Psychobiological basis of stress – focus on hypothalamic-pituitary-adrenocortical axis and autonomic nervous system

Eero Kajantie
Specialist in Pediatrics, Clinical Genetics and Public Health
National Institute for Health and Welfare, Helsinki and Oulu, Finland
University of Helsinki, Faculty of Medicine
Oulu University Hospital
Aims

• To understand basic principles of
  • HPA axis and cortisol function
  • Autonomic nervous system function
• To know how to study stress
• To appreciate consequences of chronic or severe stress across the lifecourse
• To understand differential susceptibility theory

• Focus on human studies
Outline

- What is stress and why study stress?
- Hypothalamic-pituitary-adrenal axis
- Autonomic nervous system
- How to study stress?
- Stress and health
What is stress?
What is stress?

Hans Selye 1936: ”The non-specific response of the body to any demand for change”
No agreed definition

- Selye: ”The non-specific response of the body to any demand for change”

- “We propose that the term ‘stress’ should be restricted to conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability.”

  (Koolhaas et al. Neurosci Biobehav Rev 2011)
Why study stress?

• Most measurements in human research are performed in standardised conditions (=usually resting state). For example:
  • Cognitive tests
  • Blood pressure
  • Biochemical measurements from blood

• People spend most of their time in non-resting states, such as stress
How to study stress?

Humans

• Preceived stress
  – Severe life events
  – ”Daily hassles”

• Physiological stress response
  – Physical stressors
  – Psychosocial stressors

• Consequences of stress: ”Natural experiments”
  – Abuse
  – Separation from parents
  – Preterm birth, low birth weight

Animals (experimental)

• Maternal
  – Nutrient restriction
  – Psychosocial: new social environment (species with social hierarchy)
  – Glucocorticoid administration

• Postnatal
  – Separation
  – Glucocorticoids
Hypothalamic-pituitary-adrenal axis

Acute stress

Hippocampus

Hypothalamus

Hypophysis

Adrenals

Peripheral effects

ACTH

CRH

AVP

Cortisol

CBG
"Hypothalamic-pituitary-placental" axis
Placental glucocorticoid barrier

**MOTHER**

Cortisol

Placenta 11β-HSD2

**FETUS**

Cortisone

Cortisol
Female tertiles <3.2kg, 3.2-3.7kg, >3.7kg

Male tertiles <3.5kg, 3.5-3.7kg, >3.7kg
Mechanisms of glucocorticoid action

B

Cytoplasm

HSP

GR

11β-HSD1

11β-HSD2

Nucleus

Translation

Protein

Transcription

CBG

CBG

CBG

Cortisol (F)

Cortisone (E)
Autonomic nervous system

**Parasympathetic System**
- Constricts pupils
- Stimulates flow of saliva
- Constricts bronchi
- Slows heartbeat
- Stimulates peristalsis and secretion
- Stimulates bile release
- Contracts bladder

**Sympathetic System**
- Dilates pupils
- Inhibits salivation
- Relaxes bronchi
- Accelerates heartbeat
- Inhibits peristalsis and secretion
- Stimulates glucose production and release
- Secretion of adrenaline and noradrenaline
- Inhibits bladder contraction
- Stimulates orgasm

NATIONAL INSTITUTE FOR HEALTH AND WELFARE
Stress in laboratory
- how to stimulate stress

• Physical
  – Exercise, isometric press
  – Pain (“cold pressor”)
  – Nutrients

• Psychological
  – Cognitive challenge (arithmetics, ”mirror drawing”)
  – Psychosocial “public speaking”
TSST Trier Social Stress Test
What type of stress stimulates cortisol?

Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research

Sally S. Dickerson and Margaret E. Kemeny
University of California, Los Angeles

This meta-analysis reviews 208 laboratory studies of acute psychological stressors and tests a theoretical model delineating conditions capable of eliciting cortisol responses. Psychological stressors increased cortisol levels; however, effects varied widely across tasks. Consistent with the theoretical model, motivated performance tasks elicited cortisol responses if they were uncontrollable or characterized by social-evaluative threat (task performance could be negatively judged by others), when methodological factors and other stressor characteristics were controlled for. Tasks containing both uncontrollable and social-evaluative elements were associated with the largest cortisol and adrenocorticotropic hormone changes and the longest times to recovery. These findings are consistent with the animal literature on the physiological effects of uncontrollable social threat and contradict the belief that cortisol is responsive to all types of stressors.
Figure 2. Mean (± SEM) cortisol effect size ($d$) for studies using cognitive tasks, public speaking/verbal interaction tasks, public speaking/cognitive task combination tasks, noise exposure, and emotion induction. ***$p < .001$. 

ACUTE STRESSORS AND CORTISOL RESPONSES
What can be measured?

**Easy to measure**
- Blood: ACTH, cortisol, CBG
- Saliva: cortisol

**Difficult to measure**
Wartime evacuation and HPAA responsiveness to stress at age 60 to 70

Pesonen et al. in preparation
What can be measured – autonomic nervous system

• Cardiac autonomic function
  – Heart rate variability
  – Pre-ejection period
• Circulating catecholamine concentrations
Cardiac autonomic function – heart rate variability

- 5 min recording of R-R intervals during seated rest.
- Visual inspection for artefacts and ectopic beats

R-R Intervals
769
789
770
646
665
683
Cardiac autonomic function – heart rate variability

• Time domain measures
  – Mean heart rate (HR)
  – Root mean square of successive differences (rMSSD)

• Frequency domain measures of HRV by fast fourier transform
  – Low frequency (LF) power 0.04-0.15 Hz
  – High frequency (HF) power 0.15-0.40 Hz
  – LF/HF ratio

\[ rMSSD = \sqrt{\frac{1}{N-1} \left( \sum_{i=1}^{N-1} ((R_i - R_{i+1})^2) \right)} \]

R-R Intervals
769
789
770
646
665
683