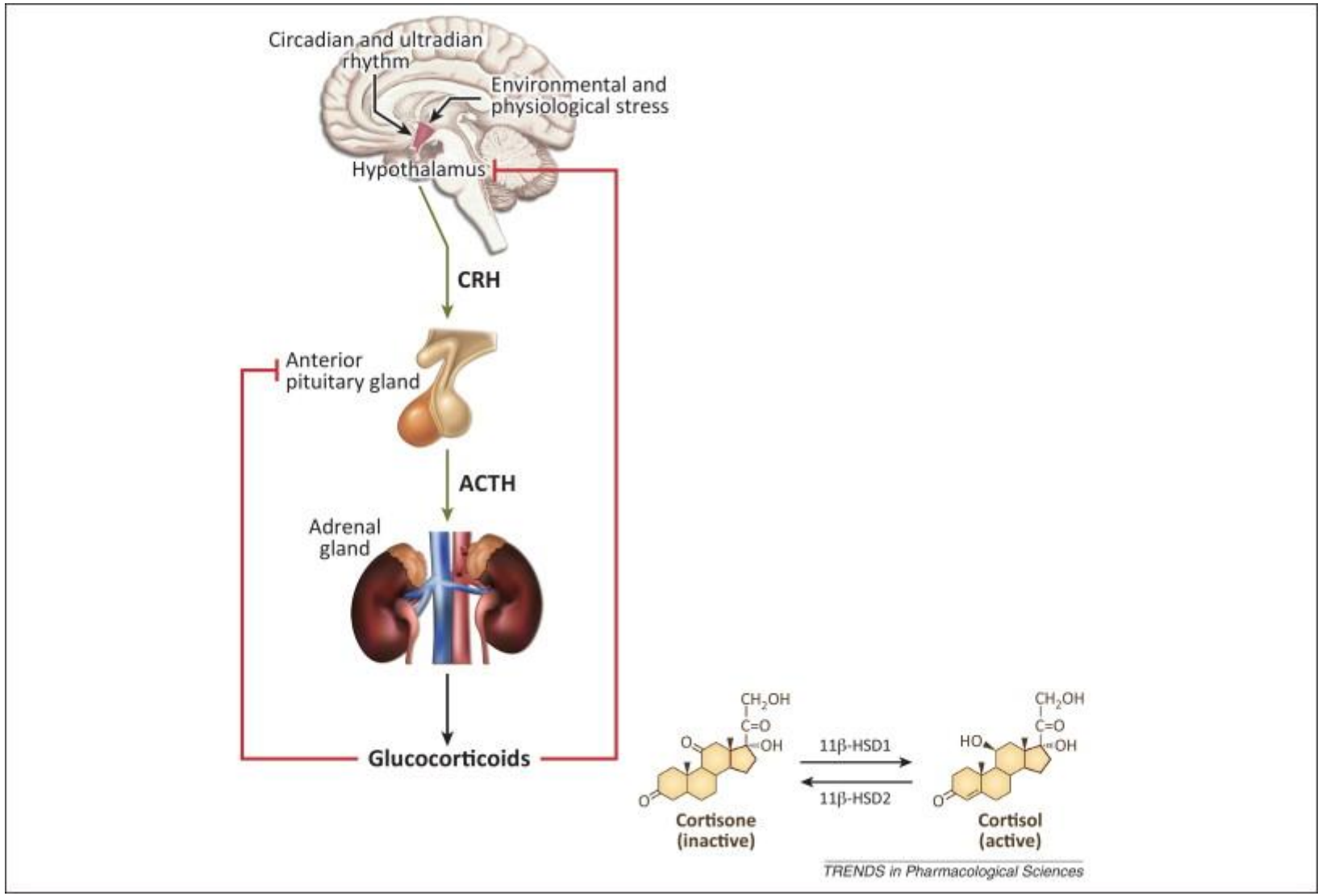
Circadian and ultradian rhythm
Environmental and physiological stress
Hypothalamus
CRH
Anterior pituitary gland
ACTH
Adrenal gland
Glucocorticoids
CH2OH
C=O
OH
O
11β-HSD1
11β-HSD2
HO
Cortisone (inactive)
Cortisol (active)
TRENDS in Pharmacological Sciences

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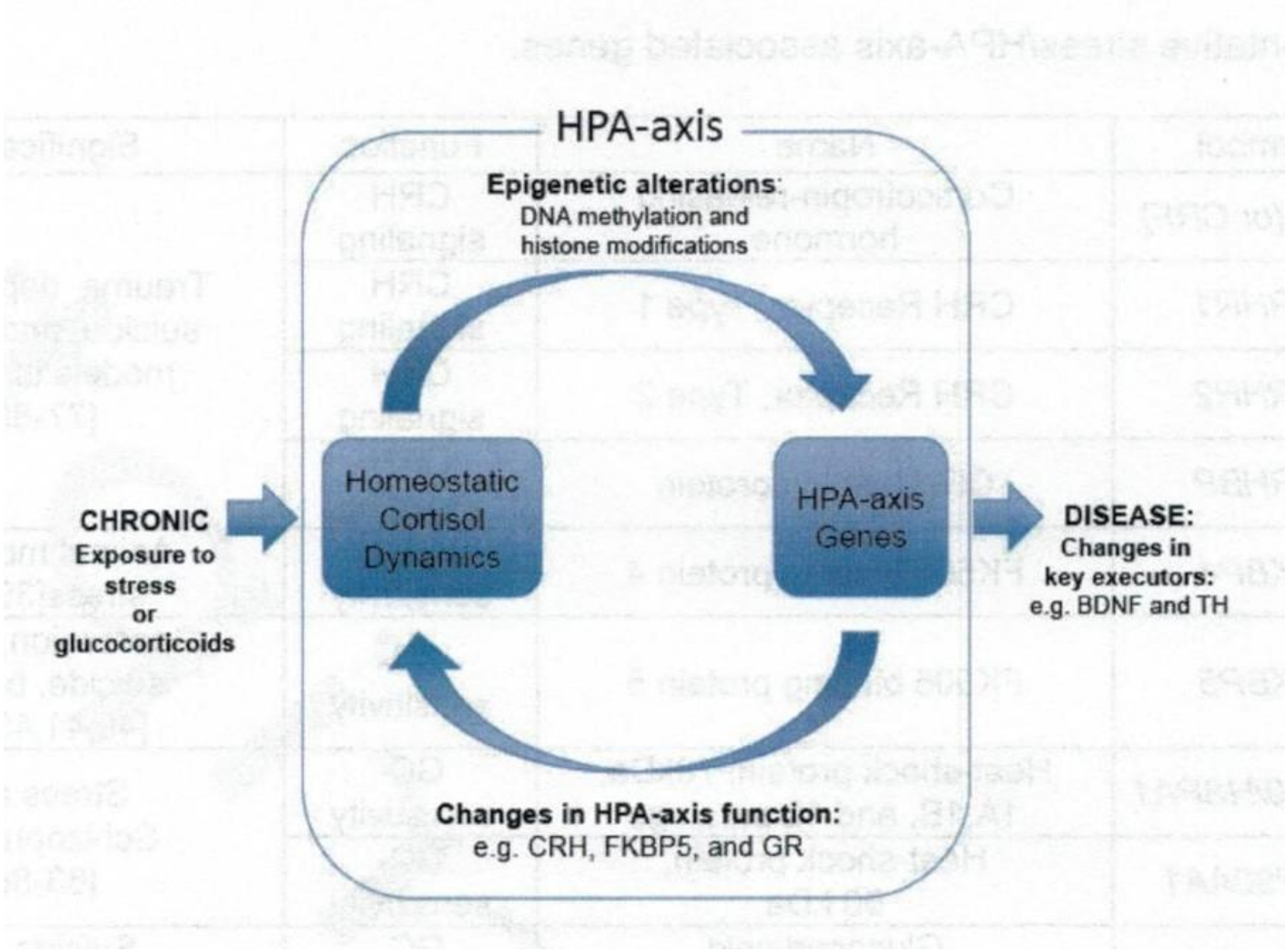
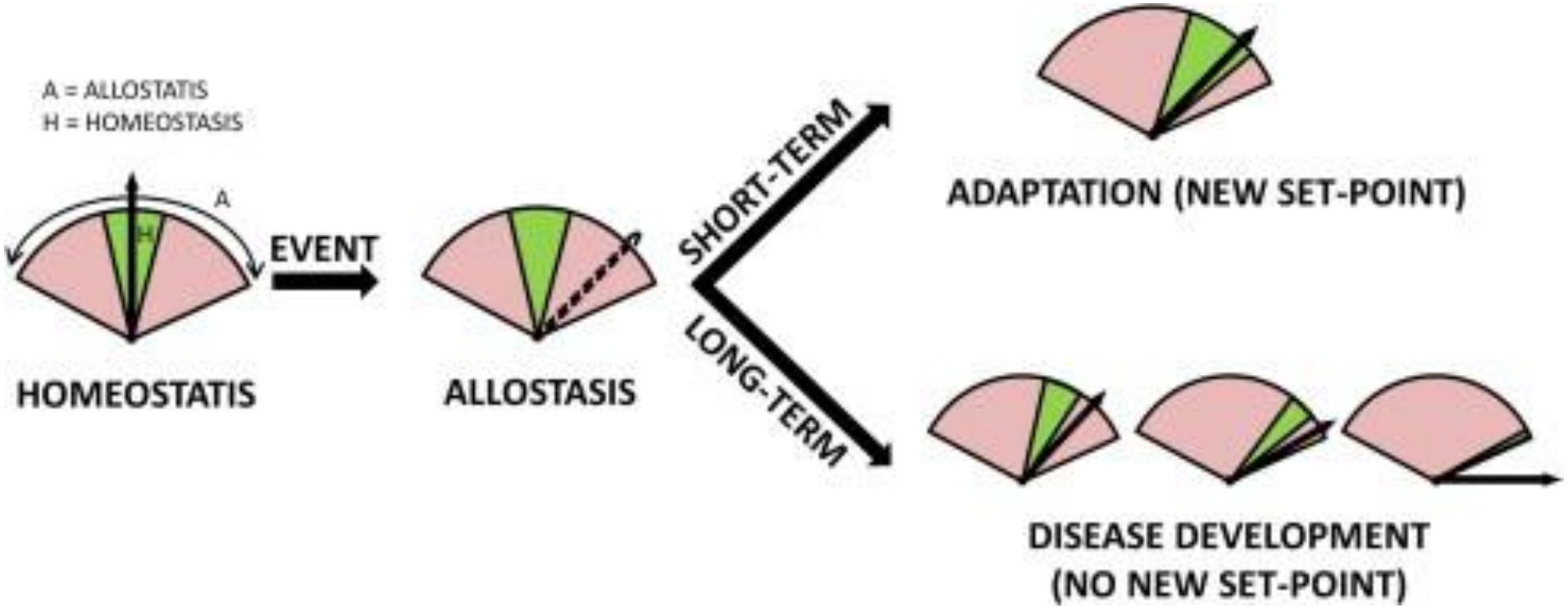
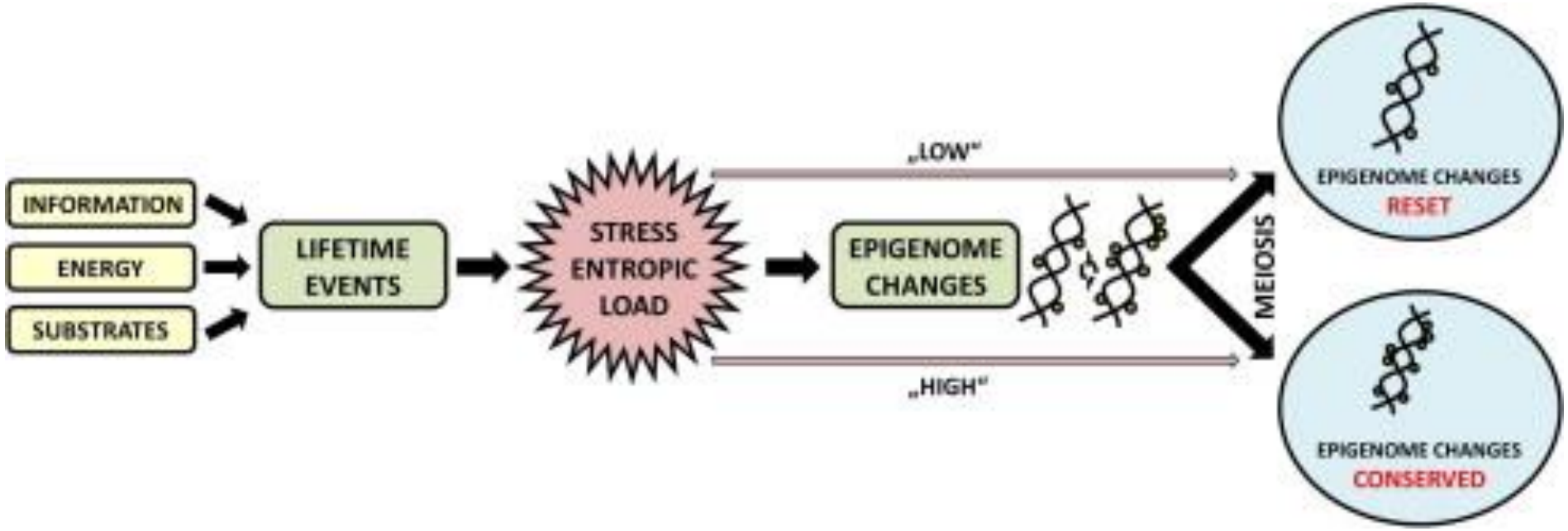

HPA-axis
Epigenetic alterations:
DNA methylation and
histone modifications
CHRONIC
Exposure to
stress
or
glucocorticoids
Homeostatic
Cortisol
Dynamics
HPA-axis
Genes
DISEASE:
Changes in
key executors:
e.g. BDNF and TH
Changes in HPA-axis function:
e.g. CRH, FKBP5, and GR

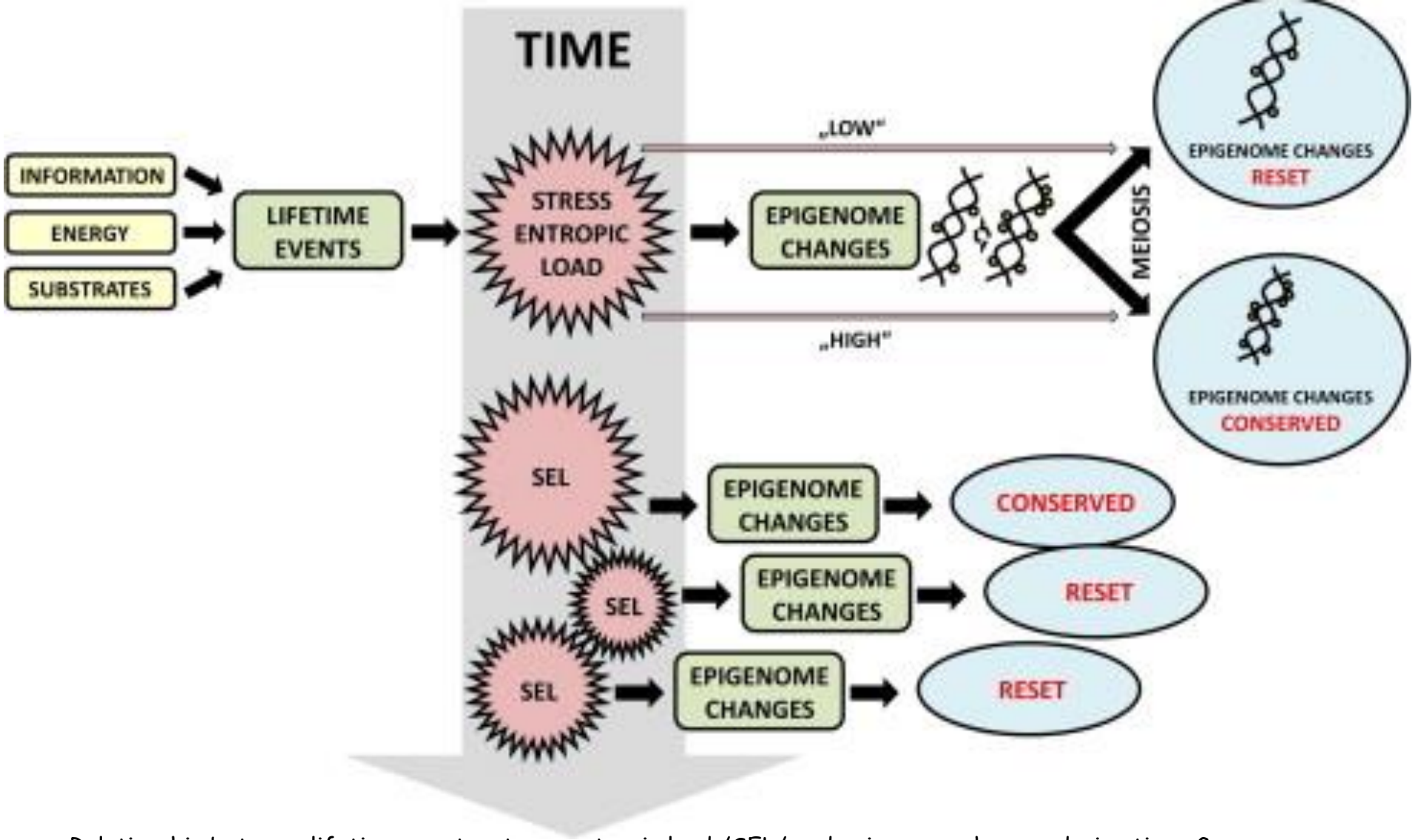


Med Hypotheses. 2014 Mar;82(3):271-4. doi: 10.1016/j.mehy.2013.12.008. Epub 2013 Dec 19.
"Stress entropic load" as a transgenerational epigenetic response trigger.
Bienertová-Vašků J[1], Nečesánek I[2], Novák J[2], Vinklárek J[2], Zlámal F[2].



