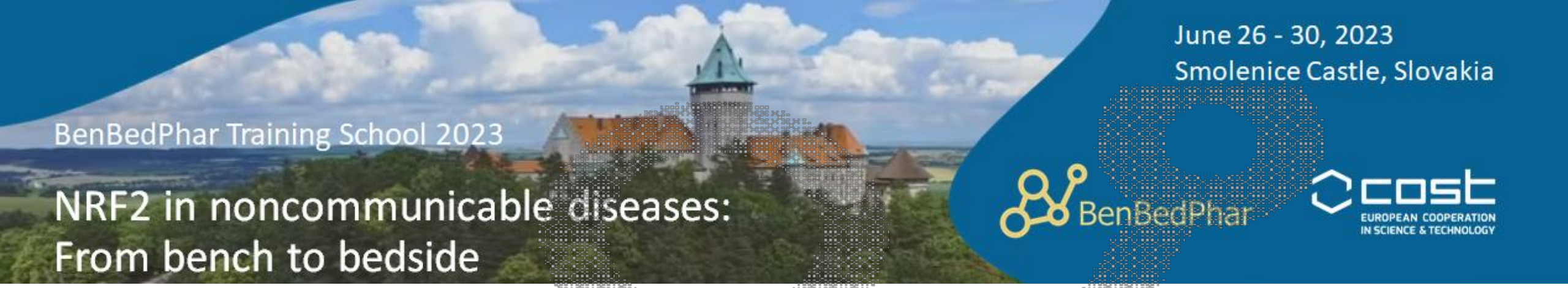

NRF2 in stress responses

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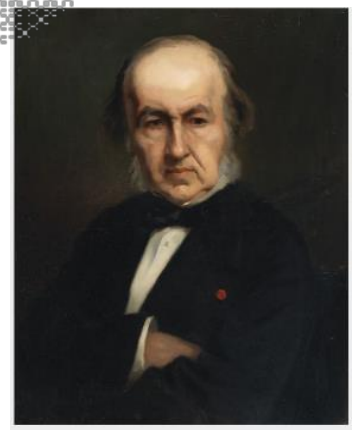
BenBedPhar

Contents of presentation

- Stress research – Bernard, Cannon
- H. Selye's stress concept
- Homeostasis, allostasis
- Stress specificity
- Neuroendocrine mechanisms in stress
- Systemic stress, local stress
- Evolution of stress concept
- NRF2 in stress

Stress research – Bernard, Cannon

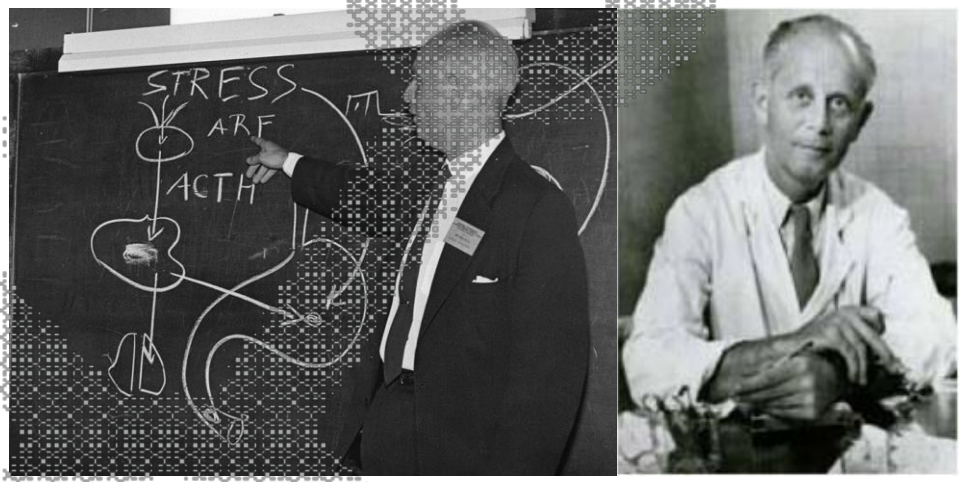


Claude Bernard (1813-1878) introduced the idea of the internal environment bathing cells —**"the milieu intérieur"** maintained by continual compensatory changes of bodily functions (1865).

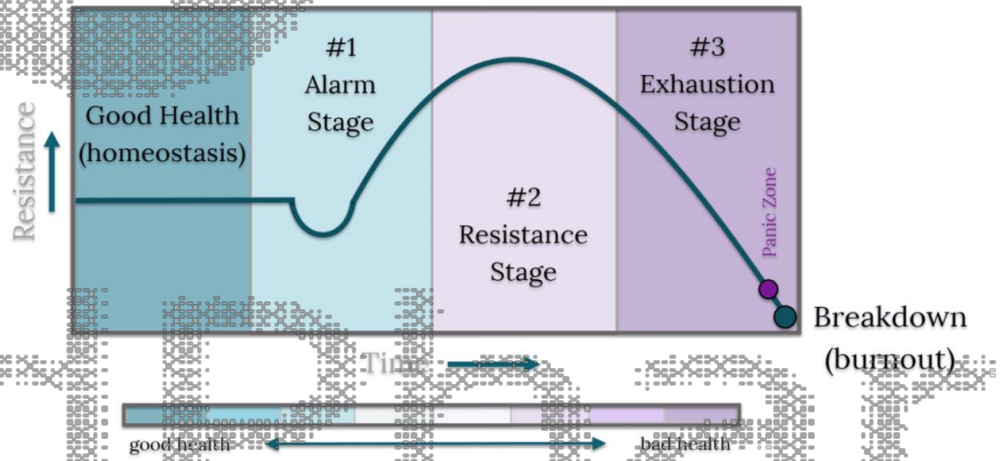
Walter B. Cannon (1871-1945) coined the word, "**homeostasis**," referring to a set of acceptable ranges of values for internal variables. Threats to homeostasis evoke activation of the **sympathoadrenal system** as a functional unit (1929-1939). He introduced „**fight or flight reaction**" as the chain of rapidly occurring reactions inside the body that helps to mobilize the body's resources to deal with threatening circumstances.

Selye's stress concept

- Hans Selye's (1907-1982) theory was the first that focused on **stress as a biological function.** He proposed that various stressors induces all: adrenal hyperactivity, lymphatic atrophy and gastric ulcers (Nature 1936, A Syndrome produced by Diverse Nocuous Agents)
- He introduced the definition of stress as the "**the nonspecific response of the body to any demand upon it**"
- He distinguished acute stress from the total response to chronically applied stressors, terming it „**general adaptation syndrome**"

