Psychological stress and inflammation

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Live Fast, Die Young.

This Chinese man lived for 256 years!
Stress-related phenotypes and disease risk

Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease

Depression, Inflammation, and Clustering of Metabolic Risk Markers

Andrea Danese, MD, MSC; Terrie E. Moffitt, PhD; HonaLee Harrington, BA; Barry J. Milne, PhD; Gailherme Polanczyk, MD, PhD; Carmine M. Partane, MD, MRCPsych, PhD; Richie Poulton, PhD; Avshalom Caspi, PhD

Lifetime History of Depression and Carotid Atherosclerosis in Middle-aged Women

Deborah J. Jones, PhD; Joyce T. Bromberger, PhD; Kim Sutton-Tyrrell, DrPH; Karen A. Matthews, PhD

Age of major depression onset, depressive symptoms, and risk for subsequent the German Study on and Dementia in Primary Care Patients (AgeCoDe)

Molecular mechanisms?


A Twin Study

Viola Vaccarino, MD, PhD; Jack Goldberg, PhD; Cherie Rooks, PhD; Amit J. Shah, MD, MSCR; Emir Veledar, PhD; Tracy L. Faber, PhD; John R. Votaw, PhD; Christopher W. Forsberg, MS; J. Douglas Bremner, MD∥

Elevated Inflammation Levels in Depressed Adults With a History of Childhood Maltreatment

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Stress and inflammation: a bidirectional relation
Stress as a fight or flight (or freeze) response

Walter Cannon, 1915
The genesis of biological ‘str’-ess

Hans Selye
1907-1982

But what is really stress?
“After the completion of our last effort to define stress (Levine and Ursin, 1991), I made myself the promise that I would never again engage in what I consider a futile exercise.”

Levine, *Psychoneuroendocrinology* 2005
Stress: definitions

- **Stressor**: Any physical or emotional challenge that threatens homeostasis
- **Stress response**: The organism’s response to a stressor (behavioral, endocrine, molecular, etc.)
- **Stress system**: The central and peripheral organs involved in the stress response
- **Stress**: Loosely defined
Acute vs. Chronic inflammation

**Acute**
- Cuts, Laceration, Stabbing
- Frostbite
- Chemical irritants
- Trauma (bruises, sprains / strains, broken bones)
- Allergic Reaction
- Burn (sun, fire, touching hot objects)
- Infection

**Chronic**
- Cardiovascular Disease
- Autism
- Rheumatoid Arthritis
- Autoimmune Disease
- Depression
- Cancer
- Alzheimer
- Neurological Disease

Inflammation
Brain/stress -> immune axis

**Stress**
- Genetic and other risk factors
- Stress-related behaviors (diet, smoking, etc.)

**Inflammation**

**Immune and inflammatory reaction**
- Cytokines, prostanoids, and platelet-activating factor, neuropeptides, other mediators

**Stress System**
- Locus caeruleus (noradrenergic system)

**CRF**
- Corticotropin
- Catecholamines
- Cortisol
- Δ⁵-Adrenal androgens

**Spinal cord**

**Postganglionic sympathetic neuron**

Danese et al.  
*PNAS*  
2006

Chrousos  
Stress and the HPA axis

Chrousos & Gold 1993; Thomassin et al. 2001
Glucocorticoids and immune regulation

Bellavast & Rivest, Frontiers in Immunology 2014
Stress, glucocorticoids, and immune system: complex relationships

• Not just immunosuppressive
• Timing and concentration critical (Liu et al. Frontiers in *Immunology* 2018)
• Pro- vs. anti-inflammatory players (Vettorazzi et al. *Nature Communications* 2015)
• Effects depend on circadian rhythm and other context (Shimba et al. *Immunity* 2018)
• Epigenetic mechanisms?
Matouk & Marsden 2010
Stress along the lifespan can shape the epigenome

Global DNA hypermethylation
Local DNA methylation changes
Changes in histone acetylation
Alterations in miRNAs

Global DNA methylation changes
Demethylation of CpGs near GRES
Altered DNA-binding of MeCP2
Changes in histone methylation
Changes in miRNA expression

Changes in DNA methylation
Histone modifications
Altered DNA-binding of MeCP2
Alterations in miRNAs
Chromatin remodeling

Prenatal life
Childhood
Adolescence
Adulthood
Late-life

Period of rapid organism-wide and tissue-specific epigenetic remodeling

Decline in epigenetic maintenance systems
Rearrangement and loss of heterochromatin

Zannas & Chrousos Mol Psychiatry 2017
Epigenetic programming by maternal behavior

Ian C G Weaver¹,², Nadia Cervoni³, Frances A Champagne¹,², Ana C D’Alessio³, Shakti Sharma¹, Jonathan R Seckl⁴, Sergiy Dymov³, Moshe Szyf²,³ & Michael J Meaney¹,²
DNA methylation changes at gene promoters

DNA demethylation at or near GREs

Stress-related phenotypes

Plasma membrane

Cytoplasm

Nucleus

Zannas & Chrousos 2017
The stress-responsive co-chaperone FKBP5

Glucocorticoid response elements in FKBP5

Long-term epigenetic programming of immune cells

Diet

NLRP3 inflammasome

Systemic inflammation

Granulocyte-monocyte precursor

Bone marrow and immune cell reactivity

Epigenomic, transcriptional and functional reprogramming

Eicke et al, *Cell* 2018
Immune -> Brain connection

Can Infection Give You the Blues?

An overactive immune response can cause depression
Pathways of immune -> brain connection

Khandaker et al. *Lancet Psychiatry* 2015
Inflammation can trigger stress
Inflammatory cells in the brain?

• Systemic inflammatory signals promote shuttling of neutrophils to the brain (Rummel et al. 2010)

• Brain T cells increase upon systemic inflammatory signals and stress exposure (Beurel et al. 2013)

• Microglia are important resident immune cells (macrophages) in the brain (Li & Barres 2017)
Stress activates brain microglia
Stress-inflammation-stress: regulatory or vicious cycle?

Immune-brain axis (top-bottom)  
*Immunopsychiatry*

Brain-immune axis (top-bottom)  
*Psychoneuroimmunology*
Ok, now what?

- Stress attenuation but not elimination
- Convert negative stress to positive
- Prevent chronic persistent stress
- Prevent stress-induced inflammation
The perception of stress is critical

“Adopting the right attitude can convert a negative stress into a positive one.”

Hans Selye

“Working hard for something we don’t care about is called stress; working hard for something we love is called passion.”