STRESS MANAGEMENT

1

- **Eustress**

  Results from something good and we react positive. Manageable Stress can lead to growth and enhanced competence

- **Distress**

  Results from something bad and we react negative. Uncontrollable, prolonged, or overwhelming stress is destructive

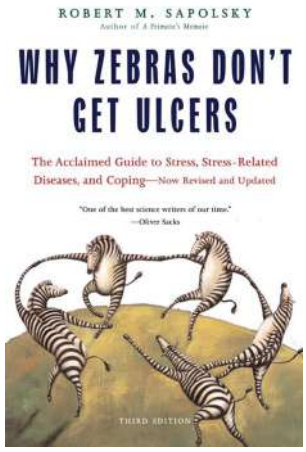
2

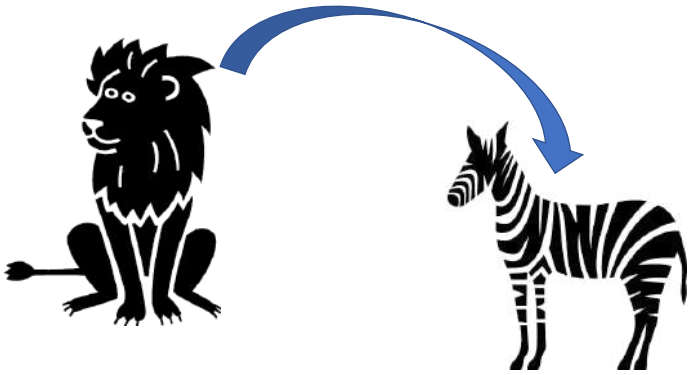
What Causes Stress?

- **Stressors**- **Physical, Emotional, Social**
- Family Relationships
- School
- Peer Groups/ Friends
- Discrimination
- Injury
- Sickness
- Fatigue
- Any Major Changes

Stressors *are things that cause stress. Almost everything is a stressor depending on the individual.*

3





The zebra's stress lasts about 3 minutes.

Run Away

FIGHT or FLIGHT

4

But you are NOT a zebra.....

Modern stressors do NOT permit fight or flight

DAMAGES

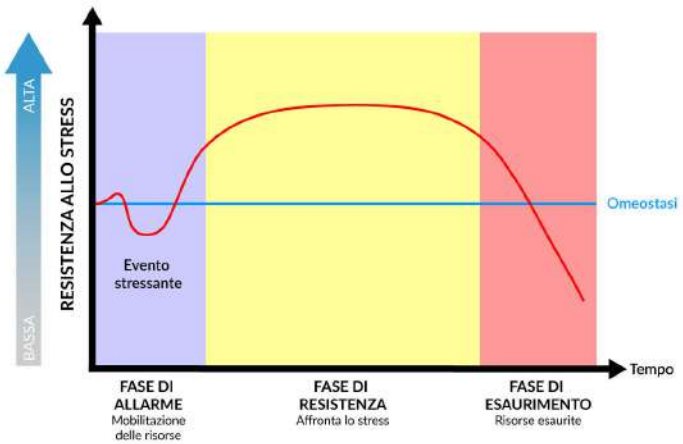
Stress response CONTINUES

5

Stages of the Stress Response

General Adaptation Syndrome of Hans Selye (1907-1982)

- **Alarm** - when one feels threatened. Activation of the fight or flight reaction
- **Resistance** - mobilization of resources to solve the problem. Continued stress causes adaptation
- **Exhaustion** - Adaptation fails and level of function decreases