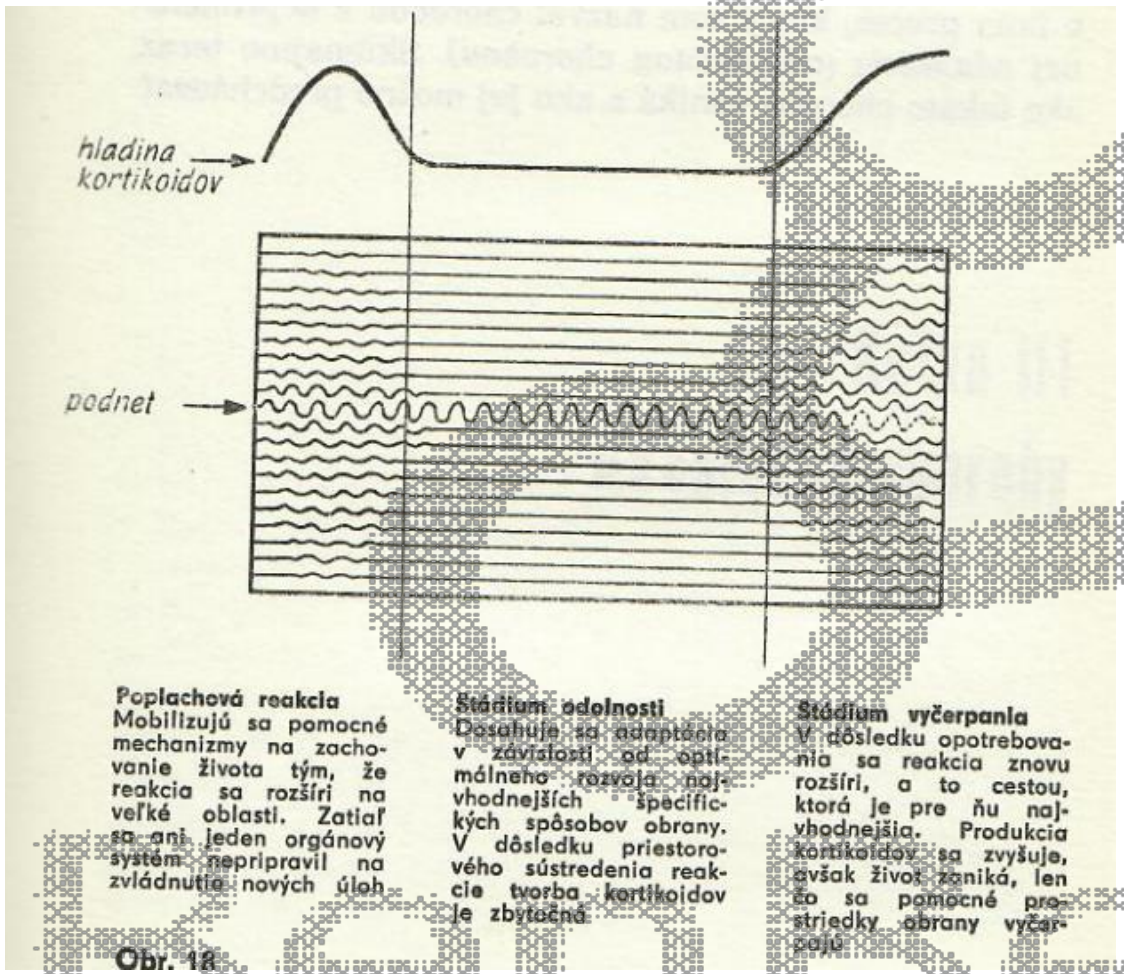


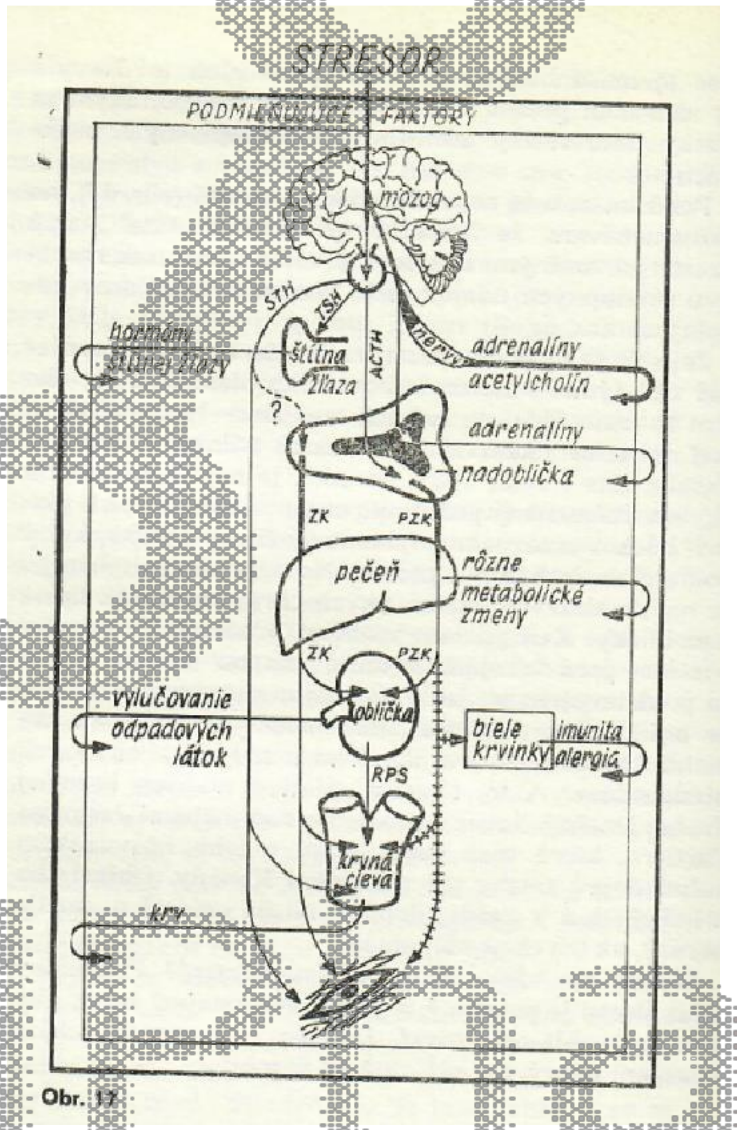
Hans Selye's General Adaptation Syndrome



https://drandrewneville.com/hans-selyes-general-adaptation-syndrome/

Selye's stress concept

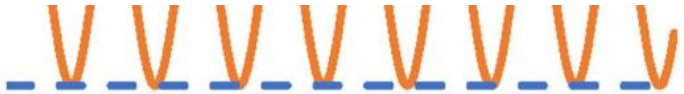




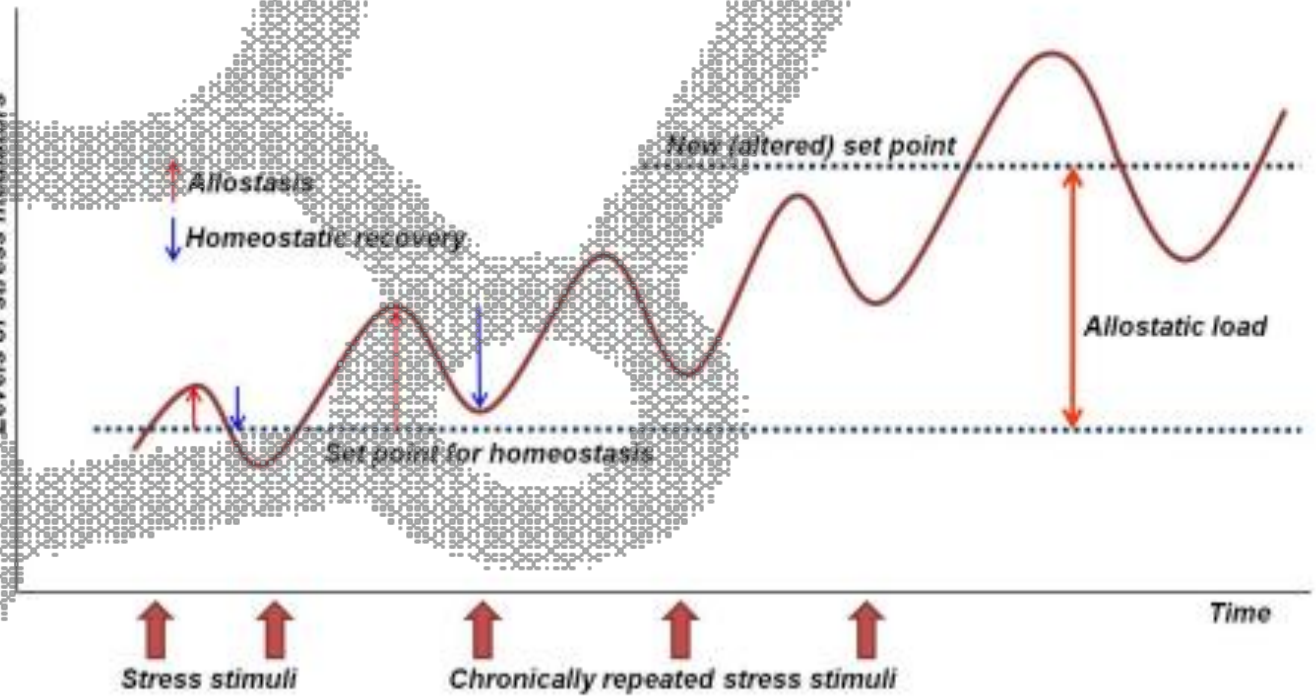
Selye, H. (1956). The Stress of Life. New York: McGraw-Hill.