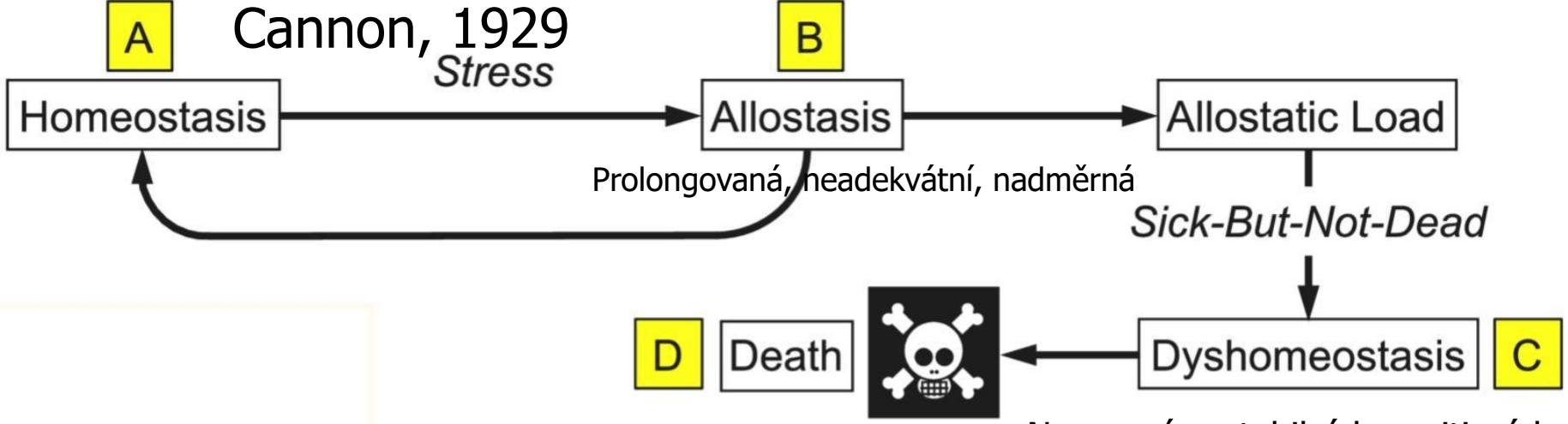
Relationship between lifetime events, stress entropic load (SEL) and epigenome changes. Lifetime events represent those events that influence the flow of energy, substrates and information within the body. Generally, the organism has to cope with these changes, whereas we consider SEL to be the universal parameter reflecting the "severity" of the influencing events. SEL therefore leads to epigenome changes that are according to SEL "severity" either conserved or reset during meosis and thus passed transgenerationally or not.

Med Hypotheses. 2014 Mar;82(3):271-4.
"Stress entropic load" as a transgenerational epigenetic response trigger.
Bienertová-Vašků J[1], Nečesánek I[2], Novák J[2], Vinklárek J[2], Zlámal F[2].



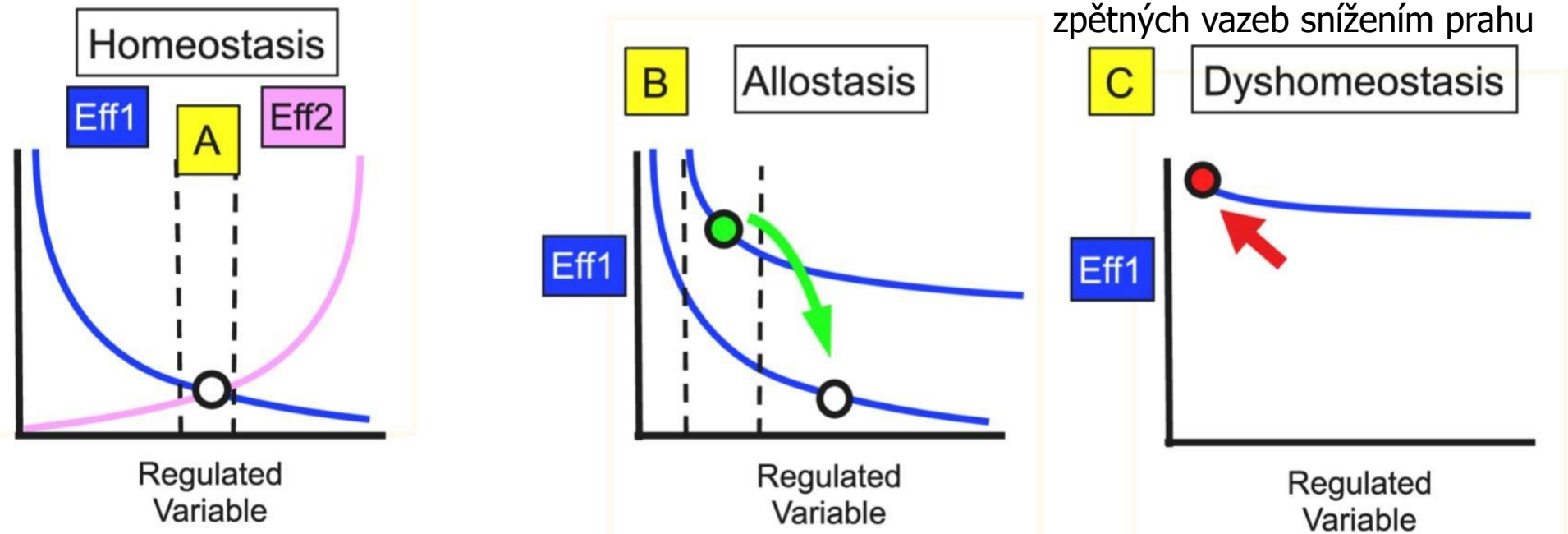
Relationship between lifetime events, stress entropic load /SEL/ and epigenome changes during time. Grey arrow represents the time flow and it should suggest that as time passes, different events are evaluated differently and their associated SEL level may consecutively increase or decrease and thus affect whether the epigenomic changes are passed to other generation or not.

Med Hypotheses. 2014 Mar;82(3):271-4. "Stress entropic load" as a transgenerational epigenetic response trigger.
Bienertová-Vašků J[1], Nečesánek I[2], Novák J[2], Vinklárek J[2], Zlámal F[2].

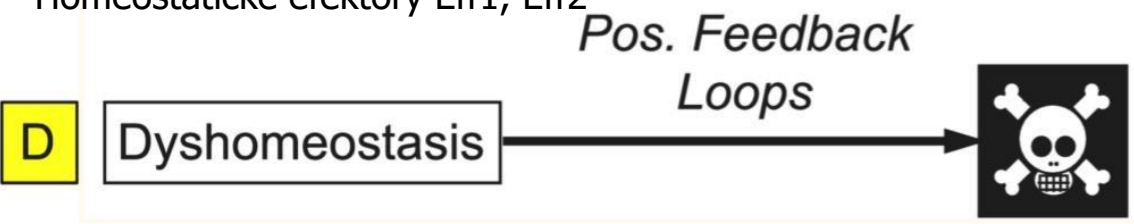


Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

Navození nestabilních pozitivních zpětných vazeb snížením prahu



Homeostatické efektory Eff1, Eff2



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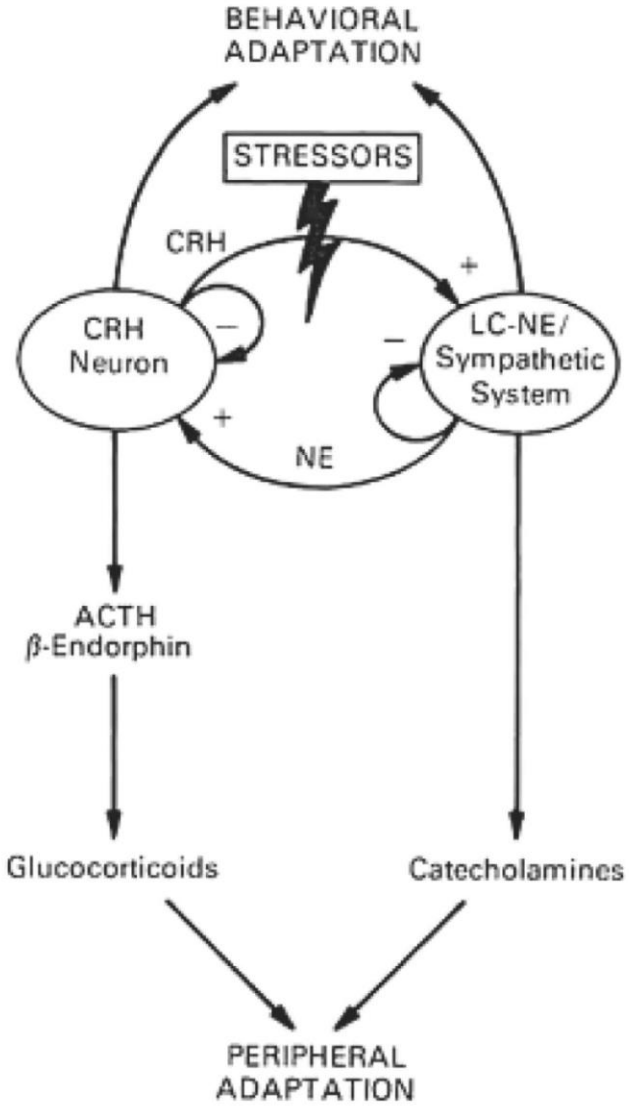