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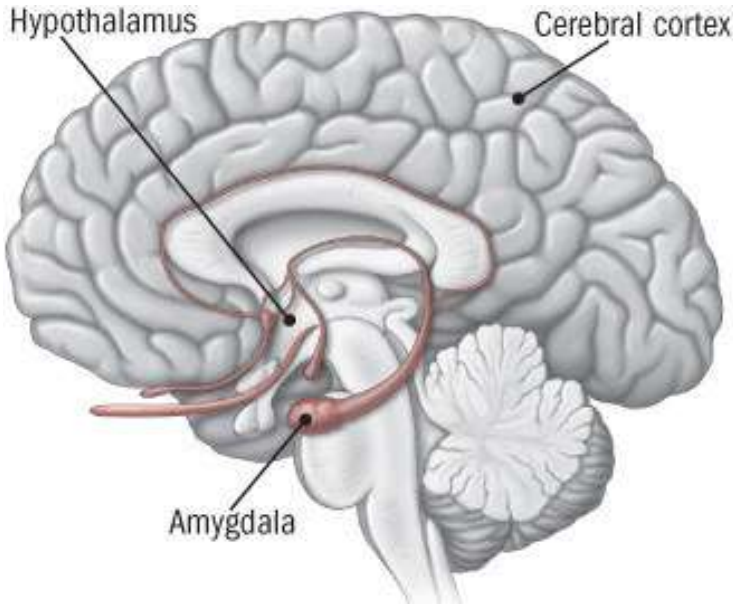
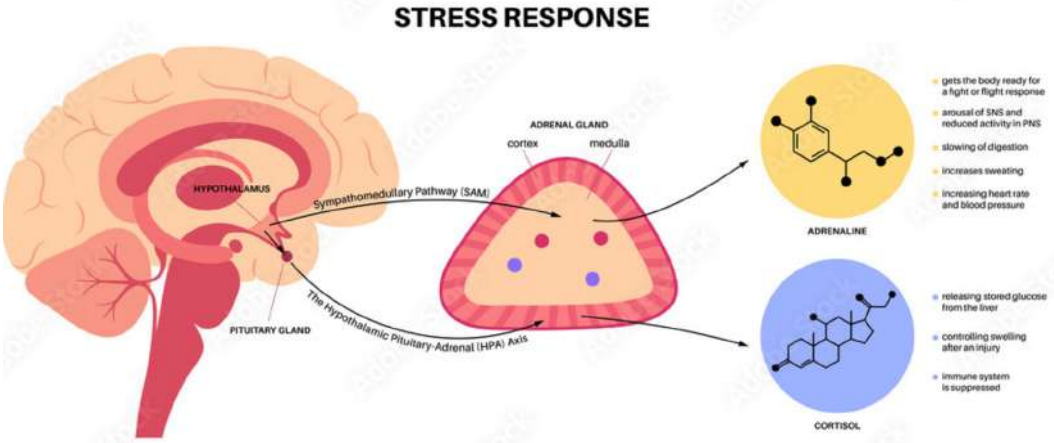


7

two main stress response systems

- **autonomic nervous system (ANS)**
- **hypothalamus–pituitary– adrenal axis (HPA axis)**

catecholamines (adrenaline and noradrenaline) and **cortisol**, play key roles in managing stress.



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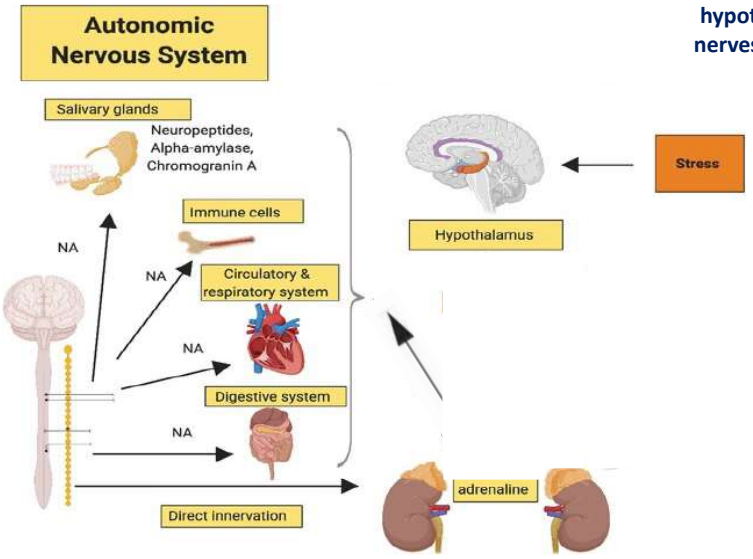
Alarm Phase (Fight-or-Flight Response)



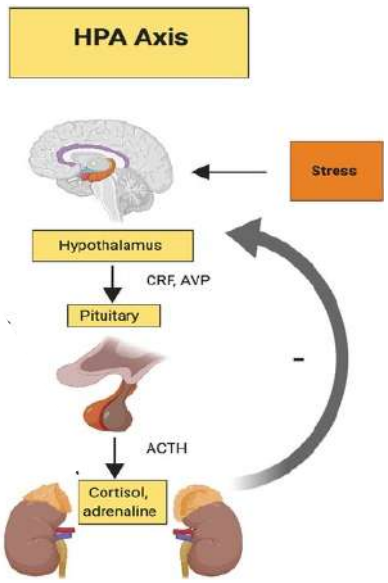
hypothalamus by stimulating the autonomic nerves sends signals to the peripheral organs:

- Catecholamines

- Increases cardiac output
- Dilates airways
- Dilates pupils
- Mobilizes glucose
- Causes vasomotor changes
- Decreases digestion
- Enhances coagulation

9

Alarm Phase (Fight-or-Flight Response)



Activation of Hypothalamic Pituitary Adrenal Axis

Cortical Steroids

- Elevates glucose
- Increases amino acids
- Increases NA resorption
- Increases extracellular fluid volume
- Inhibits histamine and bradykinin
- Suppresses the immune response

10

Alarm Phase (Fight-or-Flight Response)

Physiological Effects:

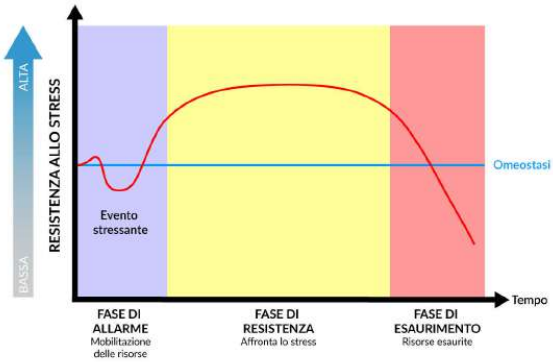
- Increased heart rate and blood pressure
- Increased respiration rate
- Heightened alertness and focus
- Dilation of the pupils
- Blood flow directed to muscles
- Increased blood glucose levels for energy

The body is now in a state of readiness to handle the immediate stressor, either by fighting or fleeing

11

Resistance

- Adaptation occurs
  - Activation of the hypothalamic pituitary adrenal axis continues
- The stressor may be resolved
  - The body returns to homeostasis
- May progress to exhaustion
  - Stress continues as resources are depleted



12

Resistance

Physiological Effects:

•Prolonged alertness and vigilance
•Increased metabolism to maintain energy levels
•Blood pressure and heart rate are elevated, but typically not as high as during the alarm phase
•Muscles may become tense as the body remains on high alert
•Immune system function may be suppressed in the long term due to the high cortisol levels

During this phase, the body is attempting to maintain a state of homeostasis while dealing with the ongoing stress. If the stressor is managed or resolved, the body can return to normal function. However, if the stressor continues for a long period, the body remains in this elevated state of arousal, which can have detrimental effects.

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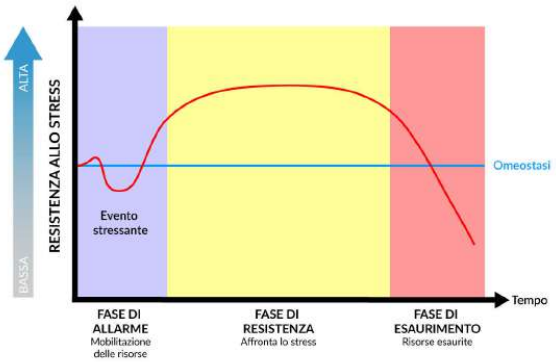
Exhaustion

- Occurs when the demands of the stress exceeds the persons ability to adapt.
- Functioning declines
- May result in health problems
  - Physical symptoms
  - Mental symptoms



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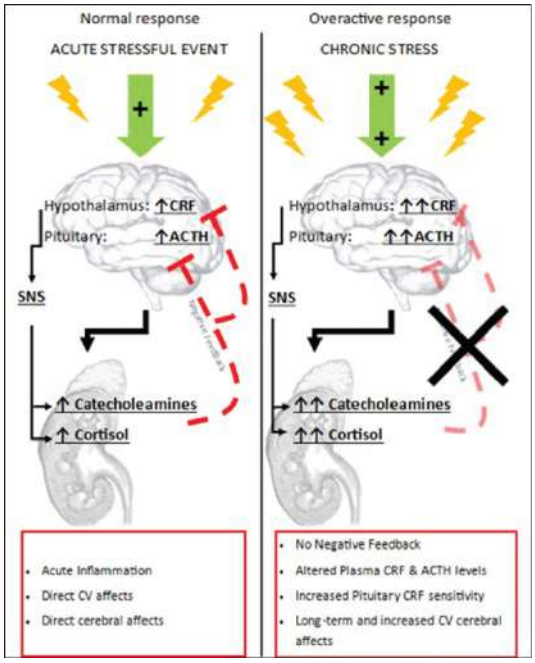
Acute Stress

