Glucocorticoid receptor (GR) induced gene expression as measure for GR sensitivity in stress-related psychiatric disorders

Andreas Menke, MD
Stress-Hormone-System
Interface between environment and genes

hypothalamic-pituitary-adrenal (HPA) axis
Findings from neuroendocrine tests:

DST

Carroll et al. 1968

Dex-CRH-Test

Heuser et al. 1994
Stress-Hormone-System
Interface between environment and genes

impaired in stress-associated disorders

Tomoshige Kino et al.

Glucocorticoids
HSPs

GRx

Cytoplasm

Nucleus

Transactivation
TF
TF

Transrepression
TFREs

GREs

ACTH

CRH

GR

GR

GR

cortisol

adrenal gland

Tomoshige Kino et al.
mRNA – target tissue?

- Blood: easy accessible = biomarker
- Monitoring: repeated measurements possible
- Blood: surrogate-tissue for brain

Whole blood: PAXGene Tubes
Pilotexperiment:

- Dexamethason 1.5 mg per os
- Illumina HumanHT-12
GR Challenge - Test

**Baseline** 3h post dex 21h post dex

cortisol suppression / mRNA

dexamethasone 1.5 mg

18:00 21:00 15:00 next day

DST
GR Challenge – Test: Major Depression

**baseline**
- healthy controls
- depressed patients

**3h post dex**
- cortisol suppression / mRNA
- dexamethasone 1.5 mg

**21h post dex**
- DST

18:00
- 21:00
- 15:00
- next day
GR-regulated genes – RNA expression arrays

<table>
<thead>
<tr>
<th>Symbol</th>
<th>FC</th>
<th>P Value</th>
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<tbody>
<tr>
<td>FKBP5</td>
<td>6.32</td>
<td>2.99e-23</td>
</tr>
<tr>
<td>SOCS1</td>
<td>3.81</td>
<td>2.57e-20</td>
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<tr>
<td>ZBTB16</td>
<td>3.33</td>
<td>1.24e-17</td>
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<td>TPST1</td>
<td>2.22</td>
<td>9.52e-16</td>
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<tr>
<td>ECHDC3</td>
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<td>CLEC4E</td>
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<td>GPER</td>
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<td>GPER</td>
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<td>DDIT4</td>
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</tbody>
</table>

- **Controls**: 2.670 genes

- Hyposensitivity
GR-induced gene expression classifies controls and patients

Controls

Patients

Dexamethasone-induced gene expression

Menke et al. 2012 Neuropsychopharmacology
Classification of controls vs. patients

- Gene-Expression: Transcripts are selected in the training sample and validated in the test sample. 
P < 0.05 and FC > 1.15

<table>
<thead>
<tr>
<th></th>
<th>Training</th>
<th>Test</th>
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<tbody>
<tr>
<td>Baseline:</td>
<td>635 transcripts</td>
<td>42% correct</td>
</tr>
<tr>
<td>Stimulated:</td>
<td>250 transcripts</td>
<td>79% correct</td>
</tr>
<tr>
<td>Dex-Suppression Cortisol</td>
<td></td>
<td>60% correct</td>
</tr>
</tbody>
</table>

Menke et al. 2012 Neuropsychopharmacology
Classification controls vs. patients

**Plasma Cortisol**

- **dexamethasone non-suppressor (n=8)**
  - 89% correctly classified,
  - specificity = 80%
  - sensitivity = 100%

- **dexamethasone suppressor (n=21)**
  - 77% correctly classified
  - specificity = 79%
  - sensitivity = 77%

GR dysregulation also identified in dex-suppressors
Job related exhaustion

- H.J. Freudenberger 1974
  Psychoanalyst from New York, USA

Job related exhaustion:
- Exhaustion after long-term emotional strain at work
- Imbalance of effort / reward

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GR Challenge – Test: Job related exhaustion

Baseline

3h post dex

cortisol suppression / mRNA

12 weeks exercise

3h post dex

cortisol suppression / mRNA

Healthy controls N=12

Patients N=12

dexamethasone 1.5 mg

18:00

21:00

18:00

dexamethasone 1.5 mg

21:00
Relief of symptoms

SMBM

Emotional numbing

Physical exhaustion

beginning       week 12

beginning       week 12

BDI

beginning       week 12

Courtesy of Beck
GR-induced cortisol suppression:

- Controls: 4.340 transcripts
- Patients: 8.629 transcripts

GR-induced gene expression:

- Controls: 4.340 transcripts
- Patients: 8.629 transcripts

GR hypersensitivity

Menke et al. 2014 PNEC
Gene expression changes before and after exercise

- Correlation controls / patients before exercise: $r = -0.164, p = 0.097$

- Correlation controls / patients after exercise: $r = 0.442; p = 2.89 \times 10^{-6}$