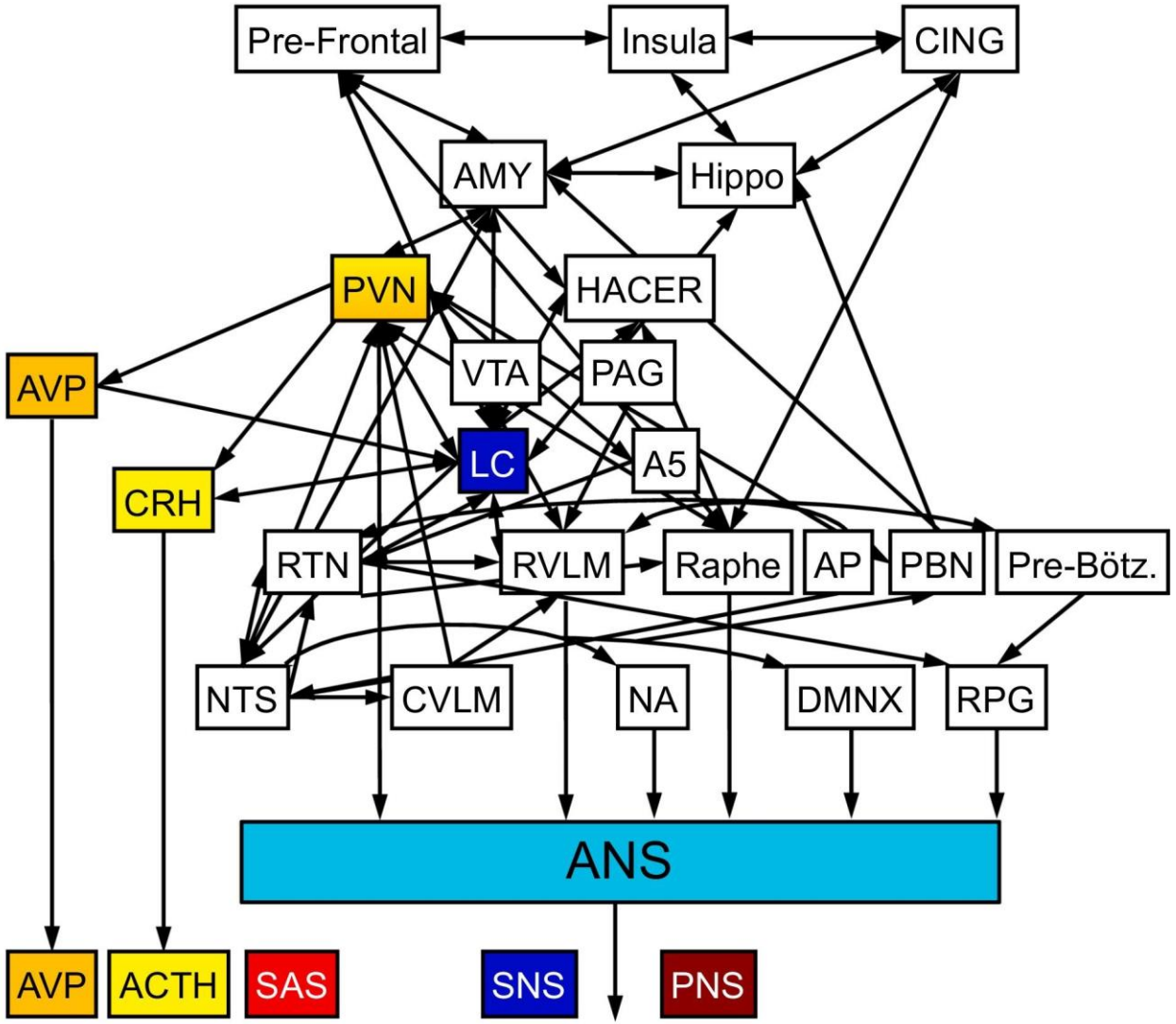

Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

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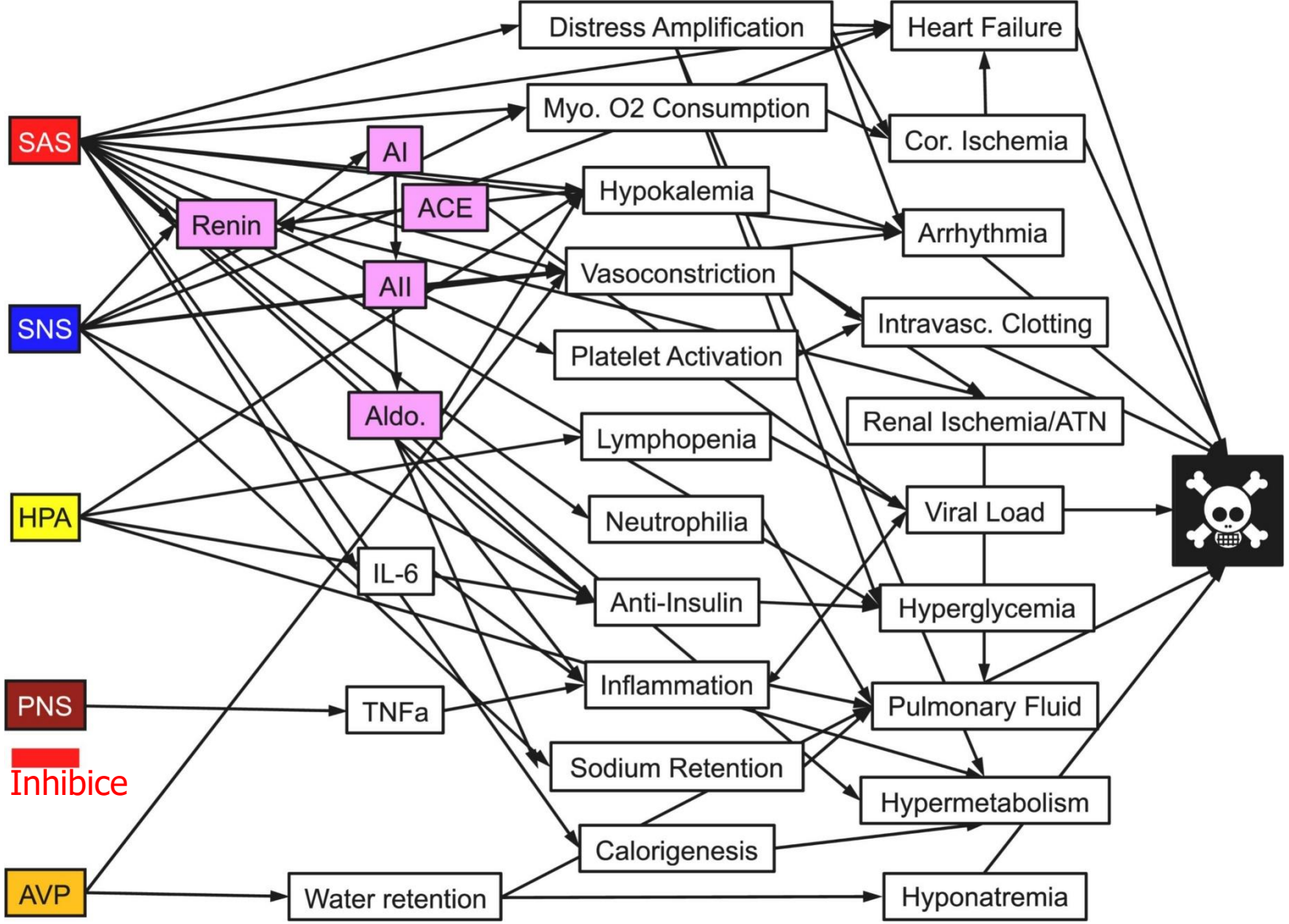
Overview of extended autonomic system (EAS)

- The EAS is conceptualized to consist of the central autonomic network (CAN);Langley's autonomic nervous system (ANS), with its three component sub-systems the sympathetic nervous system (SNS), parasympathetic nervous sys-tem (PNS), and enteric nervous system (ENS); neuroendocrine systems including the arginine vasopressin (AVP) system, hypothalamic-pituitary-adrenocortical (HPA) system, sympathetic adrenergic system (SAS), and renin-angiotensin-aldosterone system (RAS); and immune/inflammatory systems, represented by a stylized mast cell. Langley's SNS involves three chemical messengers, norepinephrine (sympathetic noradrenergic system, abbreviated as SNS in this review), acetylcholine (sympathetic cholinergic system), and epinephrine (SAS).

Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889

Od aktivace stresového systému k dyshomeostáze a smrti



Efektory CNS

Intervenující proměnné

Faktory přispívající ke chronickému onemocnění nebo smrti

Goldstein DS. Stress and the "extended" autonomic system. Auton Neurosci. 2021 Oct 2;236:102889.

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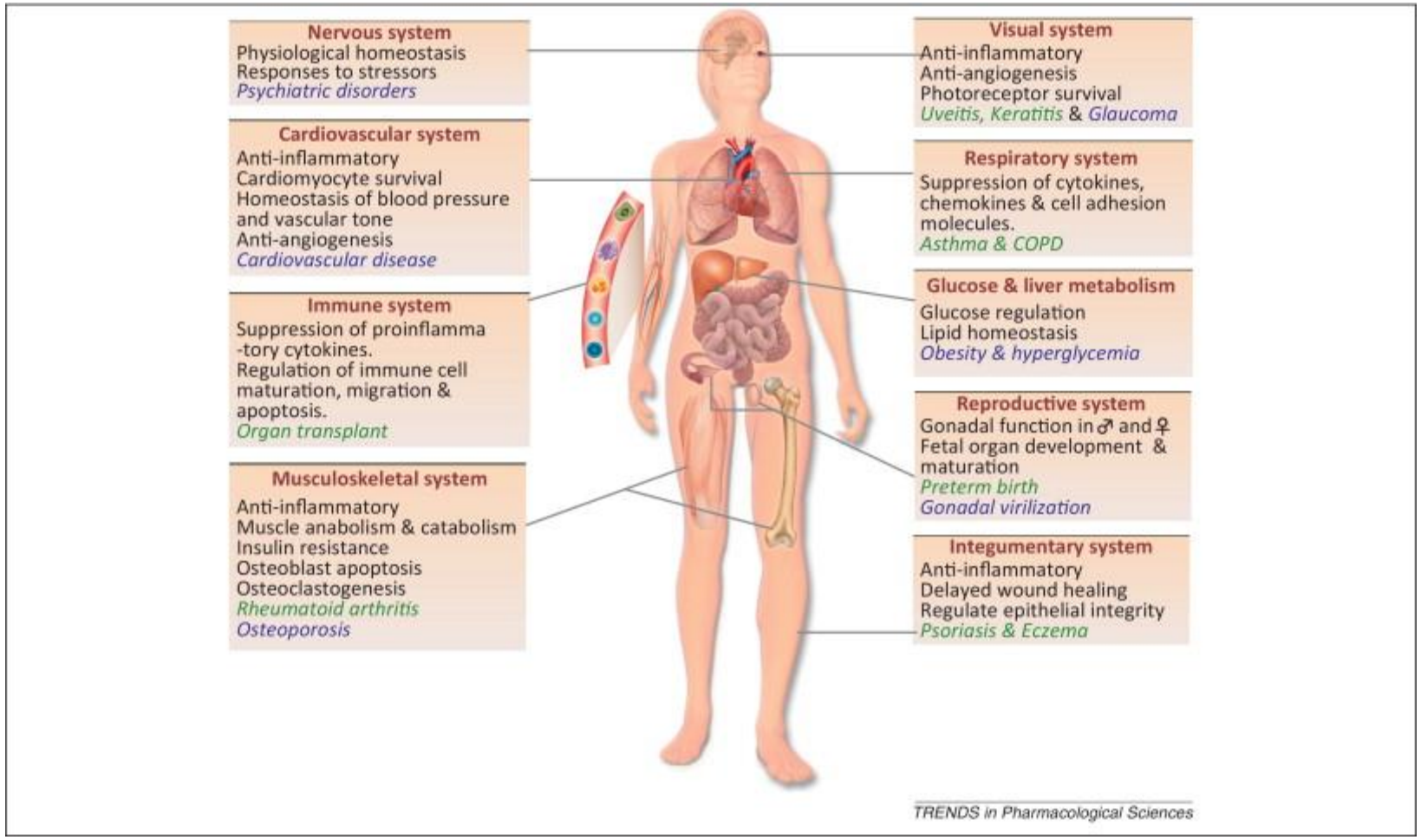

Účinky glukokortikoidů na tělní systémy

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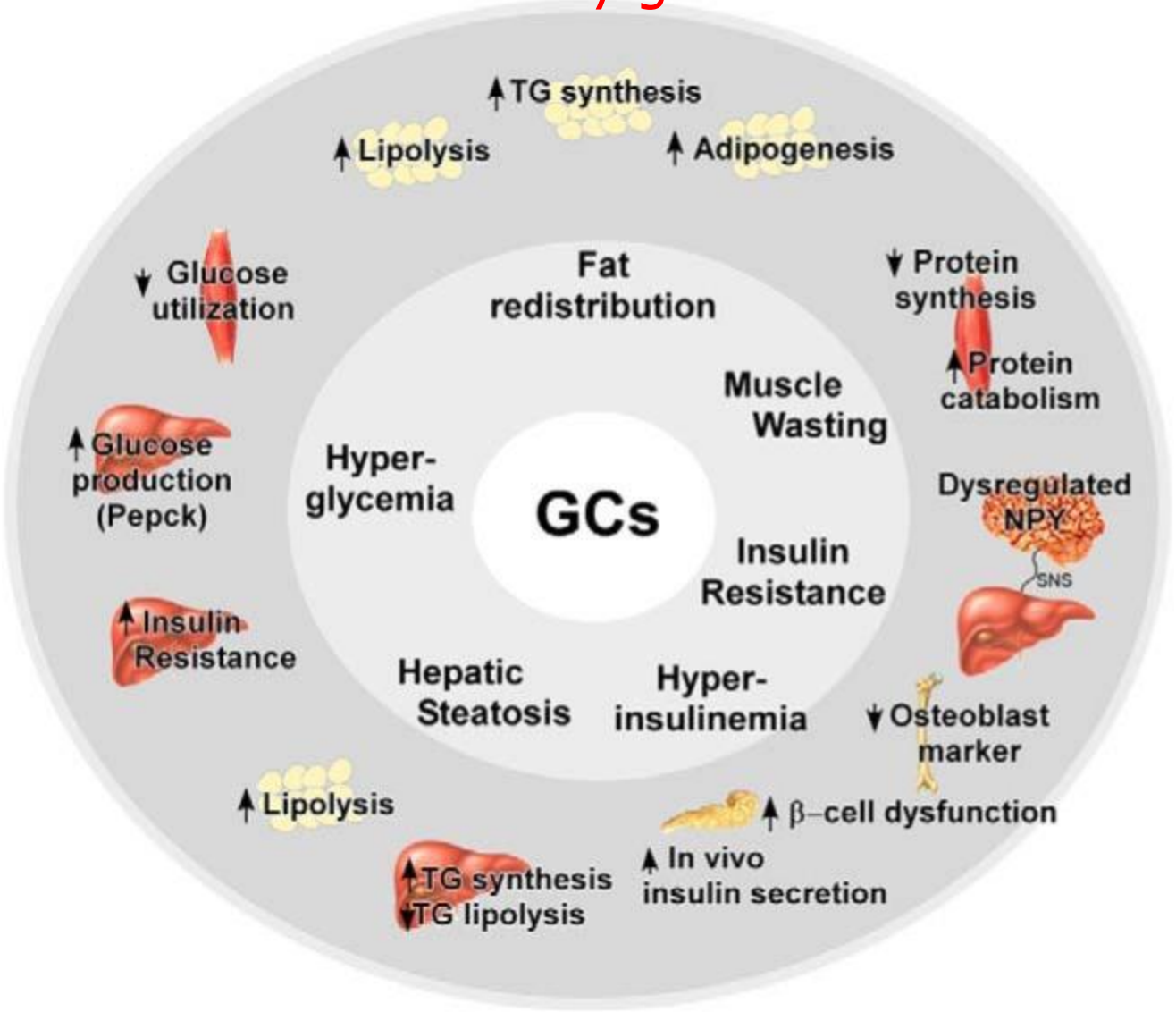
Metabolické účinky glukokortikoidů



Patel R et al., Mol Endocrinol. 2014 Jul; 28(7): 999–1011.

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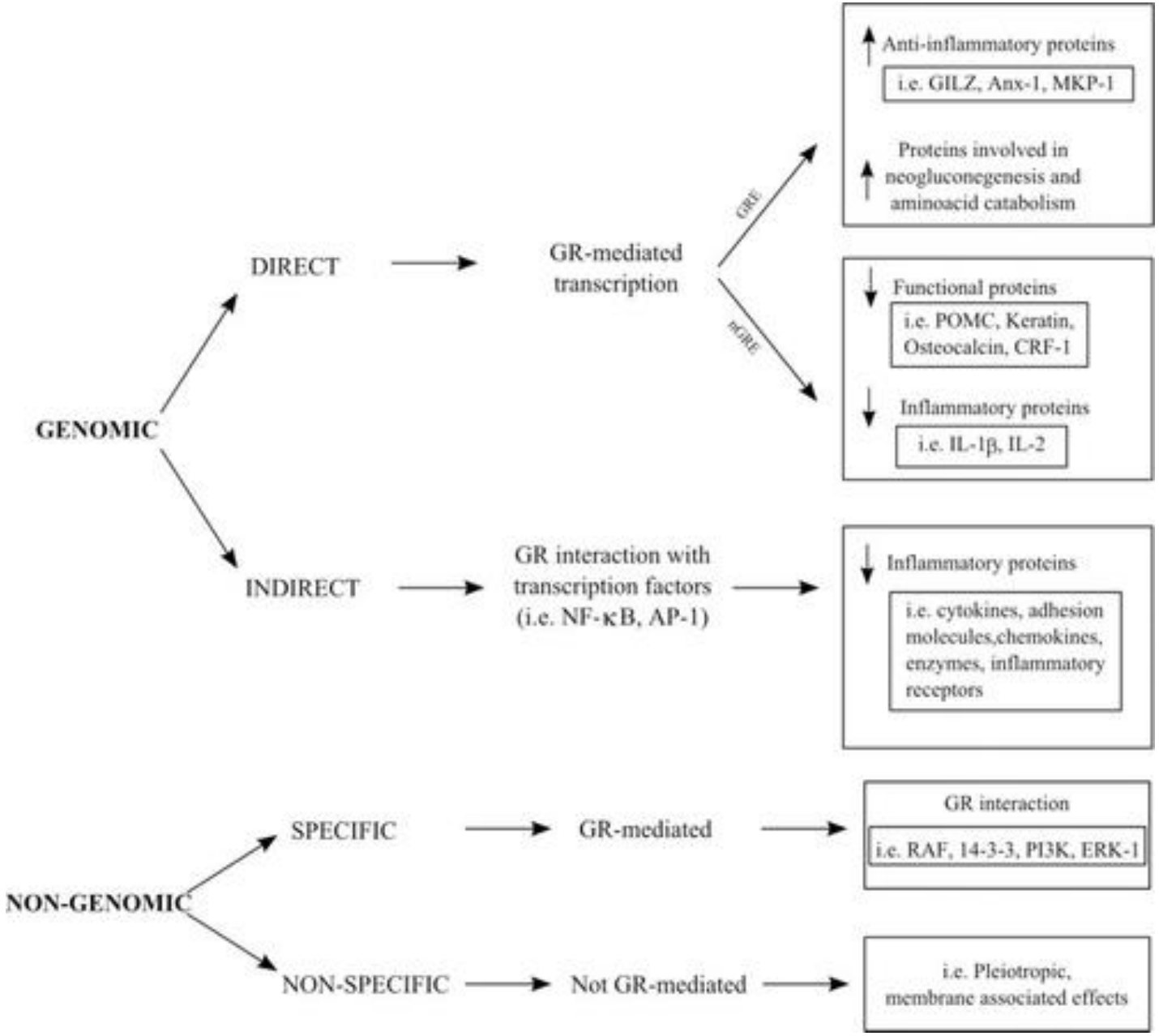
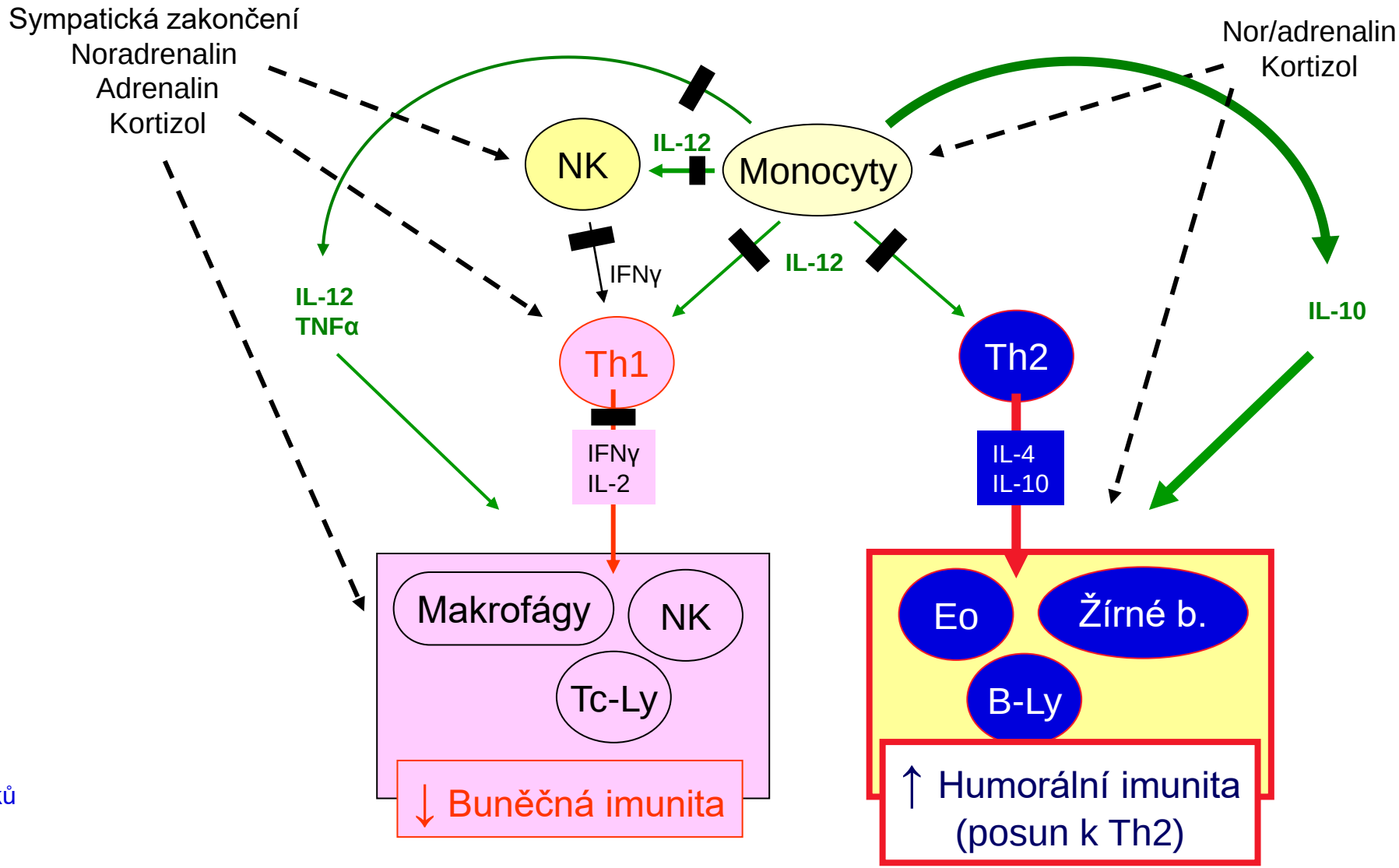


