Stress, the Brain & Depression

Cortisol-induced, serotonin-dependent anxiety – aggression drives depression.

Jelgersma Lezing – 13 November 2012 – Leiden – Ron de Kloet
Academy Professor & em. Professor Medical Pharmacology

Cortisol-induced, serotonin-dependent anxiety – aggression drives depression.

Highlights

- Some words on hormones, stress and depression
- Chronic stress and gene patterns
- Receptors, mechanism of resilience & vulnerability

HORMONES
Reproduction & Energy & Stress

Coordinate cell tissue, organ function
Communicate
Integrate functions over time

NEUROSCIENCE & ENDOCRINOLOGY
PSYCHOLOGY & PSYCHIATRY

• glucocorticoids: cortisol & corticosterone
  - Energy metabolism: appetite to disposition
  - Dampen initial stress reactions e.g. immune, inflammatory, metabolic, psychosocial responses
  - Enhance motivation, arousal, cognition
  - Promote behavioral adaptation

• mineralocorticoid: aldosterone
  - Salt homeostasis: salt appetite to volume control
  - Less known: they can amplify initial stress reactions (Selye).

Defining stress

Input (stressor) → Processing Information → Output (stress response)

- A stressor is every stimulus that is perceived as disturbance of homeostasis / integrity of the individual, evoking a response
- Physical stressors & psychological stressors

Context modulates processing

- Social rank: Dominant, status
- Social support: Family, friends
- Sense of safety: Own territory / house
- Self esteem, optimism, personality

Gig Levine. ‘Defining stress is a futile exercise’ Psychoneuroendocrinology 2005

Smelik 1990
Most severe psychological stressor
- no information, no control, no prediction, fearful

If chronic, enhanced vulnerability to
- infections, diabetes, cardiovascular diseases,
- depression, cognitive decline
- neurotoxicity; neurogenesis & plasticity down
- age-related neurodegeneration

“Wear and Tear” = “Allostatic Load”

Corticosteroids

depression & psychosis

‘Cortisol secretion is rather related to emotion and psychotic desorganisation than to depression per se’.
(Sachar 1970; Schatzberg 1985; Holsboer 2000).

but .......

Corticosteroids
depression & psychosis

But...
Elevated corticosteroids influence brain and body in major depression
- Steroid psychosis.
- Efficacy of cortisol antagonist in psychotic depression (Van der Lely & Lamberts, 1991; Belanoff et al. 2002)
- Depressive symptoms in Cushing.
- Adrenal enlargement, bone mineral loss & abdominal obesity, cardiovascular changes, suppressed immunity, remodeling neural circuitry.
Strong emotions are very well remembered.

Processing of stressful information

- Amygdala
- Hippocampus
- Prefrontal cortex

Amygdala facts linked to emotion in place, time & context

Hippocampus

Prefrontal cortex planning, coordination

Stress causes neurons to shrink or grow

...but not necessarily to die

- Prefrontal Cortex and Hippocampus
- Amygdala

Orbital Frontal Cortex

McEwen 2012

Gene products that modulate integration of newborn neurons in network: DISC-1, Glucocorticoid receptors

Control

Chronic stress

Chronic stress

NmGR

Fitszimons, van Hooijdonk, Vreugdenhil – Molecular Psychiatry sept 2012

(rat) 3 weeks of chronic unpredictable stress;
4 days of CORT Antagonist day 17 - 21: rapid recovery neurogenesis

BrdU survival

DCX neurogenesis

Stress hormone corticosterone was given to the controls and to the chronically stressed rats, mimicking an acute stress response.

3 hrs later differential gene expression patterns, but also overlap.

Some genes are suppressed during chronic stress, others enhanced.

The balance in genes encoding for resilience and vulnerability is altered!
QUESTIONS

• How does corticosteroid action change from protective to harmful?
• What is the cause?
• What are the consequences?

MR and GR in Hippocampus

‘Mineralocorticoid’ Receptor
• high affinity for Aldo + Cort
  Cortisol not degraded in brain, as in kidney
• restricted to limbic structures, Hippocampus, amygdala, PFC

Glucocorticoid Receptor
• 10-fold lower affinity Cort
• widespread, PVN, bio-amine cells
• occupied after stress

MR and GR in Hippocampus

‘Mineralocorticoid’ Receptor
• mediates cort effect on appraisal and facilitates retrieval of most appropriate response

Glucocorticoid Receptor
• mediates cort effect on storage of information in memory and facilitates recovery

Cortisol & MR / GR Balance

MR controls the onset of the stress response / pulse, which is terminated through GR.

De Kloet, Arts & Reinders
Nature Reviews Neuroscience, 2005
• Nienke van Leeuwen (9-11-2010)
Mineralocorticoid receptor gene variants: implications for stress, blood pressure and personality

• Liane Klok (15-12-2011)
Mineralocorticoid receptor in human brain Key player in resilience

Two PhD theses under the supervision of dr Roel de Rijk - Dynacorts

• Dispositional Optimism
Generalized positive outcome expectancies, life engagement, coping & future orientation.

- Relatively stable personality trait over time
- Better health outcomes
- Better subjective well-being in times of adversity
- Energetic, task focused, goal directed
- Protection against depressive symptoms


Mineralocorticoid Receptors in Limbic Brain
• Haplotype 2 linked to optimism & inversely to rumination
• Haplotype 2 protects against depression (GWAS, 2 cohorts)
• Controls onset HPA and sympathetic responses to stress
• Rapid effects on appraisal and response selection

- Decreased expression in post mortem brain, depression & chronic stress
- Induced by treatment with anti-depressants
- Agonists facilitate onset and efficacy anti-depressants
- Antagonist impair efficacy anti-depressants

Gender dependent association between MR haplotype 2 and optimism

Association in elderly cohort from Arnhem

Overall mean optimism
Females: 1.35
Males: 1.34

Giltay / Zitman / Does / de Kloet / de Rijk et al; Translational Psychiatry dec 2011
Early-life environment: low maternal care (1)

Low Maternal Care (Low LG):
↓ pre-pulse inhibition?
↓ emotional stress (CORT) response. ↓ spatial learning & memory
The cause is altered gene expression by epigenetics.

Genetic predisposition & early life environment

- ‘Multiple hit’ or ‘Cumulative stress’ hypothesis
  Individuals are more likely to suffer as adversity accumulates, but perform actually better under enriched & benefical conditions
  
  Dopamine reactive alleles

- ‘Mismatch’ hypothesis
  Individuals are more likely to suffer if a mismatch occurs between the early programming environment and the later adult environment

Some Questions

- MR : GR target for novel anti-depressants?
- Chronic stress effects reversible?
  Epigenetic targets=
- What about the implications of the Mismatch vs cumulative stress hypothesis?

Thank you!

on behalf of

Roel de Rijk, Nicole Datson Onno Meijer, Melly Otijl,
Erna Vreugdenhil, Riet van den Ven, Judith Terhorst, Danielle Champagne, Nikos Daskalakis, Sanne Claessens, Femke Groeneweg,
Yannis Zalochoras Liane Klok, Niels Speksnijder, Annelies Polman,
Nienke van Leeuwen

KNAW, TI-Netherlands, NWO, EU-Lifspan, HFSP,
Disclosures: AS Lunsbeck, Corcept Therapeutics, Dynacort