Stress System Regulation of Inflammation

Nicolas Rohleder
Department of Psychology
Volen National Center for Complex Systems
Brandeis University
Acknowledgements

- Dirk Hellhammer, University of Trier
- Clemens Kirschbaum; Technische Universität Dresden
- Gregory E. Miller and Edith Chen; Northwestern
- Jutta M. Wolf; Brandeis University
- Our Laboratory for Biological Health Psychology at Brandeis
Stress and Disease

• Stressful life events precede episodes of depression
  • 50-80% of depressed persons experienced a major life event
  • 20-25% of persons experiencing a major life event develop depression (e.g. van Praag et al. 2004)

• Stress promotes cardiovascular disease
  • 50% increase in CVD risk with high levels of work stress (e.g. meta-analysis by Kivimäki et al. 2006)

• Stress promotes HIV to AIDS progression
  • Each moderate to severe stress event increases the risk to progress to AIDS by 50% (e.g. Leserman et al. 2002)

• Stress promotes cancer progression / recurrence
  • Experimental evidence in animals & pathways in humans (e.g. Antoni et al. 2006)
Pathways between CNS and periphery

Stress

Depression
PTSD
Low SES
Etc.

Behavior

Biology

Disease

Stress System Control of Inflammation

?
Pathways between CNS and periphery

Stress

Depression
PTSD
Low SES
Etc.

Stress Systems

Behavior

Inflammation

Disease

HPA axis

GR-α GC

PNS SNS

ACh E & NE
Infection (hours to days)

Chronic low-grade Inflammation

Acute short-term response

long-term over-activity
lack of infectious stimulus
gradual increase
Low levels of inflammatory markers

NORMAL

DYSREGULATED

IL-6 & CRP

Cortisol

IL-6
CRP

Stress System Control of Inflammation
Chronic low-grade Inflammation

Effects

• triggers local inflammatory responses throughout the body

  • Stimulates *atherosclerosis* & *cardiovascular disease*  
    (e.g. Danesh, 1999)

  • Stimulates *insulin resistance* / *type 2 diabetes*  
    (e.g. Hotamisligil, 2006)

  • Stimulates *depressive symptoms, fatigue, and cognitive decline*

• CRP and IL-6 *predict mortality* in older adults  
  (e.g. Ershler, 1993; Harris et al., 1999)
Main Research Questions

• What is the role of stress and stress systems in regulation / disinhibition of inflammation?

• Is inflammation the consequence of life-long stress exposure?
Multilevel approach

- Psychosocial / behavioral level
- Systemic Level
- Cellular / functional level
- Intracellular / molecular level
Assessing Inflammatory Regulation by the HPA axis

Intracellular / molecular level

- LPS
- TLR-4
- IkB
- Degradation

DNA-binding activity of NF-kB

Expression of pro- and anti-inflammatory genes

Inflammatory gene products
Assessing Inflammatory Regulation by the HPA axis

GC sensitivity of LPS stimulated cytokine production in whole blood ex-vivo

Stimulation of pro-inflammatory cytokine production

Inhibition of pro-inflammatory cytokine production

Il-6 (ng/10^6 monocytes)

50% of cytokine production without DEX

IC_{50} = 3.34 \times 10^{-8} \text{ M DEX}

DeRijk et al. (1996)
Chronic Stress Studies

Cancer Caregiver Study

- N=18 relatives of a brain cancer patient (age 50.4 yrs. ± 3.5 SD; BMI 26.7 kg/m² ± 1 SD)
  - Patient diagnosed with glioblastoma multiforme; 5-year survival: 10-20%
- N=19 healthy matched controls (age 50.2 yrs. ± 2.6 SD; BMI 24.9 kg/m² ± 0.8 SD)
No Change in basal HPA axis activity

A

Daily Output of Salivary Cortisol (AUC)

Time (weeks)

Caregivers
Controls

Rohleder et al. (2009) J Clin Oncol
Decrease in GC sensitivity

-6.00
-6.25
-6.50
-6.75
-7.00
0 10 20 30 40 50
Time (weeks)

GC Sensitivity (log IC₅₀)