Immediate response to a threat or challenge

Chronic Stress

Ongoing exposure to stress, may seem unrelenting



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STRESS

	Acute	*Chronic*
Physical	injury	hunger, cancer
Psychological	deadline	chronic work pressure
Social	humiliation	chronic isolation

16

Signs & Symptoms of Stress

- **Cognitive**
  - Decreased concentration, comprehension, & memory
- **Behavioral**
  - Irritability, withdrawal, violence
- **Emotional**
  - Fear, anxiety, depression, fatigue
- **Physiological**
  - Increased BP, HR, Respirations, etc
  - Somatic symptoms
  - Decreased immune response

17

…in summary

The Stress-Response

•Mobilization of energy

•Increased cardiovascular tone

•Suppression of digestion

•Suppression of growth

•Suppression of reproduction

•Enhancement of immune system

•Sharpening of cognition

18

The consequences of chronic stress

- Mobilization of energy……**Fatigue, diabetes, muscle loss**
- Increased cardiovascular tone…….**Hypertension, heart disease**
- Suppression of digestion……..**Stress ulcers**
- Suppression of growth……..**Stress dwarfism**
- Suppression of reproduction……**Anovulation, erectile dysfunction**
- Enhancement of immune system……**Immune suppression, accelerated chromosomal aging of immune cells**
- Sharpening of cognition……**Impaired memory and judgement**

19

Do our genes control our stress response?

Clinical research

Genetics of stress response and stress-related disorders

Marcus Ising, PhD; Florian Holsboer, MD, PhD

JAMA Psychiatry | Original Investigation

Genetic Variants Associated With Anxiety and Stress-Related Disorders

A Genome-Wide Association Study and Mouse-Model Study

Review Article

Stress Genes: An Introductory Overview

Alberto J. L. Macario & Everly Conway de Macario

Pages 123-134 | Received 17 Jun 1996, Accepted 11 Dec 1996, Published online: 07 Jul 2009

Download citation https://doi.org/10.3109/10253899709001102

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Psychoneuroendocrinology
Volume 43, May 2014, Pages 71-80

CRHR1 genotype and history of maltreatment predict cortisol reactivity to stress in adolescents

Jennifer A. Sumner [a], Katie A. McLaughlin [b], Kate Walsh [a], Margaret A. Sheridan [c], Karestan C. Koenen [a]

> Psychoneuroendocrinology. 2018 Jan;87:173-180. doi: 10.1016/j.psyneuen.2017.10.020. Epub 2017 Oct 28.

The role of genetic variation in the glucocorticoid receptor (NR3C1) and mineralocorticoid receptor (NR3C2) in the association between cortisol response and cognition under acute stress

Thomas Plieger [1], Andrea Felten [2], Hanna Splittgerber [2], Éilish Duke [3], Martin Reuter [2]

▸ Front Psychiatry. 2023 Jun 16;14:1182345. doi: 10.3389/fpsyt.2023.1182345

Role of FKBP5 and its genetic mutations in stress-induced psychiatric disorders: an opportunity for drug discovery

Mahdi Malekpour [1,2,†,#], Dorsa Shekouh [1,†,#], Mohammad Ebrahim Safavinia [1], Shadi Shiralipour [1], Maryam Jalouli [1], Sahar Mortezanejad [1], Negar Azarpira [2,*], Niloofar Dehdari Ebrahimi [2]

21

MODES OF TRANSCRIPTIONAL REGULATION

Controlling gene expression in response to stress

Eulàlia de Nadal*, Gustav Ammerer† and Francesc Posas*

Brain, Behavior, and Immunity 25 (2011) 1305–1315

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Named Series: Epigenetics, Brain, Behavior, and Immunity

Epigenetic mechanisms in stress and adaptation

Karen R. Mifsud, María Gutièrrez-Mecinas, Alexandra F. Trollope, Andrew Collins, Emily A. Saunderson, Johannes M.H.M. Reul *

Epigenetic Influence of Stress and the Social Environment

Kathryn Gudsnuk and Frances A. Champagne

International Journal of Molecular Sciences

Review

Glucocorticoid Signaling and Epigenetic Alterations in Stress-Related Disorders

Niki Mourtzi [1], Amalia Sertedaki [1] and Evangelia Charmandari [1,2,*]

Review

Epigenomics

The epigenetic impacts of social stress: how does social adversity become biologically embedded?

