SnapShot: Stress and Disease

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**BRAIN**
- **SNS**
  - ↑ Dopamine → anxiety-like behavior
  - ↓ Striatal dopamine D2 receptor → ↑ appetite
  - ↑ Nerve firing
  - ↑ Neuron atrophy
- **HPA**
  - ↑ Disrupted circadian rhythm and hypercortisolism → depression
  - ↑ GC → dendrite retraction in hippocampus → impaired memory

**CARDDIOVASCULAR SYSTEM**
- **SNS**
  - ↑ Heart rate, hypertension
  - ↑ CVD

**STRESS-RELATED MYOCARDIAL DISEASE**
- (Takotsubo cardiomyopathy)
  - ↑ Plaque disruption
  - ↑ Platelet reactivity
  - Increased cortisol → ↓ heart rate variability

**IMMUNE SYSTEM**
- **SNS**
  - ↑ Neutrophils and inflammatory monocytes
  - ↓ Proliferation of peripheral blood T cells
  - ↓ T lymphocytes
  - ↑ Mast cell hyperactivity
  - ↓ Innervation of lymphoid tissue
  - ↓ IL12 by antigen-presenting cells
  - ↑ CRP and IL6 in blood plasma
  - ↑ Inflammation
  - ↑ HIV-1 replication in PBMCs
  - Reactivation of latent Epstein-Barr and herpesviruses
  - ↑ Inflammatory molecules (e.g., IL1, IL2, IL6, IL12)
  - ↓ AP1 and ↑ NF-κB → ↓ immune responses in leukocytes
  - ↓ Ras, RAF, and MAPK via ↓ GILZ → ↓ antigen-presenting capacity in macrophages and DC

**METABOLIC DISEASES**
- **SNS**
  - ↓ Insulin sensitivity
  - → ↓ thermogenesis

**DIABETES**
- ↓ Glucose transport system
- ↓ Glycogen synthase
- ↓ Insulin secretion

**COLON**
- **IBD**
  - ↑ Mucosal immune activation
  - ↑ IBD-associated inflammation: IL1, IL6, TNFα, IFNγ
  - ↑ Bacteria growth and virulence
  - ↑ Colonic epithelium injury
  - ↓ Bacterial permeability

**CANCER**
- **SNS**
  - ↑ Tumor burden and metastasis
  - ↓ Angiogenesis
  - ↓ Apoptosis via BAD, PKA, STAT3
  - ↓ Tumor-associated macrophages
  - ↓ Sympathetic innervation (prostate cancer development and dissemination)
  - ↑ Chemoresistance

See online version for legend and references.
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Stress is defined as any threat to an organism that triggers adaptations at a molecular, cellular, physiological, or behavioral level. Chronic activation, orchestrated by the SNS and HPA via stress hormones (NE, Epi, and cortisols), plays a key role in physiology and disease. In general, postganglionic neurons release NE, but there are two exceptions: postganglionic neurons of sweat glands (releasing acetylcholine) and chromaffin cells of the adrenal medulla (releasing Epi and NE).

Immune System

Stress exerts pleiotropic effects on the immune system and compromises both innate and adaptive immune responses. Stress hormones can act directly on macrophages, dendritic cells, T cells, B cells, and NK cells via GR and/or adrenergic receptors. NE increases proinflammatory molecules (CRP and IL6), whereas persistently high GCs reduce inflammation and induce immune suppression via NF-κB, AP1, Raf-, and MAPK-mediated signaling. Epidemiological studies indicate that chronic stress increases neutrophil and inflammatory monocyte numbers and stimulates mast cell degranulation. Chronic stress also attenuates peripheral blood T cell proliferation, reduces T cell control of latent viruses (Epstein-Barr and herpesviruses), and increases the risk of bacterial infection (e.g., H. pylori).

Cardiovascular Disease

Epidemiological studies link chronic stress with increased risk of myocardial ischemia or infarction and cardiac wall motion abnormalities. Of note, 16%-23% of all patients with CVD suffer from clinical depression. High plasma NE levels are associated with increased risk of heart failure. Altered autonomic activity during depression can lead to arrhythmias. Takotsubo cardiomyopathy, another stress-related myocardial disorder, is characterized by the sudden weakening of the myocardium in response to acute stress. SNS hypersensitivity alters cardiac wall contractility and contributes to apoptotic pathways in cardiomyocytes, contributing to CVD development. Stress also increases plaque rupture, leading to atherosclerosis, likely via adrenergic signaling in platelets.