Menke et al. 2014 PNEC
Endocrine findings not consistent (DST / Dex-CRH Test)

Impact of plasma dexamethasone concentrations on DST

Pharmacokinetics of Dexamethasone and Its Relationship to Dexamethasone Suppression Test Outcome in Depressed Patients and Healthy Control Subjects

Brendan T. O'Sullivan, David J. Cutler, Glenn E. Hunt, Craig Walters, Gordon F. Johnson, and Ian D. Caterson

The pharmacokinetics of dexamethasone (DEX) were studied in 9 drug-free melancholically depressed patients and 10 healthy control subjects matched by sex and age. Each subject received 1 mg of DEX administered orally and by the (IV) route at 11:00 pm and serial blood samples were collected over the next 17 hours until 4:00 pm. There were no significant differences between the diagnostic groups and DEX bioavailability, peak plasma level, time to maximum concentration, or in elimination half-life after oral administration. Bioavailability estimates indicated that DEX absorption was incomplete and variable (mean = 61%, SD = 14) in controls as well as depressed patients. In both groups there was a wide interindividual variability in plasma DEX levels following both oral and IV routes of administration. This variability could not be reliably predicted by differences in age, sex, or weight between subjects. The factors that accounted for most of the variability in 4:00 pm plasma DEX levels after oral administration were clearance, bioavailability, and time to reach maximum concentration. Plasma DEX levels were lower in 3 depressed nonsuppressors compared to 3 matched controls who suppressed. No single pharmacokinetic factor was shown to be responsible for the lower DEX levels in the depressed nonsuppressors. These results indicate that plasma DEX levels need to be measured in each individual during the DST procedure so that this information may be taken into consideration when interpreting DST results. © 1997 Society of Biological Psychiatry

Key Words: Dexamethasone, pharmacokinetics, depression, controls, dexamethasone suppression test

Biol Psychiatry 1997;41:574–584

Impact also on GR-induced gene expression?
GR Challenge – Test: MPI sample

baseline 3h post dex 21h post dex

cortisol suppression / mRNA dexamethasone

dexamethasone 1.5 mg

healthy controls N=133

depressed patients N=105

dexamethasone 1.5 mg

18:00 21:00

21h post dex DST/Dex-CRH test dexamethasone

15:00 next day

N=105

N=133

3h post dex

baseline

18:00 21:00 15:00

20.09.2016
GR Challenge – Test: Predict Sample (Atlanta)

Depressed patients
N=261

dexamethasone 1.5 mg
depressed patients
dexamethasone 1.5 mg
dexamethasone 1.5 mg

dexamethasone 1.5 mg
dexamethasone 1.5 mg
dexamethasone 1.5 mg

dexamethasone 1.5 mg
dexamethasone 1.5 mg
dexamethasone 1.5 mg

dexamethasone 1.5 mg
dexamethasone 1.5 mg
dexamethasone 1.5 mg

baseline 16h post dex 12 weeks therapy 16h post dex

DST/Dex-CRH test dexamethasone

Cognitive Behavioral Therapy (CBT)

23:00 15:00 next day

23:00 15:00 next day

15:00 next day

escitalopram duloxetine
Intra-individuel dexamethasone - correlation

Menke et al. 2016 PNEC
Time-dependent dexamethasone effects

3h post dex | 16h post dex | 21h post dex
--- | --- | ---
Cortisol concentrations
MPI sample
- cortisol baseline: 56.2%
- unknown: 43.8%

DST
Atlanta sample
- dexamethasone: 5.2%
- unknown: 94.8%

Modified DST
MPI sample
- dexamethasone: 24.6%
- unknown: 75.4%

Menke et al. 2016 PNEC
Time-dependent dexamethasone effects

3h post dex
- Dexamethasone: 24.7%
- Unknown: 75.3%

16h post dex
- Dexamethasone: 24.7%
- Unknown: 75.3%

21h post dex
- Dexamethasone: 41.9%
- Unknown: 54.1%
- Disease: 1.9%
- Age: 2.1%

Dex-CRH test
- Atlanta sample
- Modified Dex-CRH test
- MPI sample
GR-stimulated gene expression:
- 74.5% transcripts significantly regulated (of n=10,562; FDR<5%)
- No transcript associated with dexamethasone concentration

Classification:
- Using 12 significantly regulated transcripts:
- 72.7 % correctly classified
Discussion

Dexamethasone-stimulated gene expression:

► GR Hyposensitivity - Depression
► Outperformed endocrine tests

► GR Hypersensitivity – Job Related Exhaustion
► Normalization with improvement of symptoms

► Not influenced by dexamethasone concentration
Perspective

- Dexamethasone-stimulated gene expression in stress-associated, non-psychiatric disorders

- Cooperation with the German Comprehensive Heart Failure Center: Recruitment of patients with heart failure, with and without depression
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