Vincent T Cunliffe

22

MINI REVIEW article
Front. Psychiatry, 20 March 2020 | https://doi.org/10.3389/fpsyt.2020.00163

Epigenetics Underlying Susceptibility and Resilience Relating to Daily Life Stress, Work Stress, and Socioeconomic Status

Michael G. Gottschalk[1], Katharina Domschke[1,2] and Miriam A. Schiele[1*]

Study	Sample	Tissue	Assessment	Gene(s)/ scope	Findings
Daily life stress					
Daman and Canli (8)	105 Caucasian males	Blood	TICS for past 3 months	*SLC6A4*	↑ total-methylation as a function of chronic daily stress in *5-HTTLPR* ll genotype carriers ↑ promoter methylation as a function of chronic daily stress in *5-HTTLPR* s allele carriers
Pishva et al. (9)	112 Dutch/Belgian psychiatrically healthy individuals, a population-based replication sample of 434 individuals, 85 unaffected siblings of patients with psychosis, 110 patients with psychosis, 126 patients with a MDD lifetime history and residual symptoms	Blood, saliva, or buccal epithelium	Experience sampling method for daily stressful and pleasant events	*DNMT1, DNMT3A, DNMT3B, MTHFR*	Association of the minor *DNMT3A* rs11568424 T allele with a reduced impact of daily life stress on negative affectivity in the discovery sample, replication sample, and in the sample of patients with a MDD lifetime history
Work stress					
Alasaari et al. (6)	24 Finnish female nurses reporting high and 25 female nurses reporting low work stress environments	Blood	JCQ	*SLC6A4*	↓ promoter methylation associated with increased perceived work stress.
Miyaki et al. (7)	360 Japanese manufacturing company workers	Saliva	JCQ	*TH*	↑ overall average / promoter / 5′-regulatory region methylation associated with increased work strain
Song et al. (9)	360 Japanese manufacturing company workers	Saliva	JCQ	*BDNF*	↑ overall average methylation associated with increased work strain
Sulkava et al. (9)	59 Finnish pilots, flight attendants, and nurses (from Alasaari et al., 2014)	Blood	–	*MTNR1A*	↑ methylation levels in the *MTNR1A* promoter region associated with the minor *MTNR1A* rs12506228 A allele (discovered in a GWAS of work-related exhaustion in the same study)
SES					
Bush et al. (10)	178 kindergarten children from mixed ethnic backgrounds	Buccal epithelium	Composite measure of parental income and education used as a proxy of SES	EWAS	Overrepresentation of altered methylation at CpG sites in genes related to immune and developmental regulation functions associated with low SES
Coker et al. (11)	241 Mexican-American maternal-infant pairs	Cord blood	Neighborhood-level characteristics used as a proxy of SES	EWAS	↑ methylation of *LINE1* elements associated with low SES
Fiorito et al. (12)	Meta-analysis of 5,087 samples of independent cohorts from Australia, Ireland, and Italy	Blood	Highest level of educational attainment used as a proxy of SES	Accelerated intrinsic epigenetic aging	Increased accelerated epigenetic aging associated with low SES
Jones-Mason et al. (13)	103 late adolescents from mixed ethnic backgrounds	Blood	Hollingshead Measure of SES	*SLC6A4*	↑ methylation and low SES linked to increased reports of trauma
Laubach et al. (14)	659 maternal–infant pairs from mixed ethnic backgrounds	Cord blood and peripheral blood (9-year follow-up)	Composite measure of individual- and neighborhood-level metrics used as a proxy of SES	EWAS	Altered methylation in CpG sites mapped to *ACSF3, 7NK9C-AS1, MTMR4* and *LARP4* associated with low SES. *LARP4* methylation changes persisted into early childhood
McDade et al. (15)	486 Filipino youth	Blood	Composite measure of income, assets, and education used as a proxy of SES	EWAS	Overrepresentation of altered methylation at CpG sites in genes related to immune functions, skeletal development, and CNS development associated with low SES
Santos et al. (16)	426 infants born <28 weeks of gestation from mixed ethnic backgrounds	Placenta	Composite measure of parental education, marital status, food and nutritional service assistance, and public health insurance used as a proxy of SES	EWAS	Overrepresentation of altered methylation at CpG sites in genes related to cellular immune and stress response associated with low SES
Swartz et al. (17)	132 Caucasian adolescents	Saliva	Highest level of parental educational attainment used as a proxy of SES	*SLC6A4*	↑ methylation change over 2 years associated with low SES and increased threat-related amygdala reactivity
Uddin et al. (18)	77 trauma-exposed controls and 23 PTSD patients, primarily with African-American background	Blood	Highest level of educational attainment used as a proxy of SES	EWAS	Methylation×SES interaction occurred primarily in genes related to nervous system function