Homeostasis, allostasis, allostatic load

maintenance of a stable internal environment



achieving stability through change



Lu S, Wei F, Li G. Cell Stress. 2021 Apr 26;5(6):76-85. doi: 10.15698/cst2021.06.250.

Lee, Do Yup, et al., doi:10.5483/bmbrep.2015.48.4.275.

Stress as highly specific response

Selye's doctrine of non-specificity underwent experimental testing, which **failed** to confirm it.

„...results are inconsistent with Selye's doctrine of nonspecificity and the existence of a unitary "stress syndrome," and they are more consistent with the concept **that each stressor has its own central neurochemical and peripheral neuroendocrine "signature."**

Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity

KAREL PACAK,[1,2] MIKLOS PALKOVITS,[3] GAL YADID,[4] RICHARD KVETNANSKY,[5] IRWIN J. KOPIN,[1] AND DAVID S. GOLDSTEIN[1]
[1]Clinical Neuroscience Branch, National Institute of Neurological Disorders and Stroke and [2]Laboratory of Cell Biology, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892; [2]Department of Medicine, Washington Hospital Center, Washington, District of Columbia 20010; [4]Department of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel 52100; and [5]Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovak Republic 81000

Pacak, Karel, Miklos Palkovits, Gal Yadid, Richard Kvetnansky, Irwin J. Kopin, and David S. Goldstein. Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity. *Am. J. Physiol.* 275 (*Regulatory Integrative Comp. Physiol.* 44): R1247–R1255, 1998.—Selye defined stress as the nonspecific response of the body to any demand. Stressors elicit both pituitary-adrenocortical and sympathoadrenomedullary responses. One can test Selye's concept by comparing magnitudes of responses at different stress intensities and assuming that the magnitudes vary with stress intensity, with the prediction that, at different stress intensities, ratios of increments neuroendocrine responses should be the same. We measured arterial plasma ACTH, norepinephrine, and epinephrine in conscious rats after hemorrhage, intravenous insulin, subcutaneous formaldehyde solution, cold, or immobilization. Relative to ACTH increments, cold evoked large norepinephrine responses, insulin large epinephrine responses, and hemorrhage small norepinephrine and epinephrine responses, whereas immobilization elicited large increases in levels of all three compounds. The ACTH response

stressor. In this report, we call this the doctrine of nonspecificity.

Selye focused on the hypothalamic-pituitary-adrenocortical (HPA) system as a key effector of the stress response. The HPA activation attending stress was thought to be part of a constellation of stereotypical neural and endocrine responses. Administration of ACTH can elicit all three components of the pathological triad, and some have even defined stress empirically as that which increases plasma ACTH concentrations (8). Selye did not claim that ACTH, or high circulating levels of adrenocortical steroids, can elicit the pathological triad.

Numerous studies, however, have demonstrated differential neuroendocrine responses during exposure to different stressors. For instance, glucopenia evokes selective adrenomedullary and pituitary-adrenocortical activation (10, 22, 23); orthostasis, hyperthermia, and cold exposure evoke selective sympathoneural acti-

Stress as highly specific response

Psychology, 2015, 6, 1786-1794
Published Online November 2015 in SciRes. http://www.scirp.org/journal/psych
http://dx.doi.org/10.4236/psych.2015.614175

Scientific Research Publishing

A Critical Review of Selye's Stress Theory: The Statistical Analyses of Selye's Own Experimental Data Disprove It

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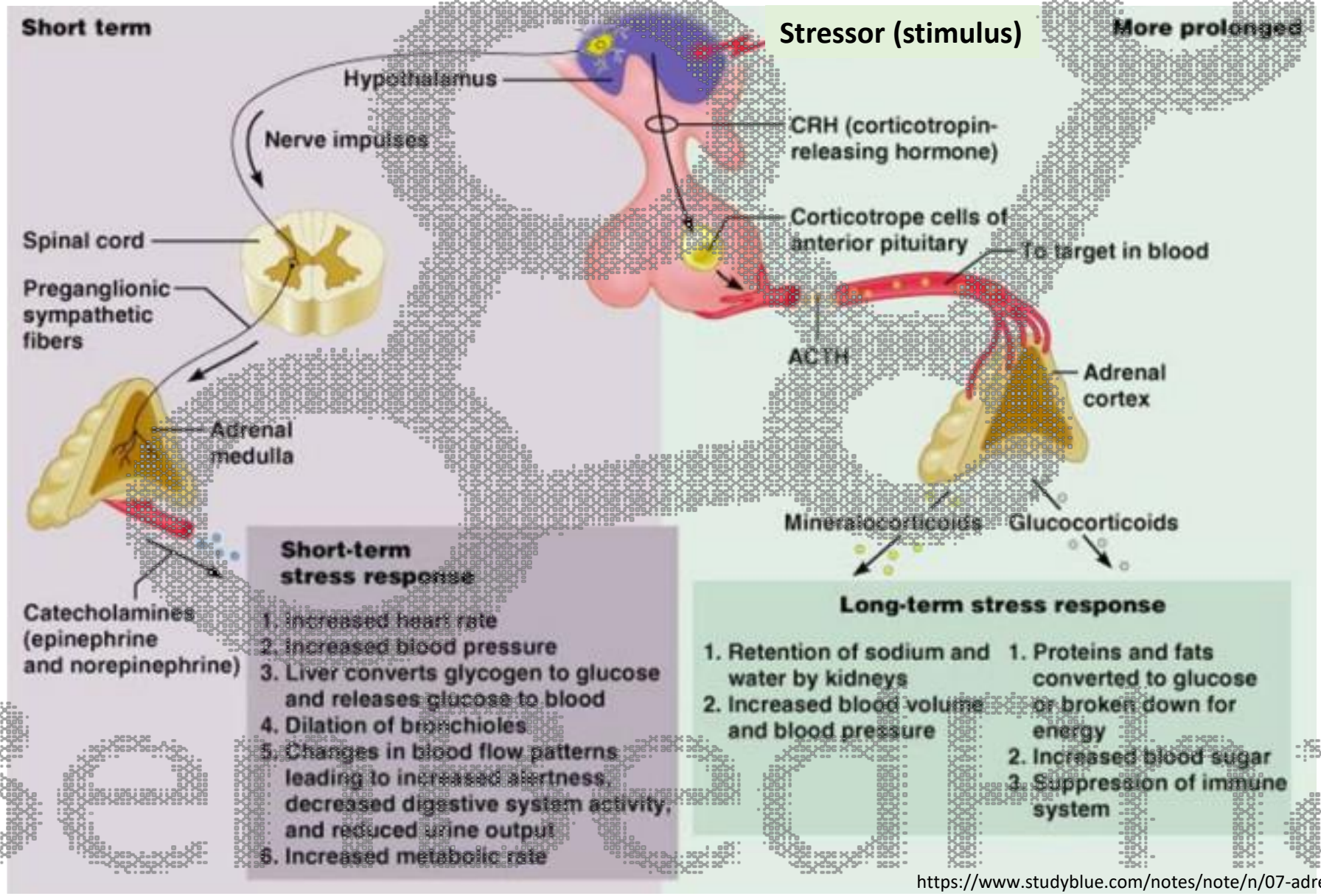
Observed patterns of stress:

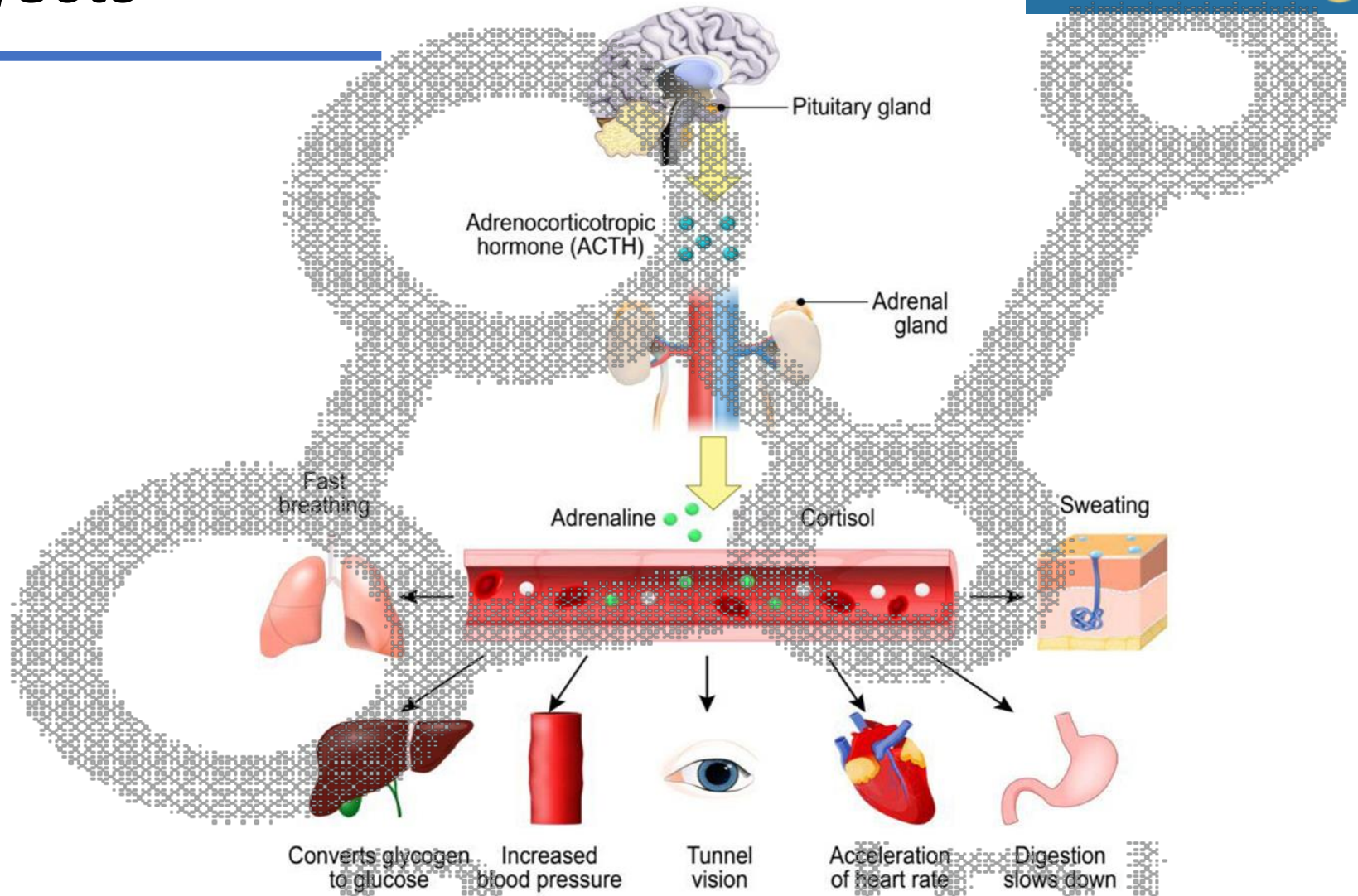
1. thymus involution and adrenal enlargement
2. decrease in the thymus weight without changes in the adrenal weight
3. no change in either the thymus or adrenal weight

Neuroendocrine mechanisms in stress



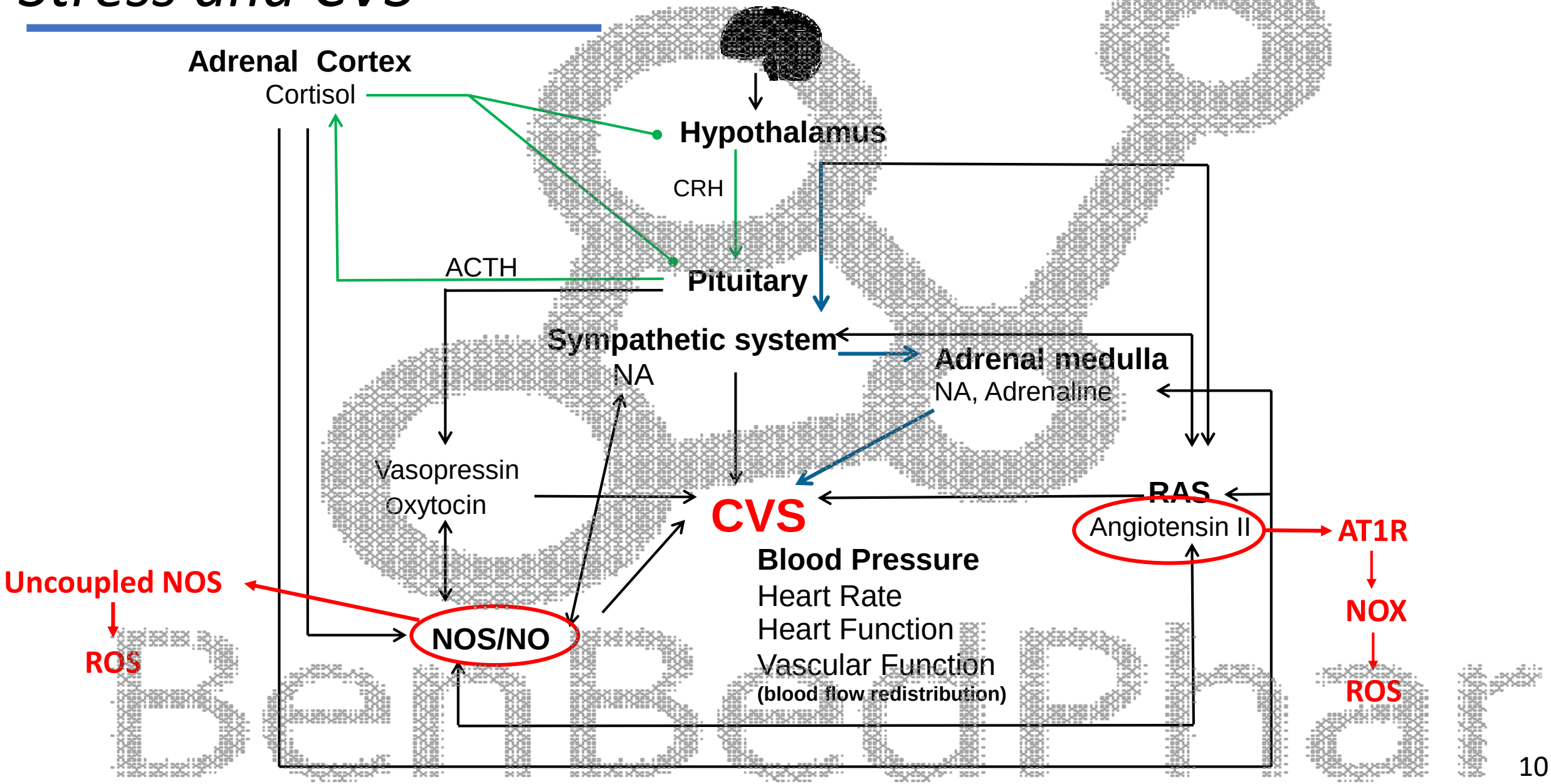
https://www.studyblue.com/notes/note/n/07-adrenalglands/deck/1109539