Brain

NE directly stimulates dopaminergic neurons in the midbrain and the brain stem, resulting in anxiety-like behavior and depression. Stress-induced activation of the SNS increases the firing of brain neurons in prefrontal cortex and amygdala and contributes to development of hypertension and depression. Stress compromises neuronal plasticity in the hippocampus, leading to psychiatric disorders (depression). In preclinical models, chronic restraint stress disrupts serotonin (5-HT) secretion in the prefrontal cortex, leading to abnormal morphology and atrophy of pyramidal cells. Patients with depression have altered HPA activity, blunted circadian rhythm, and elevated cortisol, primarily due to GR dysfunction such as reduced GR expression, lower binding affinity, impaired nuclear translocation, or interaction with other transcription factors (NF-κB, AP1). Such dysfunction paradoxically elevates levels of proinflammatory cytokines. Further, increased cortisol promotes atrophy of nerves within the hippocampus, leading to loss of hippocampal volume.

Cancer

Epidemiological studies implicate severe life stressors in breast cancer initiation, whereas studies on rodents solidify the role of chronic stress as a driver of ovarian, breast, and prostate cancer growth and metastasis. Chronic stress may lead to epigenetic heritable modifications, suggesting a possible propagation across generations. In an ovarian carcinoma mouse model, chronic restraint stress increased tumor burden and enhanced angiogenesis and tumor production of vascular endothelial growth factor (VEGF). NE also promotes resistance to anoxia, inhibits apoptosis, and increases tumor cell invasion and metastasis, macrophage infiltration, and chemoresistance.

Colon

Stress can trigger the onset of IBS, a chronic lower gastrointestinal tract disorder characterized by abdominal pain and distension, visceral hypersensitivity, disturbed gastrointestinal motility, and changes in stool form or frequency. IBS is associated with increased intestinal permeability related to release of acetylcholine and CRH and to activation of muscarinic receptor. Patients with IBS show altered function of HPA axis with blunted ACTH levels and elevated cortisol.

Chronic stress can predispose to IBD that arises from inappropriate activation of the mucosal immune system, leading to chronic inflammation and epithelial injury. IBD patients have elevated levels of IL1β, IL6, IL8, IFNγ, and TNFα. Genome-wide association studies have identified IBD susceptibility loci containing genes associated with cytokine and chemokine signaling (e.g., chemokine ligands, several ILs, IFNγ, and STAT proteins) that can be influenced by adrenergic signaling.

IBD patients have increased risk of colitis-associated colorectal cancer. Biobehavioral stress factors directly stimulate growth and progression of colon cancer cells. Rodent studies show that NE and Epi promote colon cancer growth, which is attenuated by α- and/or β-adrenergic receptor antagonists. Epidemiological studies also suggest that β-blockers may reduce colon cancer progression, but randomized prospective studies are needed. Recently, NE was found to enhance pathogenic bacterial growth and attachment to colon cancer cells, revealing the involvement of the gut microbiome in colorectal cancer development.

Metabolic Disease

Chronic stress plays an important role in several metabolic diseases. In preclinical models of obesity, cortisol is implicated in reduced insulin secretion. NE turnover in brown adipose tissue is decreased, resulting in decreased thermogenesis; increased HPA axis activity plays a prominent role in diabetes, and GC are associated with both decreased insulin sensitivity in liver and decreased glucose transport in skeletal muscle, adipocytes, and hippocampal astrocytes.

ABBREVIATIONS

ACHT, adrenocorticotropic hormone; AP1, activator protein 1; BAD, Bcl2-associated agonist of cell death; CRP, C-reactive protein; CRH, corticotropin-releasing hormone; CVD, cardiovascular disease; DC, dendritic cells; Epi, epinephrine; GC, glucocorticoids; GILZ, glucocorticoid-induced leucine zipper; GR, glucocorticoid receptor; HPA, hypothalamo-pituitary-adrenal axis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IFNγ, interferon-γ; IL, interleukin; MAPK, mitogen-activated protein kinase; NE, norepinephrine; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; NK, natural killer cells; PBMC, peripheral blood mononuclear cells; PKA, protein kinase A; STAT, signal transducers and activators of transcription; SNS, sympathetic nervous system; TNFα, tumor necrosis factor alpha.

REFERENCES


388.e1 Cell Metabolism 23, February 9, 2016 ©2016 Elsevier Inc. DOI http://dx.doi.org/10.1016/j.cmet.2016.01.015