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Psychoneuroendocrinology
Volume 150, April 2023, 106045

Mild daily stress, in interaction with *NR3C1* DNA methylation levels, is linked to alterations in the HPA axis and ANS response to acute stress in early adolescents

Viktorie Chubar[a], Thomas Vaessen[b,c], Wim Van den Noortgate[b], Erika Lutin[d,e], Guy Bosmans[f], Brom Bekaert[a,f], Karlo Van Leeuwen[g], Filip Calders[g], Sofie Weyn[h], Patricia Bijttebier[h], Luc Goossens[f], Stephan Claes[a,i]

Journal of Affective Disorders
Volume 331, 15 June 2023, Pages 287-299

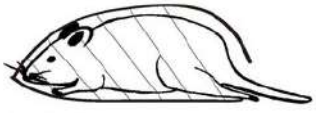
DNA methylation in regulatory elements of the *FKBP5* and *NR3C1* gene in mother-child binomials with depression

Mariana S. Mendonça[a], Paula M. Mangiavacchi[b], Ana V. Mendes[c], Sonia R. Loureiro[c], Rocio Martin-Santos[d,e], Leonardo S. Glória[f], Wilson Marques[c], Silmara P.G. De Marco[c], Milton M. Kanashiro[g], Jaime E.C. Hallak[c,d], José A.S. Crippa[c,d], Álvaro F.L. Rios[a]

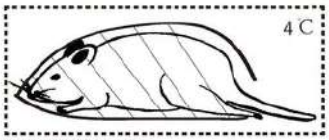
24

How do you study stress in an animal?

- expose them to a stressor
- induce a metabolic physiological stress

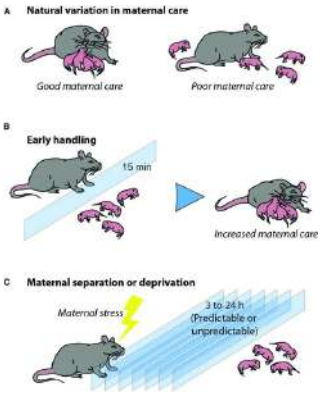


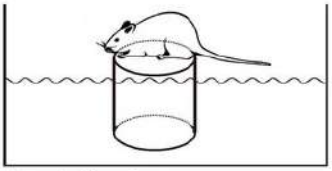
Restraint Stress



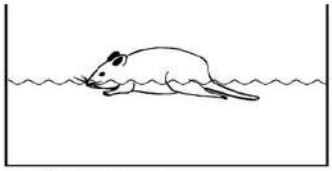
Cold Restraint Stress

Examples of stress in rats





Water Avoidance Stress



Forced Swimming Stress

25

Biomedicine & Pharmacotherapy 108 (2018) 1404-1411

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Human PBMCs fight or flight response to starvation stress: Increased T-reg, FOXP3, and TGF-β1 with decreased miR-21 and Constant miR-181c levels

Mahsa Rahmani[a,b], Mousa Mohammadnia-Afrouzi[b,c,d], Hamid Reza Nouri[b], Sadegh Fattahi[b], Haleh Akhavan-Niaki[b], Amrollah Mostafazadeh[b,*]

[a] Students Research Committee, School of Medicine, Babol University of Medical Sciences, Babol, Iran
[b] Cellular and Molecular Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[c] Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[d] Immunoregulation Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

in vitro ?

in humans ?