Systemic effects

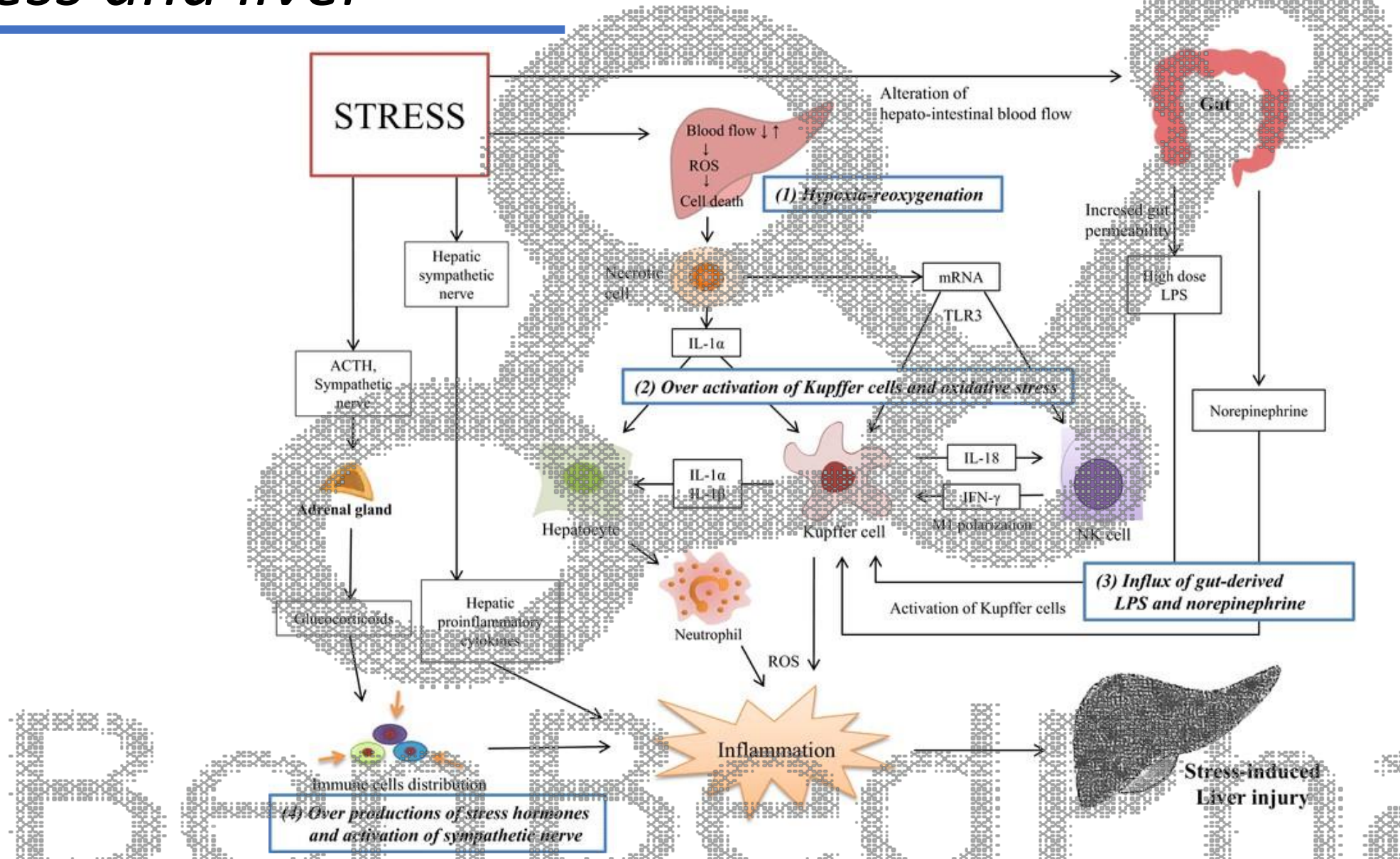


https://premierneurologycenter.com/blog/6-ways-stress-affects-your-brain/

Stress and CVS



Stress and liver



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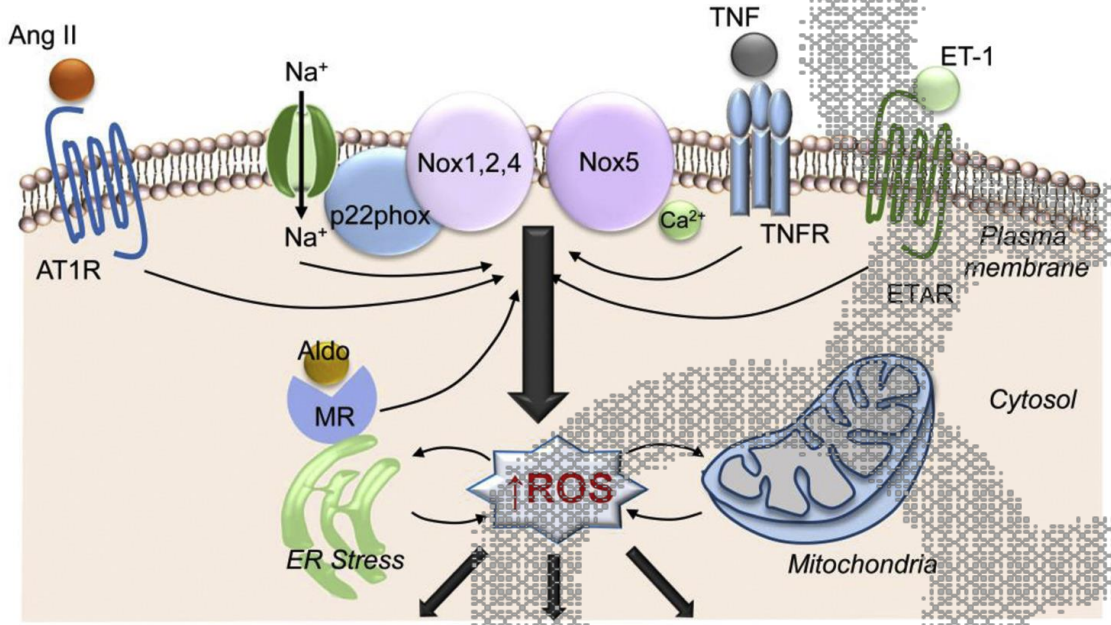