Genomové a negenomové účinky kortikoidů

Patel R et al., Mol Endocrinol. 2014 Jul; 28(7): 999–1011

Rovnováha Th1 a Th2 a stres



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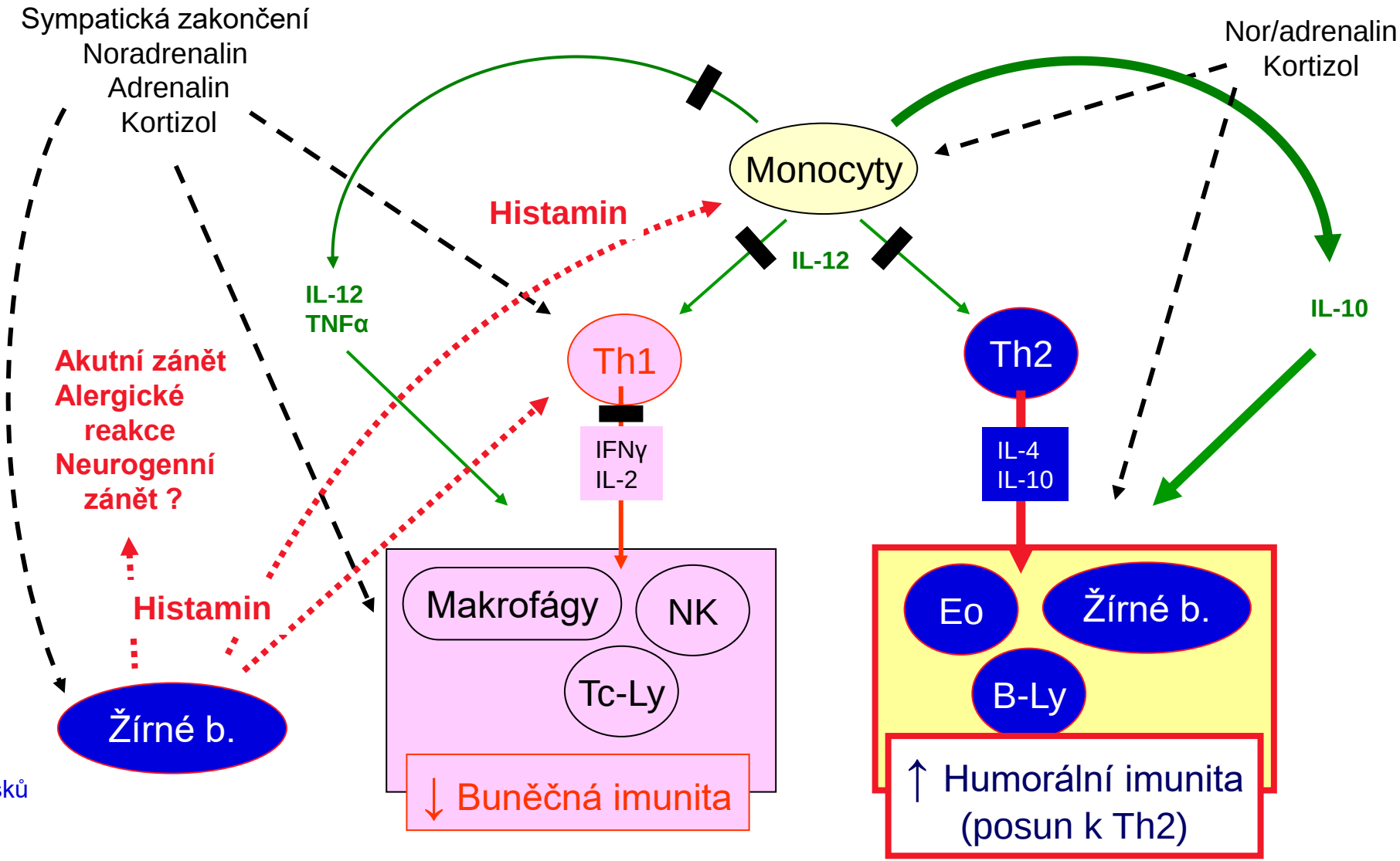
Rovnováha Th1 a Th2, stres a akutní zánět



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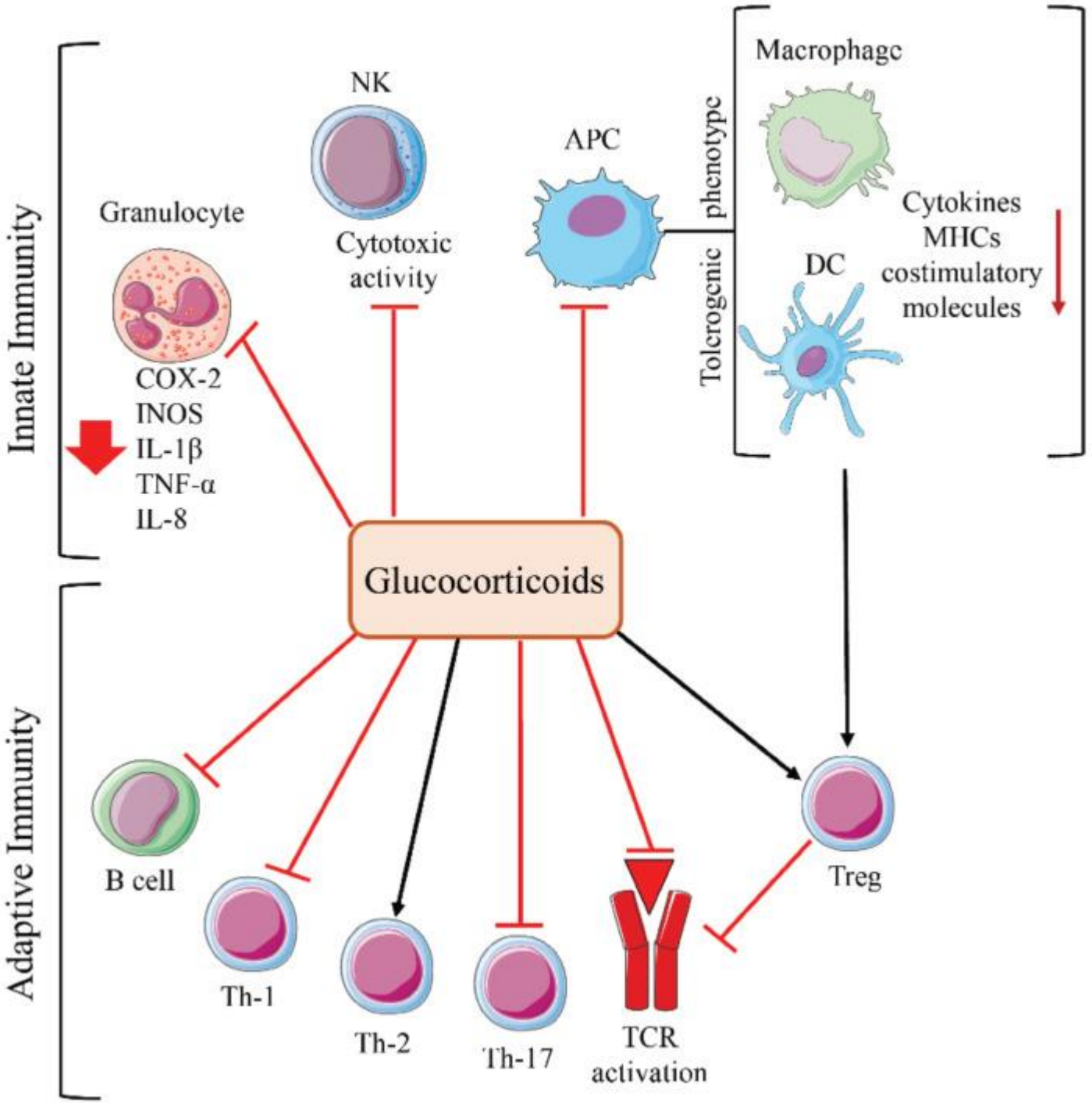

Adorisio S. Cells. 2021 Sep; 10(9): 2333.

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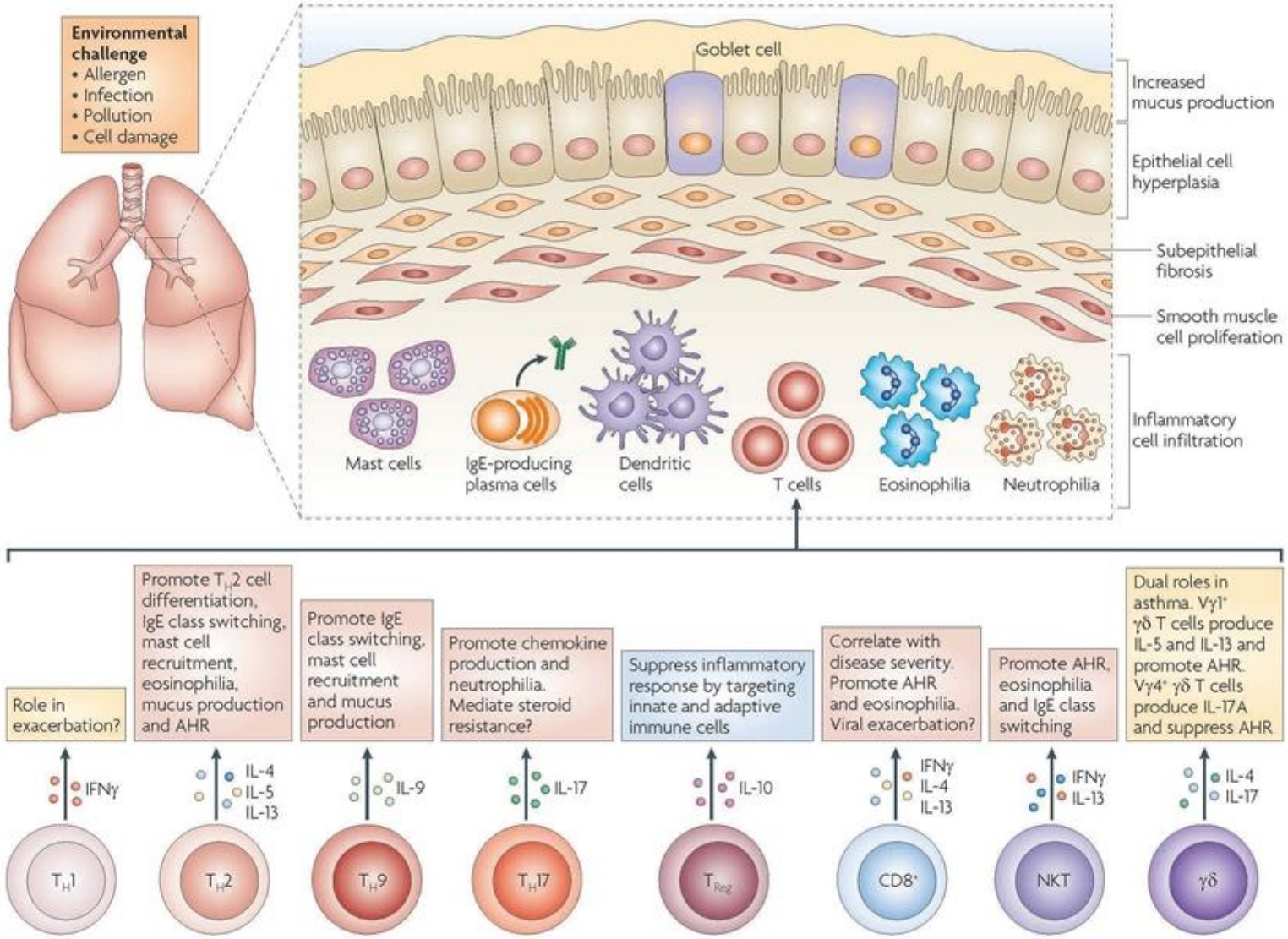
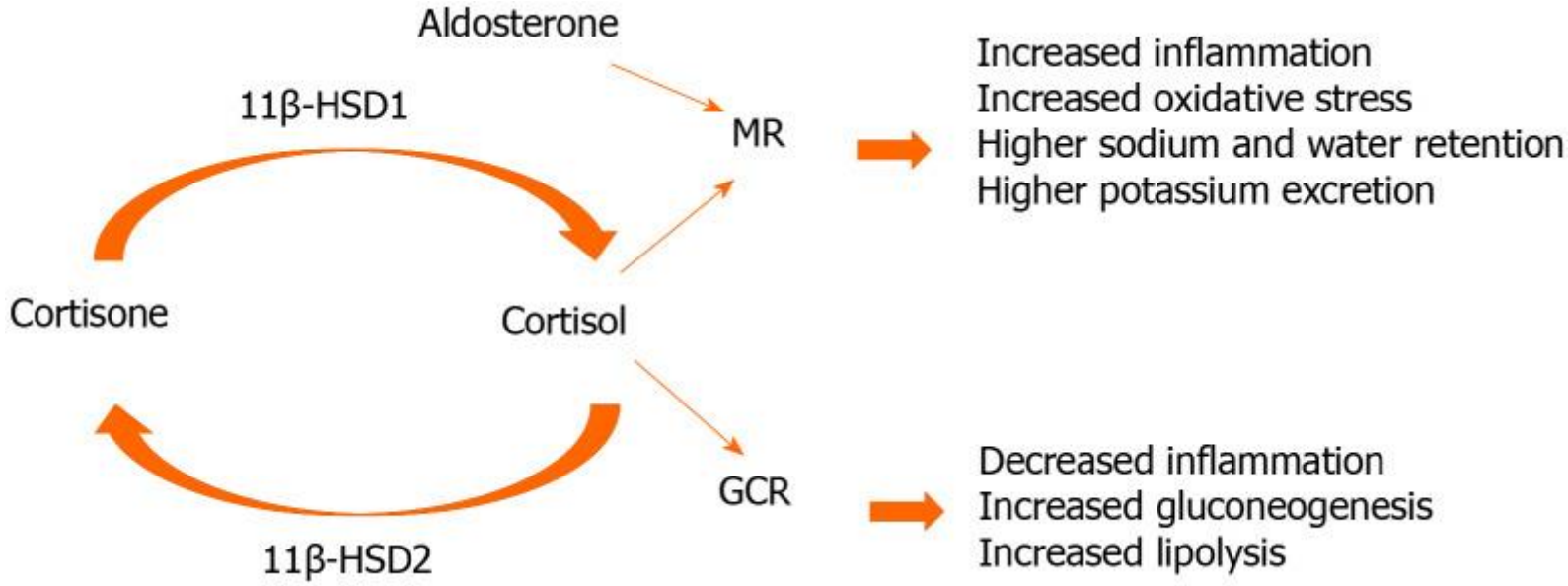


Figure 1 | **T cells involved in the induction of the allergic phenotype.** Asthma is a heterogeneous disease that is characterized by airway hyperresponsiveness (AHR), recruitment of inflammatory leukocytes to the lung and tissue remodelling, including mucus production and airway smooth muscle changes. A number of different T cell subsets are thought to influence the nature and magnitude of the allergic immune response by the cytokines that they secrete. T helper 2 (T_H2) cells are thought to promote eosinophil recruitment, in conjunction with nature killer T (NKT) cells and $CD8^+$ T cells. By contrast, T_H1 cells and T_H17 cells are thought to be associated with severe, steroid-resistant asthma, which is often marked by neutrophilic infiltrates. Regulatory T (T_{Reg}) cells and subtypes of γδ T cells are able to downregulate pulmonary immune responses and are thought to be important for maintenance of immune homeostasis in the lungs. The nature and magnitude of allergic inflammation in the lung is influenced by external environmental stimuli, such as exposure to allergens and pollution as well as infection with pathogens. IFNγ, interferon-γ; IL, interleukin.