Li et al. BMC Cancer (2020) 20:627
https://doi.org/10.1186/s12885-020-07118-3

BMC Cancer

RESEARCH ARTICLE Open Access

Starvation stress attenuates the miRNA-target interaction in suppressing breast cancer cell proliferation

Jinhui Lü[1†], Chuyi Zhang[1†], Junyi Han[2†], Zhen Xu[1], Yuan Li[1], Lixiao Zhen[1], Qian Zhao[1], Yuefan Guo[1], Zhaohui Wang[1,3], Evelyne Bischof[4,5*] and Zuoren Yu[1*]

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…so stress might be responsabile of

Review Article | Published: 10 September 2021

Stress and cancer: mechanisms, significance and future directions

Anabel Eckerling, Itay Ricon-Becker, Liat Sorski, Elad Sandbank & Shamgar Ben-Eliyahu

Nature Reviews Cancer **21**, 767–785 (2021) | Cite this article

5346 Accesses | **2** Citations | **91** Altmetric | Metrics

THE ASSOCIATION BETWEEN STRESS AND DRINKING: MODIFYING EFFECTS OF GENDER AND VULNERABILITY

DEBORAH A. DAWSON, BRIDGET F. GRANT, W. JUNE RUAN

Alcohol and Alcoholism, Volume 40, Issue 5, September/October 2005, Pages 453–460, https://doi.org/10.1093/alcalc/agh176

Published: 21 June 2005

MENU | Mental Health › Eating Disorders › Binge Eating Disorder › Reference

How Does Stress Affect Binge Eating?

By Stephanie Watson

Medically Reviewed by Jennifer Casarella, MD on September 27, 2020

Curr Neuropharmacol. 2015 Jul; 13(4): 494–504. PMCID: PMC4790405

Published online 2015 Jul. doi: 10.2174/1570159X13041508311505O7 PMID: 26412069

The Effects of Psychological Stress on Depression

Longfei Yang,[a] Yinghao Zhao,[b] Yicun Wang,[a] Lei Liu,[a] Xingyi Zhang,[b] Bingjin Li,[a,*] and Ranji Cui[a,*]

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Front Hum Neurosci. 2017; 11: 316. PMCID: PMC5476783

Published online 2017 Jun 20. doi: 10.3389/fnhum.2017.00316 PMID: 28676747

Inflammation: The Common Pathway of Stress-Related Diseases

Yun-Zi Liu, Yun-Xia Wang, and Chun-Lei Jiang*

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Stress Biology and Aging Mechanisms: Toward Understanding the Deep Connection Between Adaptation to Stress and Longevity

Elissa S. Epel, Gordon J. Lithgow Author Notes

The Journals of Gerontology: Series A, Volume 69, Issue Suppl_1, June 2014, Pages S10–S16, https://doi.org/10.1093/gerona/glu055

ublished: 08 May 2014 **Article history**

Review › Clin Chim Acta. 2020 Apr;503:163-168. doi: 10.1016/j.cca.2020.01.019 Epub 2020 Jan 24.

Stress and neurodegeneration

Carmen Peña-Bautista [1], Esther Casas-Fernández [1], Máximo Vento [1], Miguel Baquero [2], Consuelo Cháfer-Pericás [2]

Affiliations + expand

PMID: 31987795 DOI: 10.1016/j.cca.2020.01.019

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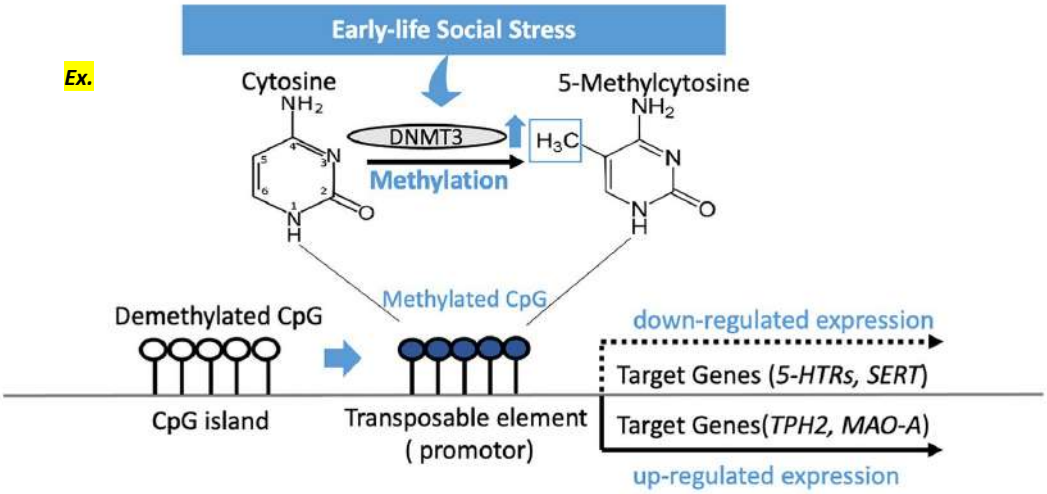
…and which genes should I look at??