Rohleder et al. (2009) J Clin Oncol

Cellular / functional level

low

high

Decrease in GC sensitivity

Inhibition of pro-inflammatory cytokine production

50% of cytokine production without DEX

IC₅₀: 3.5 * 10⁻⁸ M DEX

Stimulation of pro-inflammatory cytokine production

+ LPS

GC Sensitivity (log IC₅₀)

 hpA axis Control of inflammation

Caregivers

Controls
Decrease in anti-inflammatory gene expression

Inhibitory kappa-B
Increase in Inflammation

A

CRP (mg/L; log-transformed)

Time (weeks)

Caregivers

Controls

CRP > 3mg/l

Rohleder et al. (2009) J Clin Oncol
Stress effects on GC sensitivity of inflammation

- Acute stress: Age and sex-steroid specific effects (summarized in Rohleder et al., 2003)

- Chronic stress: development of GC resistance explains inflammatory disinhibition (e.g. Miller et al. 2003, Rohleder et al. 2009)

- PTSD: increased GC sensitivity with hypocortisolism (Yehuda et al., 1991, 2003; Rohleder et al., 2004; summarized in Rohleder et al., 2010)

- Depression: decreased GC sensitivity (Miller et al., 2005; summarized in Rohleder et al., 2010)
Summary - Chronic Stress

- Chronic stress affects all levels of functioning:
  - accelerates inflammatory disinhibition
  - important mechanism is development of GC resistance
Next Question:

Role of repeated acute stress events throughout the life span?
Next Question:

Role of repeated acute stress events throughout the life span?

Assessment of stress response patterns

Assessment of stress response patterns
Response Pattern Study

1. Typical Response
2. Missing Response
3. Inadequate Recovery
4. Non-habituation
5. Sensitization

“Maladaptive” patterns

Acute stress exposure

Assessment of stress response patterns

2nd exposure
Study protocol

Trier Social Stress Test (TSST)

Salivary Cortisol

Plasma IL-6

day 1

day 2
Cortisol Response to Repeated Stress

- Significant time effect ($F=17.75; p<0.01$)
- Significant day by time interaction ($F=3.26; p<0.05$)

Habituation of HPA axis response
IL-6 Response to Repeated Stress

Significant time effect ($F=46.99; p<0.01$)

Significant day by time interaction ($F=4.18; p<0.05$)

Sensitization of IL-6 response
Stronger HPA axis habituation predicts stronger habituation of the IL-6 response (more HPA habituation = less IL-6 sensitization)
Can we understand and potentially modify maladaptive stress response patterns?

Potential determinants of habituation vs. non-habituation:

- Rumination
- Stress appraisals
- Self-compassion
Rumination predicts 2\textsuperscript{nd} day cortisol responses

\begin{align*}
\text{Cortisol Change From Baseline to Peak (nmol/l)} & \quad r = 0.49, p = 0.009 \\
\text{State Rumination Scores Day 1} & \\
\end{align*}

Danielle Gianferante
Stress appraisals predict 2\textsuperscript{nd} day cortisol responses

Primary appraisal:
- $r = 0.33; p = 0.07$

Secondary appraisal:
- $r = -0.49; p < 0.01$

Luke Hanlin
Predictors of 2\textsuperscript{nd} day inflammatory responses

**Subjective Social Status**

\[ r = -0.51; \ p = 0.017 \]

![Graph showing the relationship between Subjective Social Status and IL-6 response.](image)

**Meaning and Purpose**

\[ r = -0.50; \ p = 0.04 \]

![Graph showing the relationship between Meaning and Purpose in Life and IL-6 response.](image)
Self-Compassion and inflammatory responses

Self-compassion predicts baseline IL-6 on day 2: $r = -0.32; p = 0.06$

Juliana Breines
Summary and Conclusions
**Chronic stress:**
- accelerates inflammatory disinhibition
- Important mechanism is development of GC resistance

**Stress response patterns**
- Non-habituation of HPA axis predicted by appraisals and rumination
- Sensitization of IL-6 predicted by subjective social status and purpose in life
Next Steps

• Better understand stress system regulation of inflammation
  • Catecholamine sensitivity of the inflammatory response
  • Understanding the anti-inflammatory properties of the parasympathetic nervous system

• Understand and modify maladaptive stress response patterns
  • Test cross-sectional and prospective relationships with health & disease
  • Test short-term and longer term interventions based on current findings with rumination and self compassion
Thank you!