Funkce receptorů pro glukokortikoidy a mineralokortikoidy a role izoenzymů 11β-hydroxysteroid dehydrogenázy.
Kortizol se váže exkluzivně na své receptory, ale afinita glukokortikoidů a mineralokortikoidů k mineralokortikoidním receptorům je srovnatelná. V epiteliálních tkáních aktivace mineralokortikoidních receptorů vede k expresi proteinů regulujících transport iontů a vody, což vede k reabsobci sodíku a vody, exkreci sodíků, ke zvýšení extracelulárního volumu, zvýšení krevního tlaku.
Mineralokortikoidní receptor je aktivován aldosteronem a kortizolem. Cílové buňky pro aldosteron exprimují 11- β hydroxysteroid dehydrogenázu (11β-HSD) 2, která konvertuje kortizol na kortizon. Kortison má velmi slabou afinitu k mineralokortikoidnímu receptoru. 11β-HSD1 aktivuje naproti tomu funkčně inertní kortizon na aktivní kortizol, což podporuje místní glukokortikoidní aktivitu.

Vassiliou AG et al., *World J Crit Care Med* 2021; 10(4): 102-111

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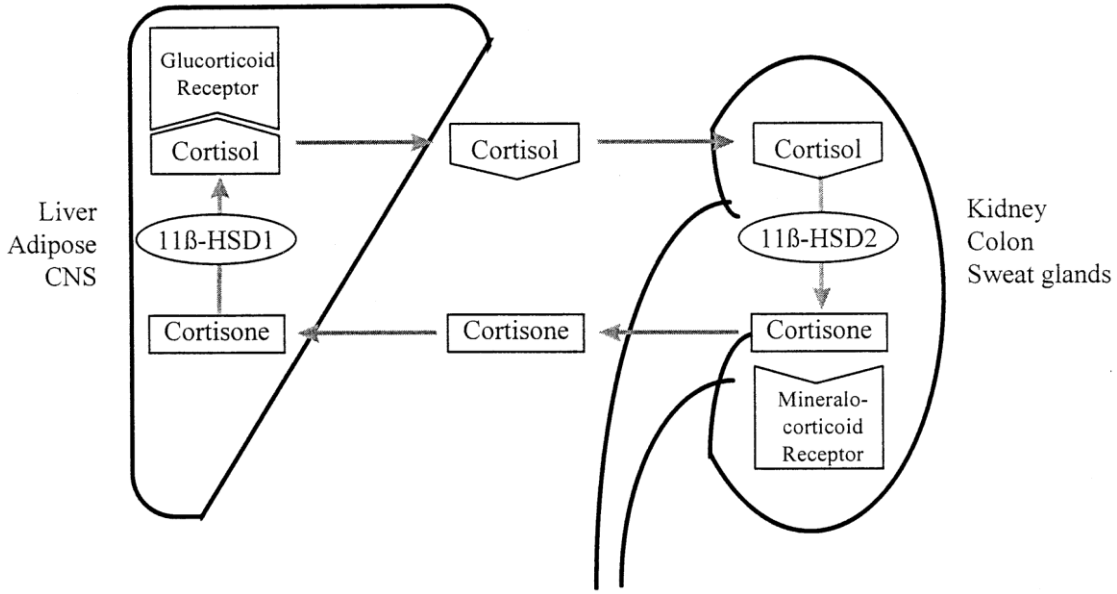
Figure 1. Contrasting functions of the isozymes of 11ß-HSD. 11ß-HSD2 is an exclusive 11ß-dehydrogenase that acts in ...



Endocrinology, Volume 142, Issue 4, 1 April 2001, Pages 1371–1376, https://doi.org/10.1210/endo.142.4.8114

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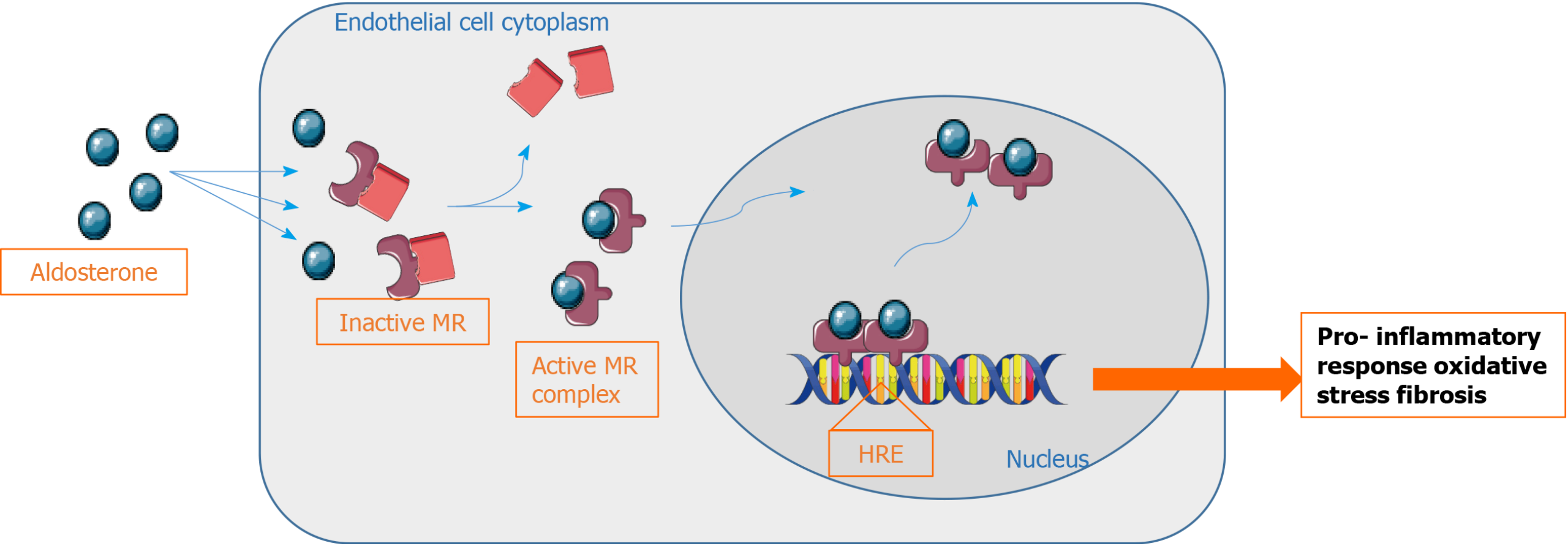

Vassiliou AG et al., *World J Crit Care Med* 2021; 10(4): 102-111

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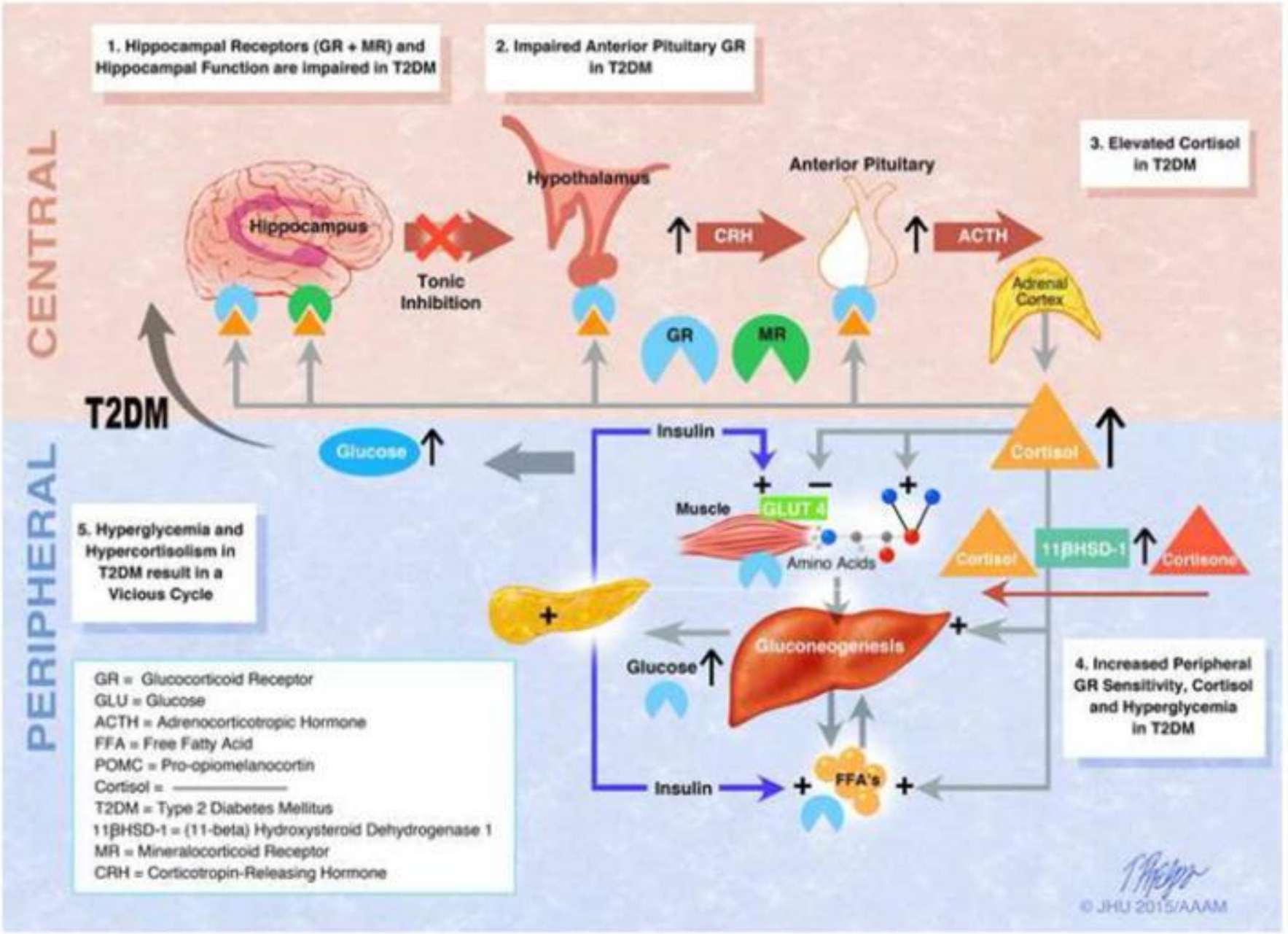

Joseph J.J. et al., Psychoneuroendocrinology. 2015 Dec; 62: 327–335.

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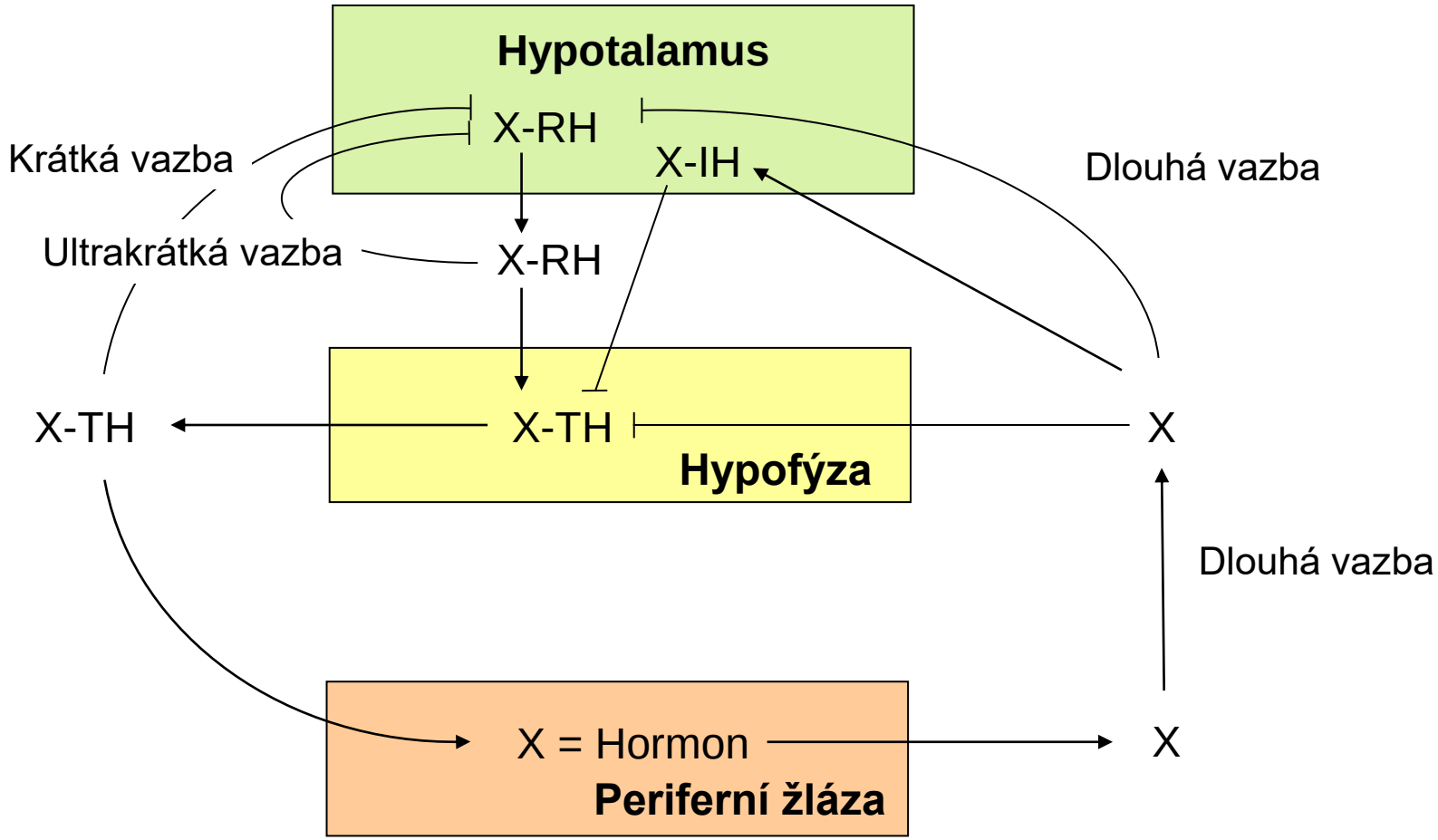
Regulace systému pomocí zpětných vazeb