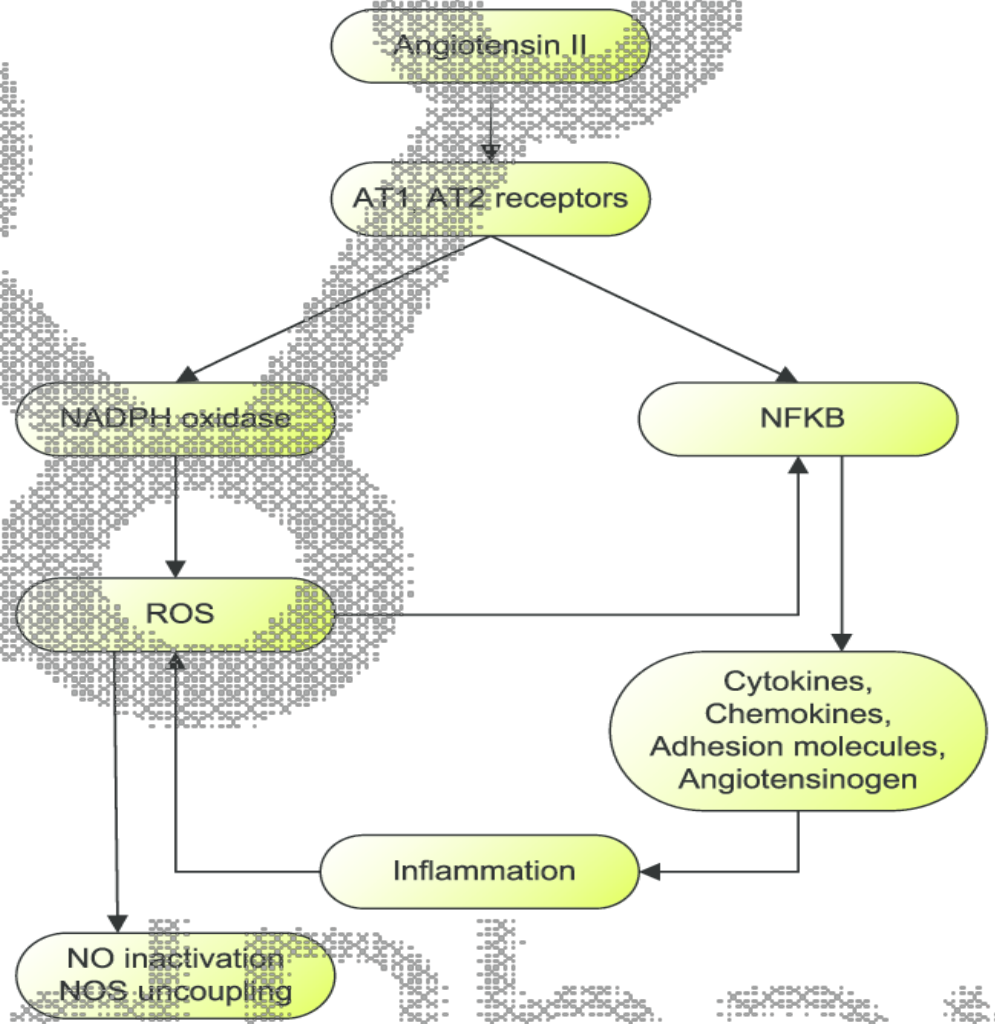
Systemic stress and local stress





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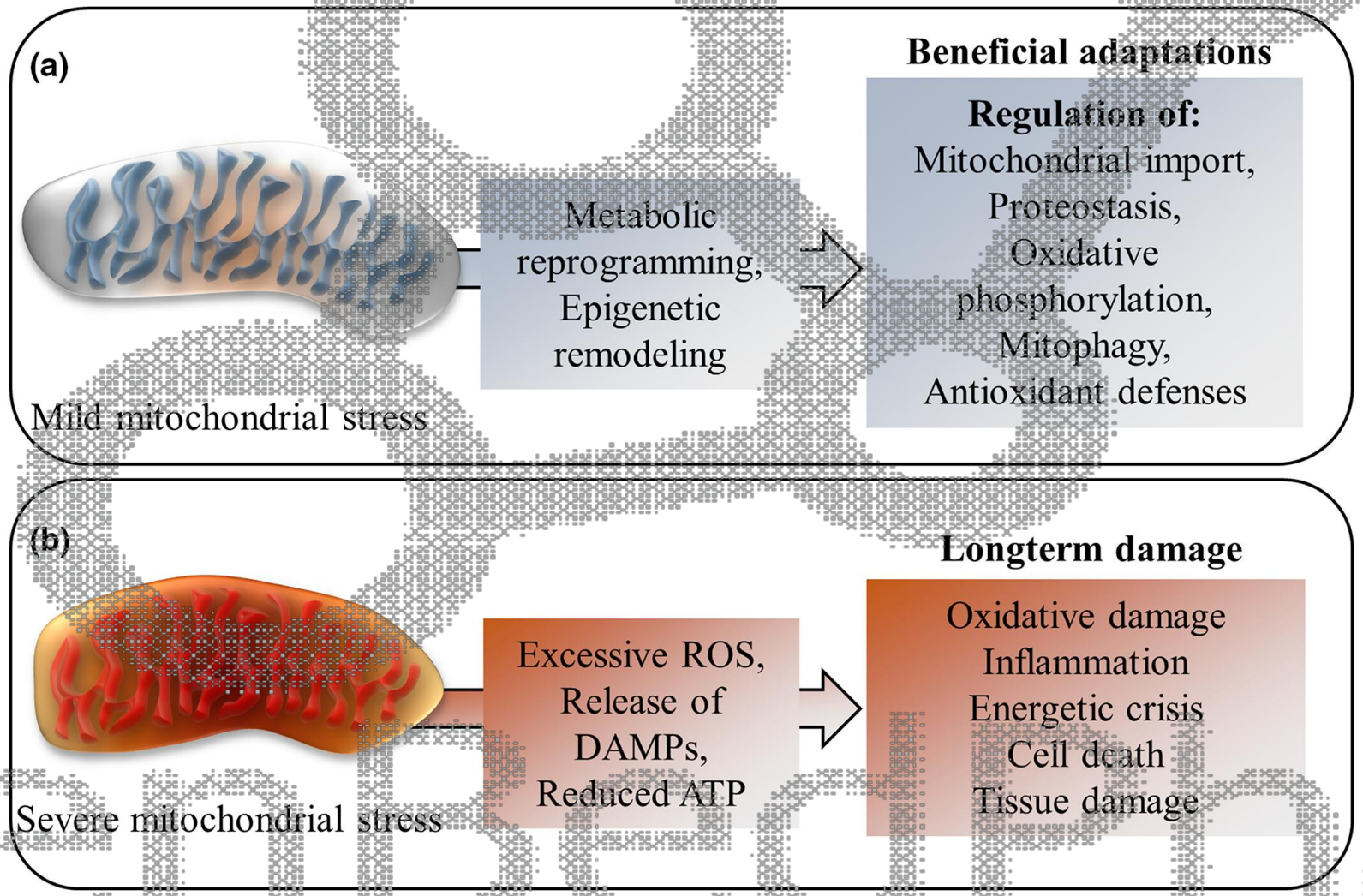
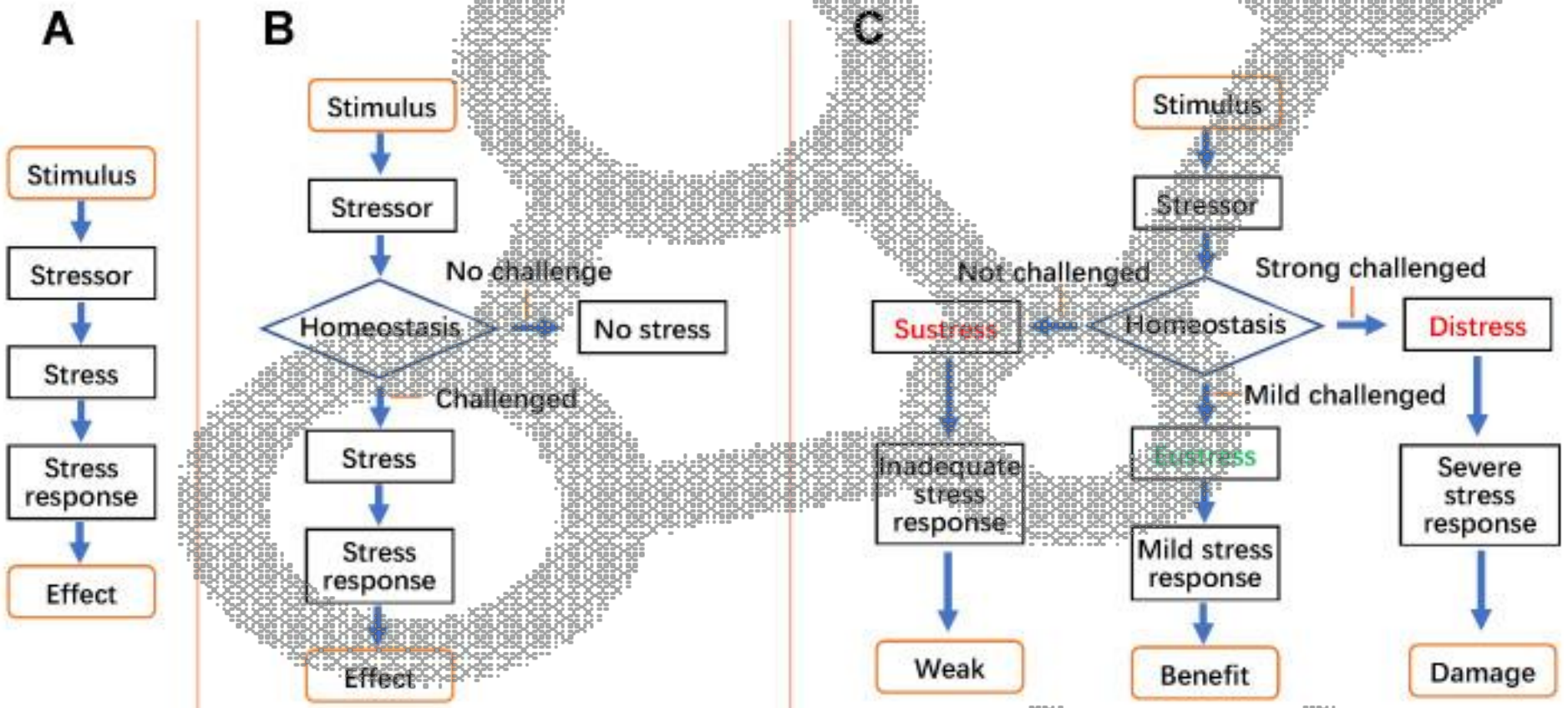
Vaziri N., IJKD 2, (1), 2008, P. 1-10.