Genetic and Epigenetic Consequence of Early-Life Social Stress on Depression: Role of Serotonin-Associated Genes

Ex.



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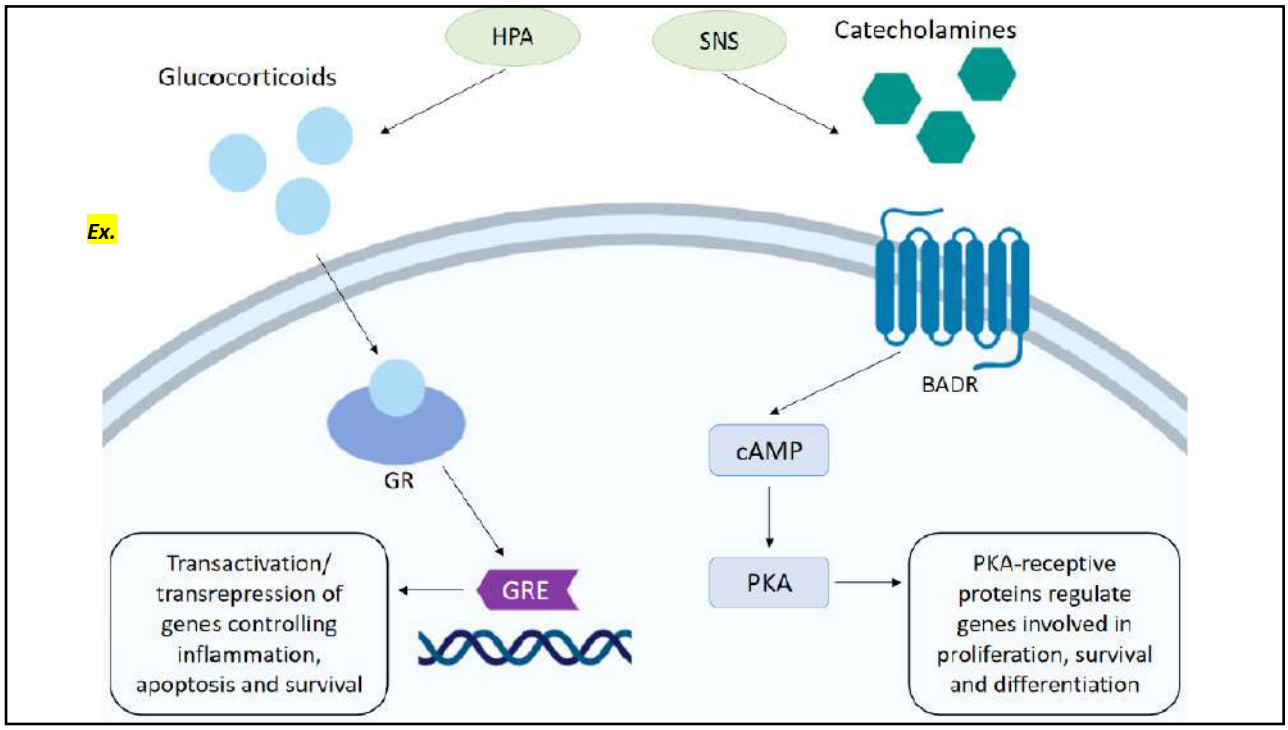
HPA
SNS
Catecholamines
Glucocorticoids
Ex.
BADR
GR
cAMP
Transactivation/ transrepression of genes controlling inflammation, apoptosis and survival
GRE
PKA
PKA-receptive proteins regulate genes involved in proliferation, survival and differentiation

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