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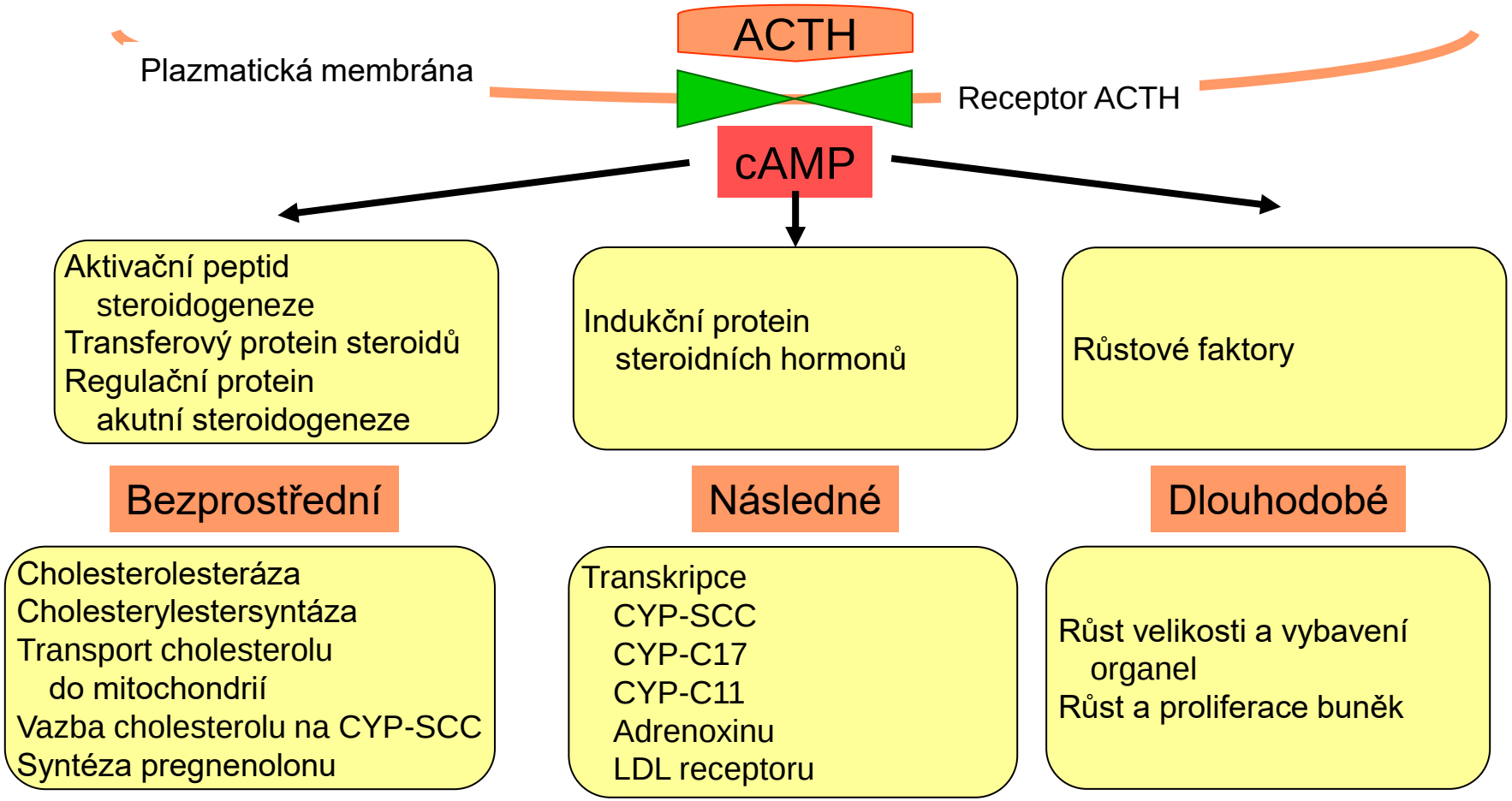
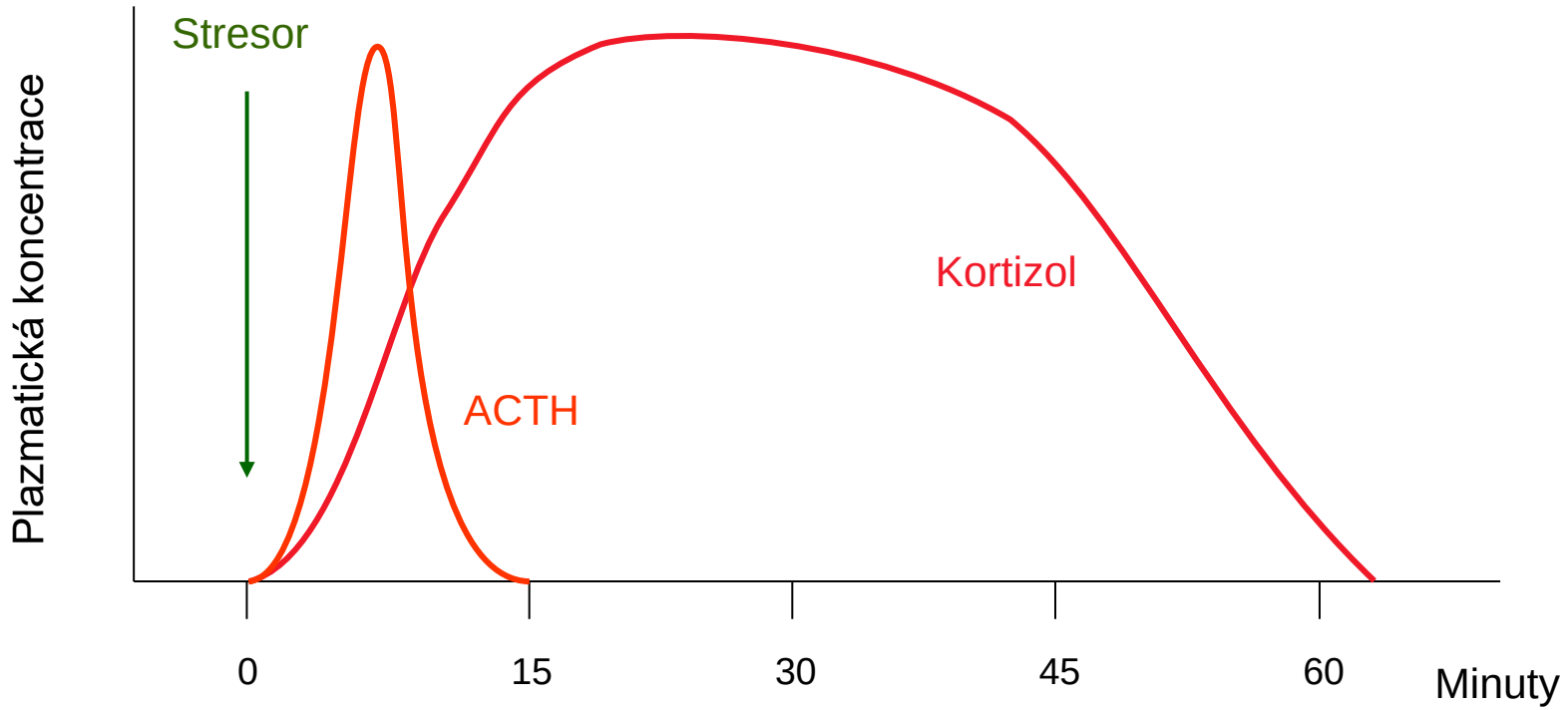
Účinky ACTH

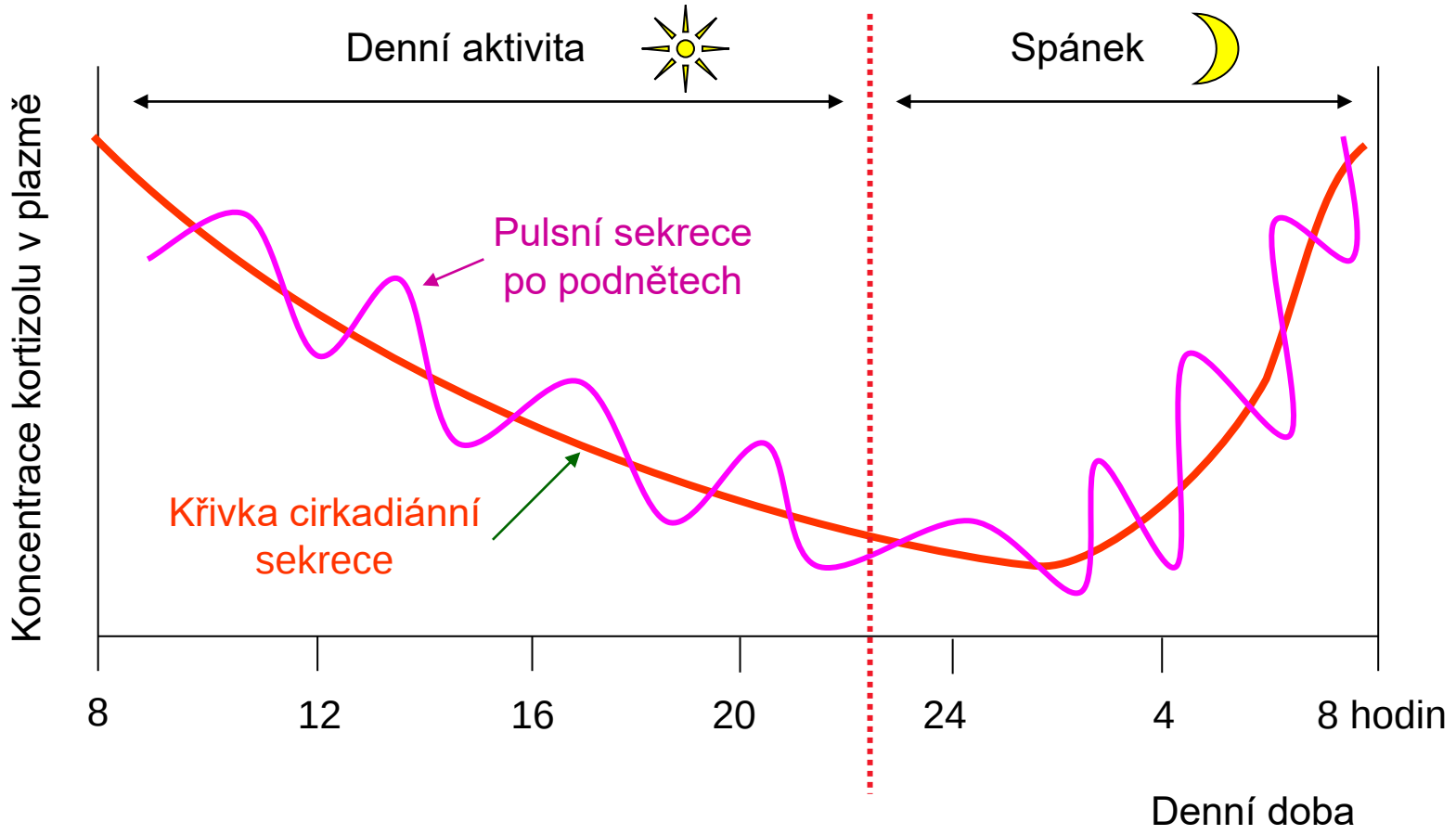

Plazmatická membrána
ACTH
Receptor ACTH
cAMP
Aktivační peptid
steroidogeneze
Transferový protein steroidů
Regulační protein
akutní steroidogeneze
Indukční protein
steroidních hormonů
Růstové faktory
Bezprostřední
Následné
Dlouhodobé
Cholesterolesteráza
Cholesterylestersyntáza
Transport cholesterolu
do mitochondrií
Vazba cholesterolu na CYP-SCC
Syntéza pregnenolonu
Transkripce
CYP-SCC
CYP-C17
CYP-C11
Adrenoxinu
LDL receptoru
Růst velikosti a vybavení
organel
Růst a proliferace buněk

Vliv stresu na plazmatické hladiny ACTH a kortizolu



(Podle Felker B and Hubbard JR: In Handbook of Stress Medicine, CRC Press, Boca Raton, FL, 1998)

Pulzní a diurnální sekrece glukokortikoidů



(Podle Felker B and Hubbard JR: In Handbook of Stress Medicine, CRC Press, Boca Raton, FL, 1998)

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Schéma komunikace mezi imunitním a neuroendokrinním systémem