Mitochondrial stress



Aging Cell, Volume: 22, Issue: 2, First published: 15 January 2023, DOI: (10.1111/acel.13770)

Evolution of the concept of stress

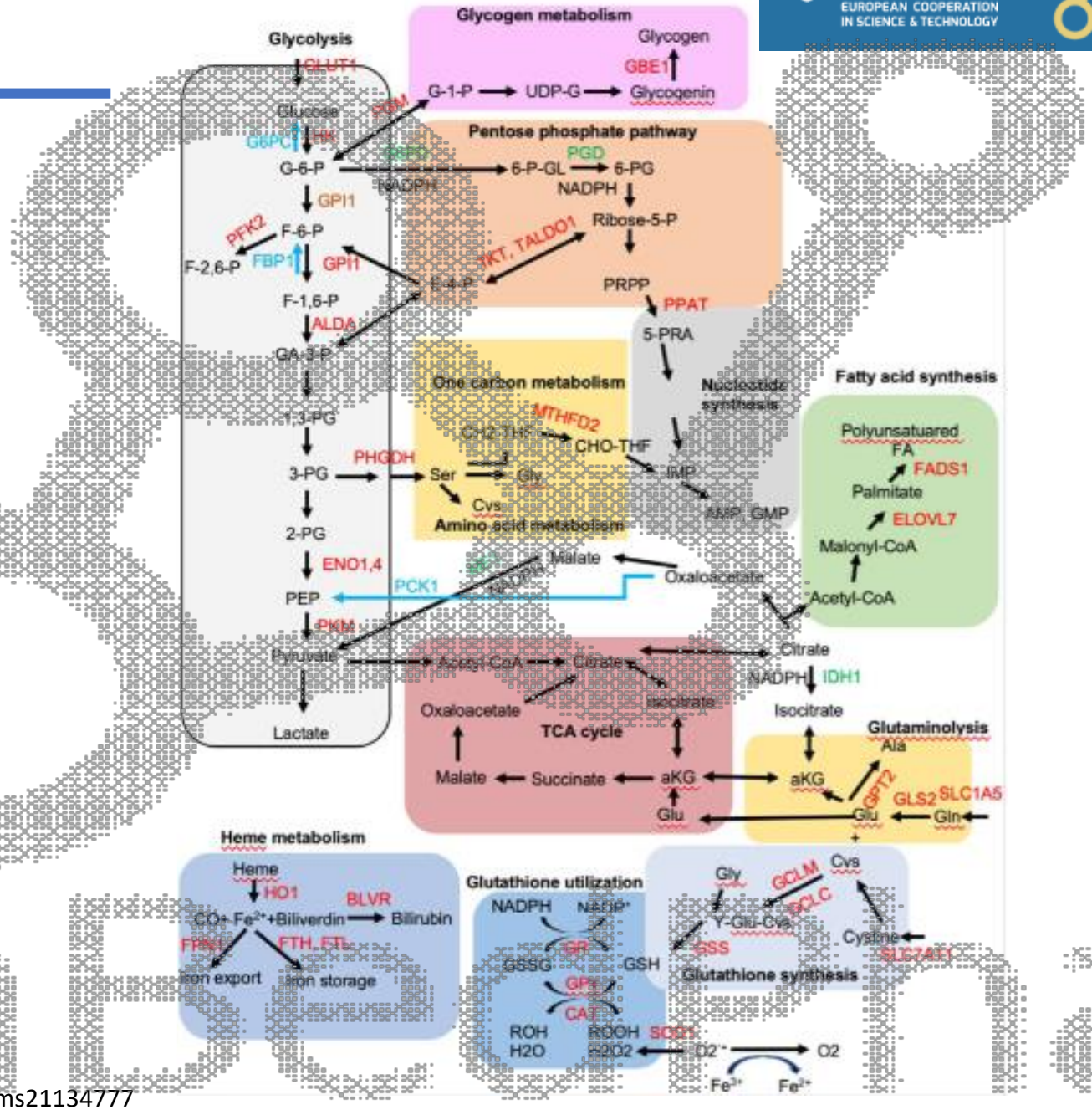


Lu S, Wei F, Li G. Cell Stress. 2021 Apr 26;5(6):76-85. doi: 10.15698/cst2021.06.250.

NFR2 in stress

NRF2 regulates genes

Glycolysis
Gluconeogenesis
Glycogen metabolism
Pentose phosphate pathway
One carbon metabolism
Amino acid metabolism
Nucleotide biosynthesis
Glutaminolysis
Fatty acid synthesis,
Heme metabolism
Glutathione synthesis



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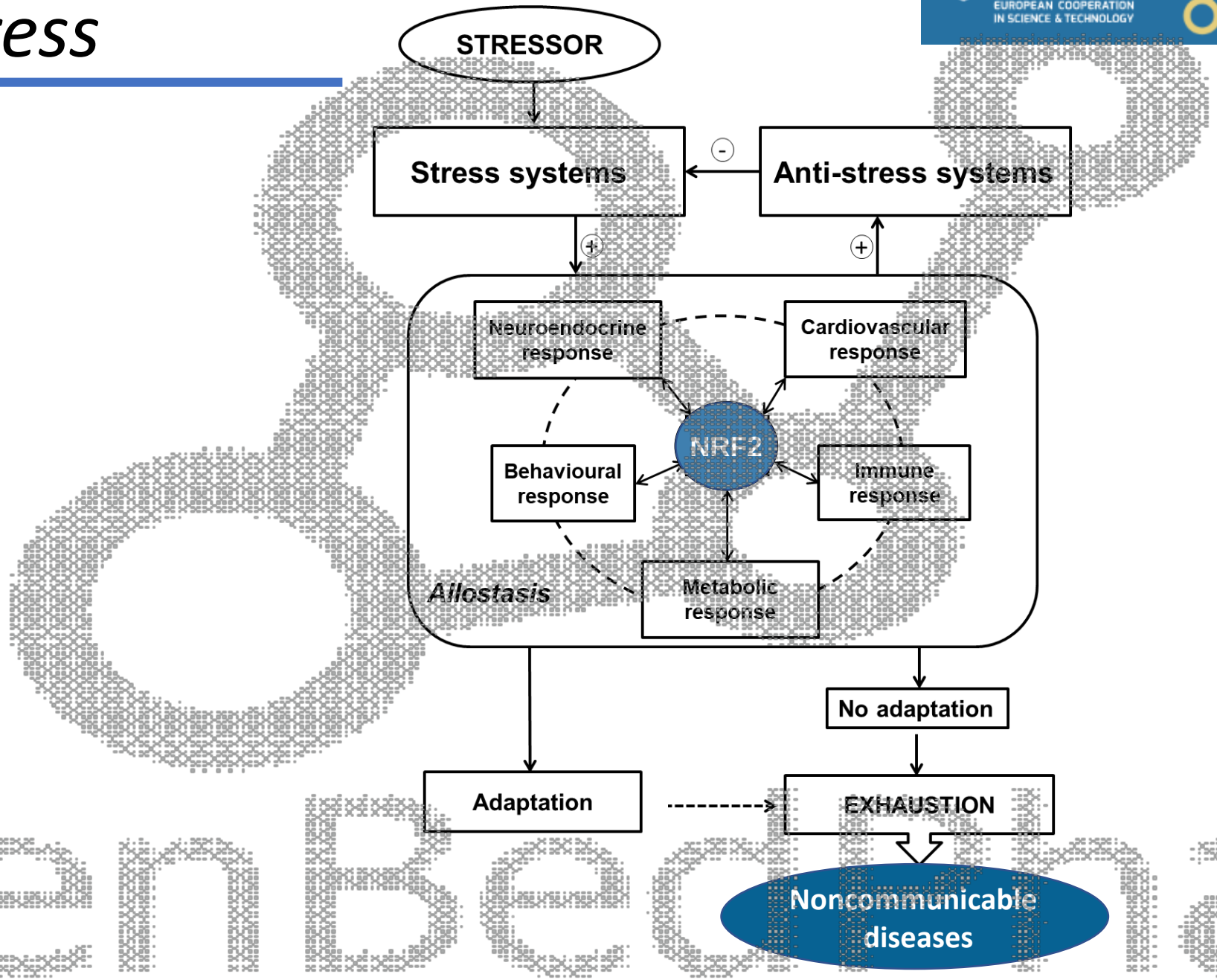
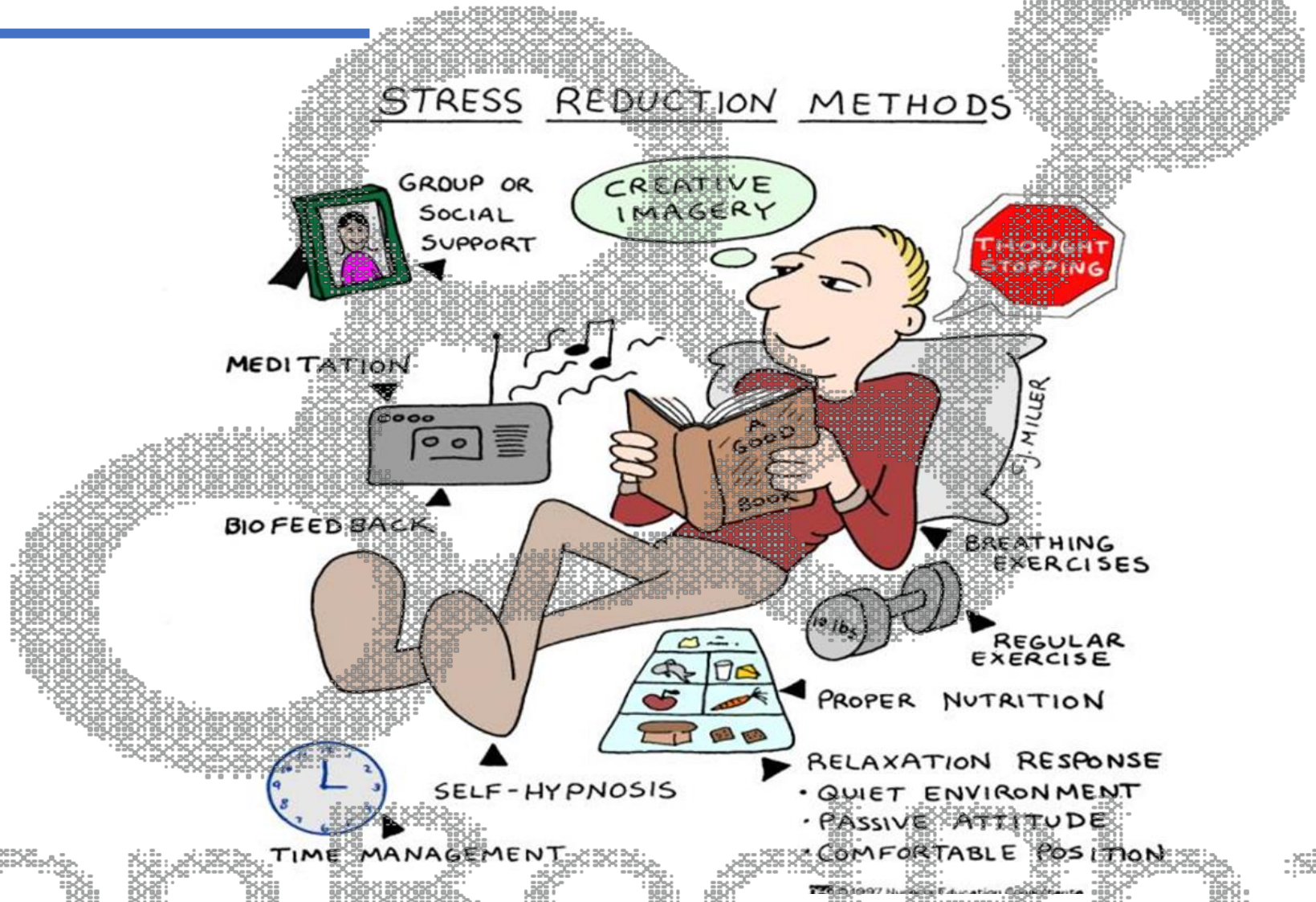
NFR2 in stress



Relax



Thank you for your attention!