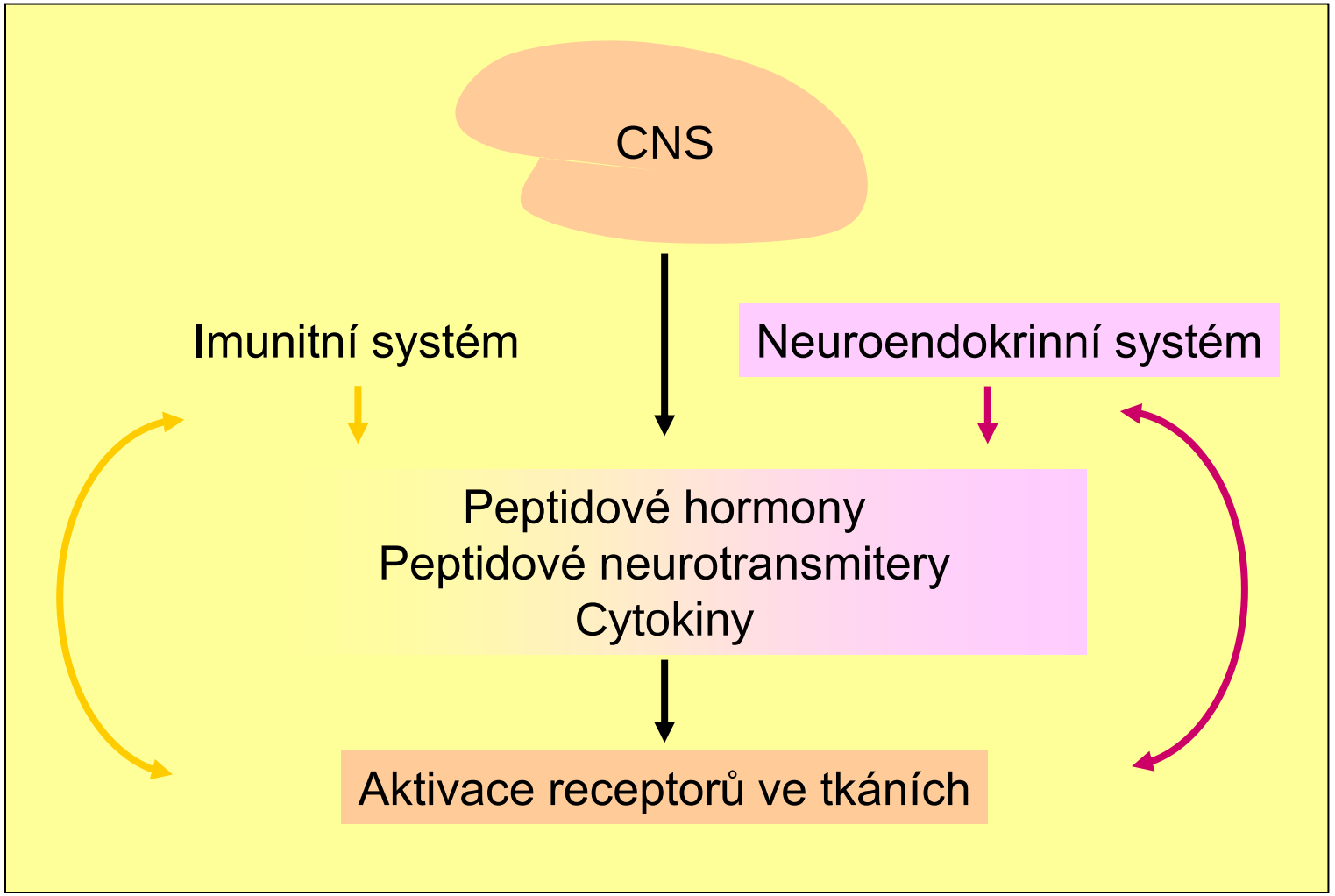

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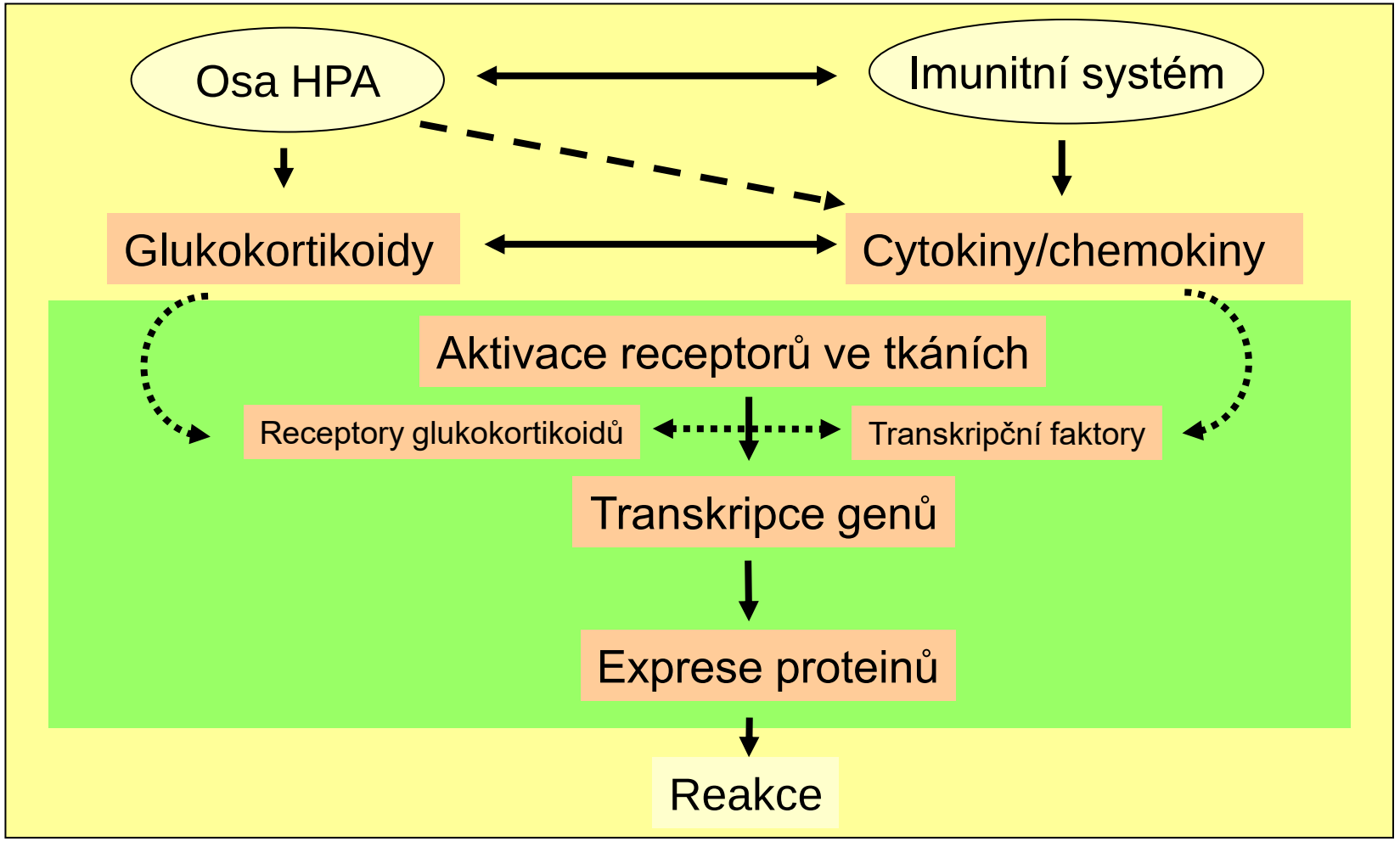
Schéma komunikace mezi osou HPA a imunitním systémem



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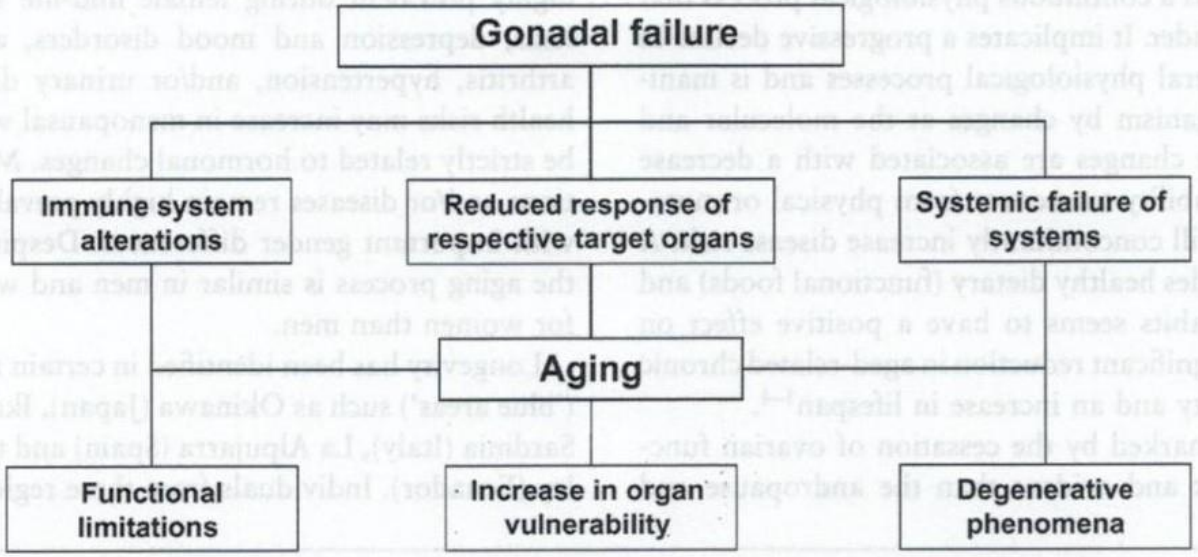


Figure 1 Gonadal failure and aging are closely related and have some gender differences. The menopause is a more abrupt gonadal aging process than the andropause. Modified from Pérez-López, reference 1

Charakteristiky časného vývoje

- Characteristics of the early environment, starting in utero or even before, can represent major risk factors for a lifetime of physical and mental health problems for the individual.
- The 'fetal programming hypothesis' (Seckl and Holmes, 2007), the 'developmental programming hypothesis' (Barker, 2004, Langley-Evans, 2006, Langley-Evans, 2015), and the 'Developmental Origins of Health and Disease (DOHaD) hypothesis' (Barker, 1990, Barker, 2004) specifically state that, during critical or sensitive periods of development, a disturbance in environmental factors, such as exposure to nutrient restriction, exposure to glucocorticoids or synthetic glucocorticoids, has an organizational effect on biological systems with a long development and/or intrinsic plasticity to react and adapt to environmental influences.

Pinheiro RL, Areia AL, Mota Pinto A, Donato H. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. Acta Med Port. 2019 Mar 29;32(3):219-226.

Charakteristiky časného vývoje

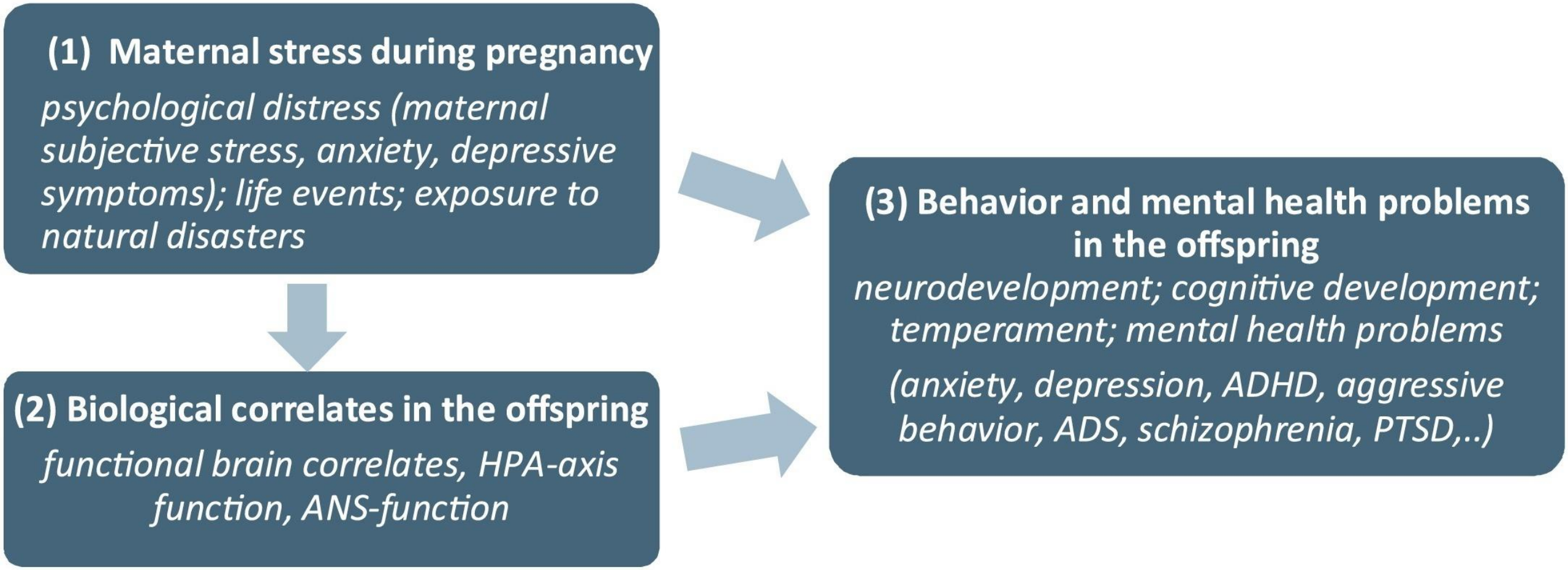
- These systems include the central nervous system (CNS), autonomic nervous system (ANS), neuro-endocrine (hypothalamic-pituitary-adrenal (HPA) axis), cardiovascular, and immune systems.
- Their plasticity is highest during early development when the organ systems are still immature. Following exposure to prenatal challenges, induced changes, such as an altered set-point in HPA-axis, changes in glucocorticoid receptor sensitivity, changes in proteins and neurotransmitters involved in neuronal development and function in the CNS will enhance susceptibility to somatic diseases and mental health problems which, in interaction with genetic liabilities and postnatal challenges, will determine ultimate health status. Indeed, over the past 30 years, human studies have gathered robust epidemiological and mechanistic data showing that the most powerful early environmental factors capable of influencing offspring development and health in later life are prenatal stressors, including maternal stress, malnutrition and maternal immune-related factors.

Pinheiro RL, Areia AL, Mota Pinto A, Donato H. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. Acta Med Port. 2019 Mar 29;32(3):219-226.

Charakteristiky časného vývoje

- Among the first observations were that a lower birth weight – taken as a proxy measure of prenatal exposure to environmental adversity – is a risk factor for the development of cardiovascular and metabolic diseases such as arterial hypertension, coronary heart disease, obesity, and type 2 diabetes, as well as mental health problems such as depression. Although much less examined, accumulating evidence mostly gathered during the last decade, is showing how maternal psychological distress, as well as stress from exposure to life events and natural disasters during pregnancy, gives rise to behavior and mental health problems.

Pinheiro RL, Areia AL, Mota Pinto A, Donato H. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. Acta Med Port. 2019 Mar 29;32(3):219-226.



Pinheiro RL, Areia AL, Mota Pinto A, Donato H. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. Acta Med Port. 2019 Mar 29;32(3):219-226.

Maternální stres

- In women, maternal stress is a significant risk factor for preterm birth and low for gestational age birth weight babies.
- Later in life, other adverse offspring phenotypes are reported in rodents, including: dysregulated stress responses and increased anxiety- and depression-like or passive stress coping behaviours, hypertension; impaired glucose regulation, insulin resistance and diet-induced obesity; abnormal neural development and cognitive impairments; as well as aberrant social and reproductive behaviours.
- Comparable phenotypes have been described in humans whose mothers experienced stress during pregnancy.

Sze Y, Brunton PJ. How is prenatal stress transmitted from the mother to the fetus? J Exp Biol. 2024 Mar 7;227(Suppl_1):jeb246073

„Post traumatic stress disorder“ (PTSD)

- PTSD is a high-profile clinical phenomenon with a complicated psychological and physical basis. The development of PTSD is associated with various factors, such as traumatic events and their severity, gender, genetic and epigenetic factors.
- PTSD is a chronic impairing disorder harmful to individuals both psychologically and physically. It brings individual suffering, family functioning disorders, and social hazards. The definition and diagnostic criteria for PTSD remain complex and ambiguous to some extent, which may be attributed to the complicated nature of PTSD and insufficient research on it.

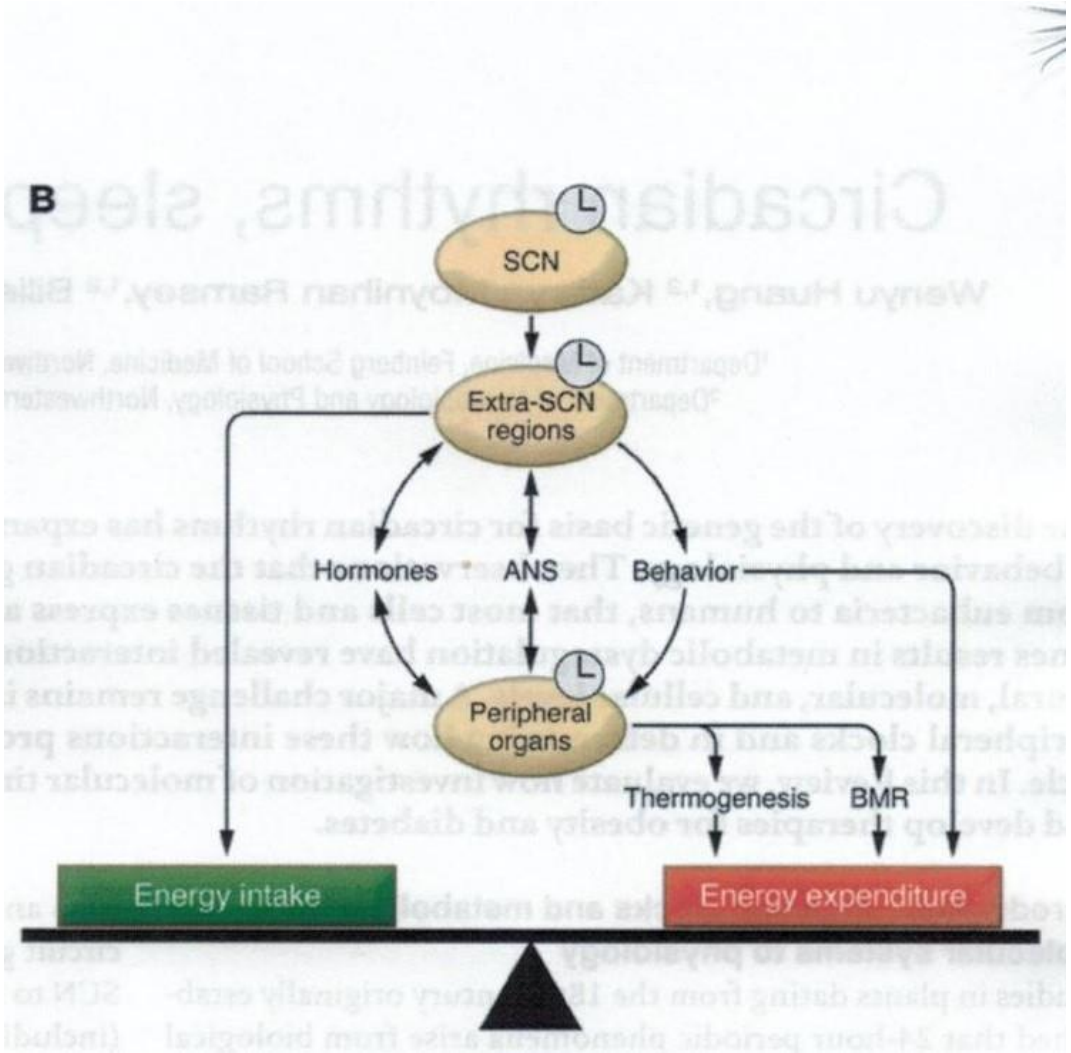
„Post traumatic stress disorder“ (PTSD)

- The underlying mechanisms of PTSD involve changes in different levels of psychological and molecular modulations. Thus, research targeting the basic mechanisms of PTSD using standard clinical guidelines and controlled interference factors is needed. In terms of treatment, psychological and pharmacological interventions could relief PTSD symptoms to different degrees. However, it is necessary to develop systemic treatment as well as symptom-specific therapeutic methods. Future research could focus on predictive factors and physiological indicators to determine effective prevention methods for PTSD, thereby reducing its prevalence and preventing more individuals and families from struggling with this disorder.

Chronic cardinal symptoms: re-experiencing, hyper-arousal, avoidance, dissociation

- The pathognomonic sign of PTSD is re-experiencing the traumatic scene with the same distress, perceptions, emotions and dissociation that were originally experienced. Internal feelings of anxiety and negative thoughts are also recalled. These episodes can occur during sleep – as traumatic nightmares, and during waking periods – as flashbacks. Other manifestations are possible: intrusive memories perceived as distinct from the original event; mental ruminations about the event; delusions of re-experiencing the event by recognising elements of it in the environment; elementary motor phenomena replicating the motor response from the time of the event; and repetitive behaviours (fugue, crying, self-harm or aggression).

Auxéméry Y. Post-traumatic psychiatric disorders: PTSD is not the only diagnosis. Presse Med. 2018 May;47(5):423-430.



Cirkadiánní systém prostřednictvím transkripční a translační aktivity umožňuje denní synchronizaci fyziologických procesů v živém organismu.

Stimuly ovlivňující reaktivní a anticipační odpovědi osy HPA

"Reaktivní" odpovědi	"Anticipační" odpovědi
Bolest (viscerální a somatická)	Vrozené programy Predátoři Nezvyklé podmínky okolního prostředí Sociální změny
Neuronální homeostatické signály: Stimulace chemoreceptorů Stimulace baroreceptorů Stimulace osmoreceptorů	Druhově specifické podněty (např. osvětlené prostředí pro hlodavce, temná prostředí pro lidi)
Humorální homeostatické signály: Glukóza Leptin Insulin Renin-angiotenzin-aldosteron Atriální natriuretický factor Jiné	Paměťové programy Klasicky podmíněné stimuli Kontextem podmíněné stimuli Negativní posilování/frustrace
Humorální prozánětlivé signály: IL-1 IL-6 TNF-α Jiné	

Akutní odpověď na stres

- Adaptivní, umožňující přežití
- Ačkoliv se v různých situacích volí různé reakce, cíl je vždy stejný = přežití
- *Metabolické*: ↑glykémie
- *Kardiovaskulárně/respirační*-doprava glukózy ke svalům, srdci a mozku
- *Analgézie*
- *Inhibice procesů snižujících šanci na přežití* (rozmnožovací chování, jídlo, procesy v GIT, deprese imunitního systému)

Akutní odpověď na stres – metabolické efekty

- Účel: zvýšit glykémii prostřednictvím katecholaminů a glukokortikoidů
- Uptake glukózy je inhibován a syntéza proteinů, mastných kyselin a glykogenu je zastavena.
- Lipolýza, glykogenolýza, proteolýza
  - katecholaminy mají spíše krátkodobé efekty na glykémii
  - glukoneogeneza (glukokortikoidy mají spíše dlouhodobé efekty na glykémii)

Akutní odpověď na stres – kardiovaskulární a respirační efekty

☺Účel: zvýšit kardiovaskulární tonus k rychlé dodávce mobilizované glukózy a kyslíku nejpotřebnějším tkáním

☺Uvolnění vasopresinu z axonových terminál neurohypofýzy vede k reabsorbci vody v ledvinách. Účel: zvýšení náplně CV systému

Akutní odpověď na stres – analgézie

☺Účel: snížit vnímání bolesti

☺Rozeznáváme dvě formy analgézie indukované stresem (SIA)

- ☺na opiátech závislá SIA (enkefaliny a β-endorfin)
- ☺na opiátech nezávislá SIA (glutamát)

☺Během stresové reakce se mohou obě formy SIA kombinovat.

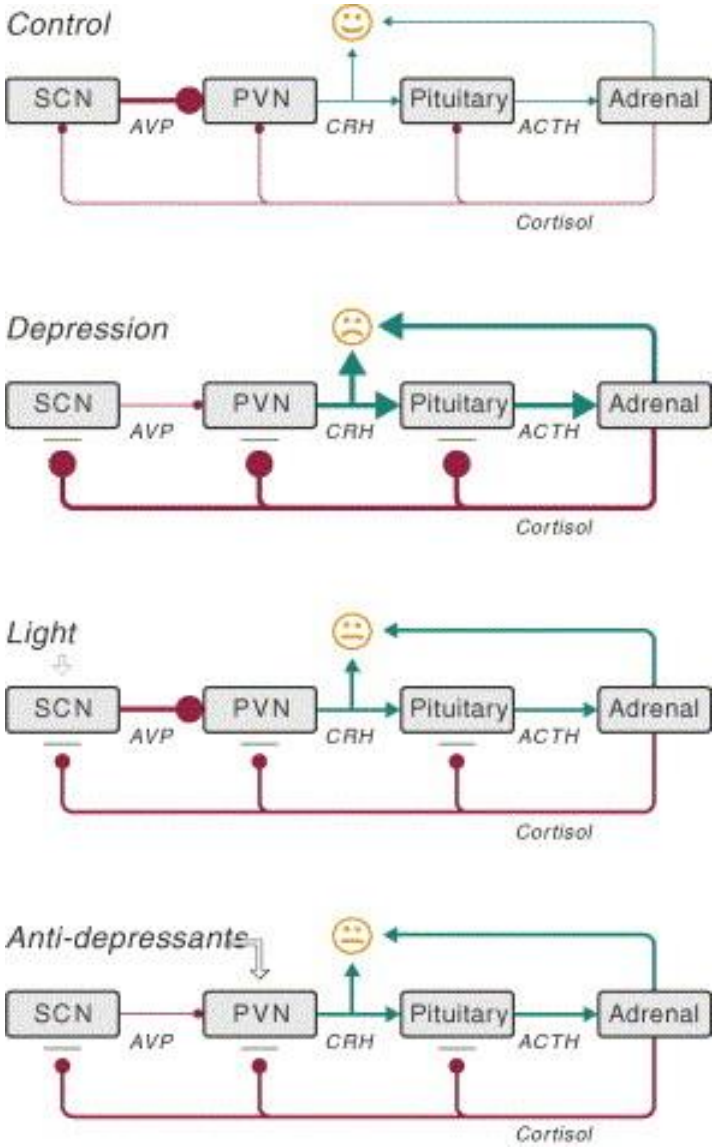
Chronická odpověď na stres

☹Maladaptivní = s efekty pokození organismu

☹Chronický stres může vést k onemocnění jako žaludeční vředy, viscerální obezita, snížený růst, zvýšené riziko nemoci koronárních cév

☹Chronický stres ovlivní chování:

- ☹Inhibice reprodukce
- ☹Chronický stres je asociován s některými psychiatrickými stavy/nemocemi (deprese, syndrom vyhoření).


Control
SCN
AVP
PVN
CRH
Pituitary
ACTH
Adrenal
Cortisol
Depression
SCN
AVP
PVN
CRH
Pituitary
ACTH
Adrenal
Cortisol
Light
SCN
AVP
PVN
CRH
Pituitary
ACTH
Adrenal
Cortisol
Anti-depressants
SCN
AVP
PVN
CRH
Pituitary
ACTH
Adrenal
Cortisol

K předchozímu obrázku

- Schematic illustration of an impaired interaction between the decreased activity of AVP in the SCN and the increased activity of CRH neurons in the paraventricular nucleus (PVN). The HPA system is activated in depression and affects mood, via CRH and cortisol. A decreased amount of AVP-mRNA of the SCN in depression was found. The decreased activity of AVP neurons in the SCN of depressed patients is the basis of the impaired circadian regulation of the HPA system in depression. Increased levels of circulating glucocorticoids decrease AVP-mRNA in the SCN, which will result in smaller inhibition of the CRH neurons
- Pathogenesis of depression: In depressed patients, stress acting on the HPA system results in a disproportionally high activity of the HPA system because of a deficient cortisol feedback effect due to the presence of glucocorticoid resistance. The glucocorticoid resistance may either be caused by a polymorphism of corticosteroid receptor or by a developmental disorder. Also AVP neurons in the SCN react to the increased cortisol levels and subsequently fail to inhibit sufficiently the CRH neurons in the PVN of depressed patients. Such an impaired negative feedback mechanism may lead to a further increase in the activity of the HPA system in depression. Both high CRH and cortisol levels contribute to the symptoms of depression. Light therapy activates the SCN, directly inducing an increased synthesis and release of AVP that will inhibit the CRH neurons. Anti-depressant medication generally inhibits the activity of CRH neurons in the PVN.
-

Role mnohočetných faktorů v rozvoji stresu

Dominantní a subdominantní primáti:

- Ve stabilních podmínkách (území se nemění) mají dominantní samci nižší hladiny GCs než subdominantní
- V nestabilních podmínkách mají dominantní samci glukokortikoidy stejně vysoké nebo vyšší než subdominantní
- Úroveň dominance samců je v nepřímé úměře s jejich plazmatickými hladinami glukokortikoidů

Role psychologických faktorů v rozvoji stresu

☺"Good state of mind" - pozitivní rysy osobnosti:

☺Sociální podpůrné skupiny – formují se nesexuální přátelství osob opačného pohlaví

☺Trénink – schopnost předvídat stresovou situaci a schopnosti přebírat nad ní kontrolu

☺Transformace agresivity při ztrátě možnosti bojovat (sport)

„Schopnost uvažovat o souladu a eleganci v přírodních jevech je jedním z nejuspokojivějších prožitků, kterých je člověk schopen. Když hledíme na něco většího, než je naše vědomé já, naše denní starosti se ve srovnání s tím zmenšují. Nastupuje vyrovnanost a pokoj mysli, kterých lze dosáhnout jedině stykem s něčím vznešeným“.

Děkuji vám za pozornost

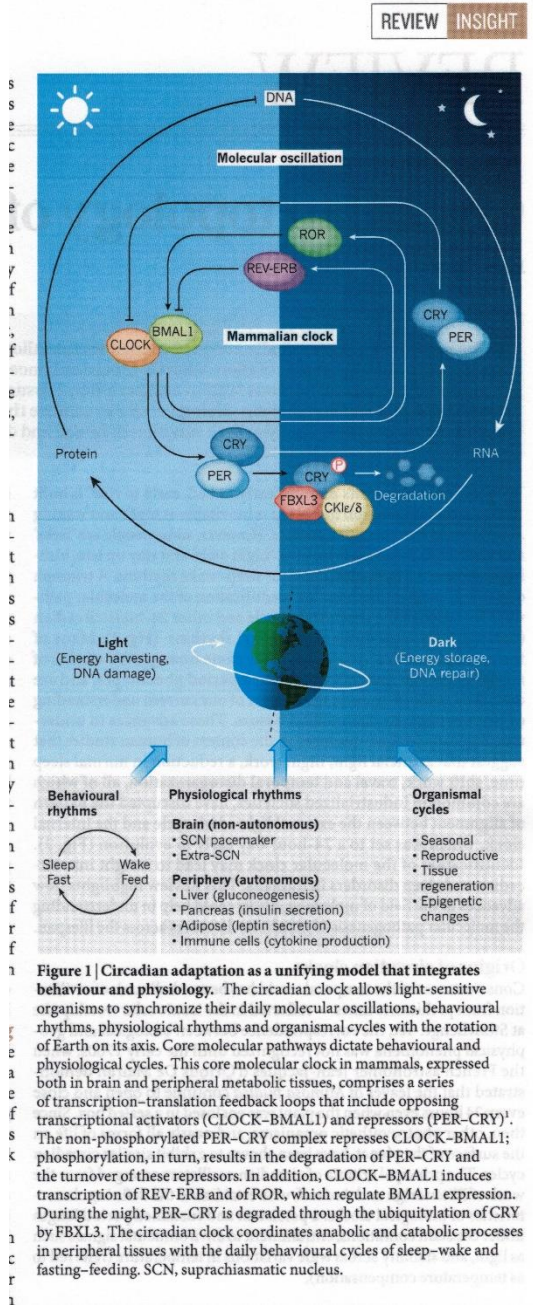
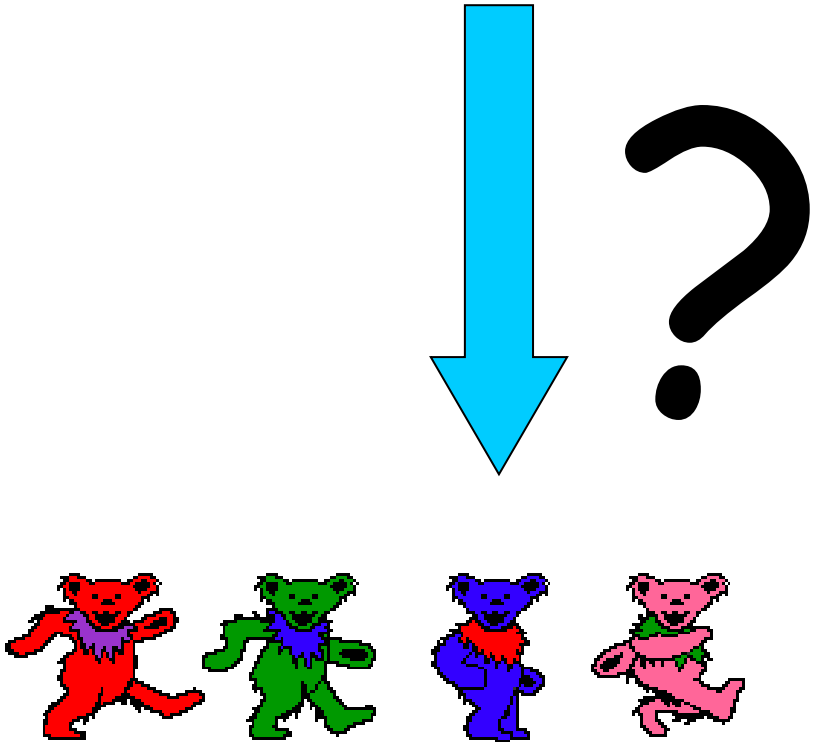


Figure 1 | Circadian adaptation as a unifying model that integrates behaviour and physiology. The circadian clock allows light-sensitive organisms to synchronize their daily molecular oscillations, behavioural rhythms, physiological rhythms and organismal cycles with the rotation of Earth on its axis. Core molecular pathways dictate behavioural and physiological cycles. This core molecular clock in mammals, expressed both in brain and peripheral metabolic tissues, comprises a series of transcription–translation feedback loops that include opposing transcriptional activators (CLOCK–BMAL1) and repressors (PER–CRY)[1]. The non-phosphorylated PER–CRY complex represses CLOCK–BMAL1; phosphorylation, in turn, results in the degradation of PER–CRY and the turnover of these repressors. In addition, CLOCK–BMAL1 induces transcription of REV-ERB and of ROR, which regulate BMAL1 expression. During the night, PER–CRY is degraded through the ubiquitylation of CRY by FBXL3. The circadian clock coordinates anabolic and catabolic processes in peripheral tissues with the daily behavioural cycles of sleep–wake and fasting–feeding. SCN, suprachiasmatic nucleus.



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