The Hypothalamic Pituitary Adrenal Axis in Gulf War Veterans

Julia Golier, MD
Mount Sinai School of Medicine, New York, NY
James J Peters VAMC, Bronx, NY

Initial Rationale for studying HPA axis in GWV

- The hypothalamic-pituitary-adrenal axis (HPA) is a complex set of direct influences and feedback interactions among the hypothalamus, the pituitary gland and the adrenal gland.
- Constitutes a major part of the neuroendocrine system that controls reactions to stress and regulates many processes including the immune system, mood, memory and metabolism.
- Relevance to GWV
  - Illness followed deployment and environmental exposures in combination with physical and psychological stressors
  - HPA axis has reciprocal connections with multiple systems implicated in GWI: autonomic NS, immune system, central nervous system, metabolic
  - Chronic multisymptom illness overlaps with other conditions associated with HPA axis disturbance (chronic fatigue, fibromyalgia, depression)
  - Study of HPA axis does not imply that etiology is presumed to be psychological stress
The Dexamethasone Suppression Test

- Dexamethasone is an exogenous steroid that provides negative feedback to the pituitary to suppress the secretion of ACTH. Assess a specific part of the HPA axis. DEX binds to glucocorticoid receptors in the pituitary gland resulting in regulatory modulation.
- The strength of cortisol suppression reflects negative feedback mechanism.
- Non-suppression of cortisol and glucocorticoid resistance has been described in Major Depression, enhanced suppression observed in PTSD.

Cortisol response to low-dose DEX in Gulf War veterans and non-deployed controls

- Plasma cortisol measured at 08:00 h on two consecutive days, before and after administration of 0.5mg of DEX at 23:00 h
- No main effect of group on cortisol levels
- Group X DEX interaction: F(3,48)=6.41, p=0.001
- GWV with no psych disorder group and the GWV PTSD + group had significantly greater response to DEX than the healthy non-deployed group (p’s= 0.002 and p=0.006 respectively).

Golier et al., Psychoneuroendocrinology, 2006
Cortisol response to low-dose DEX in Gulf War veterans and non-deployed controls

GWV had significantly greater percent cortisol suppression than non-deployed veterans controlling for weight, smoking, PTSD and MDD.

PTSD was not associated with cortisol suppression.

ACTH response to low-dose DEX in GWV with and w/o PTSD and non-deployed controls

No group differences in basal 8 am ACTH DEX level

Significantly lower post-DEX ACTH levels in GWV with (p=0.03) and without (p=0.03) PTSD as compared to non-exposed subjects.
DST associated with reported exposure to PB and some health symptoms

Gulf War veterans who reported ingestion of anti-nerve gas pills (pyridostigmine bromide) had a significantly higher percent cortisol suppression than those who did not (adjusted mean (SE) 97.9 (6.9)% vs. 68.8 (11.6); F(1,30)=4.66, p=0.039).

Combat exposure and other environmental exposures were not associated with DST.

Sx domains of Gulf War Illness derived from health symptom scale:
- Mood-cognitive sx : r=0.15, df=32, p=0.40
- Musculoskeletal sx: 0.44, df=32, =0.009
- Fatigue: r=0.13, df=32, p=0.45

Descriptive Data

DST Results in GWV with CMI*

*Chronic multisymptom illness, Kansas definition
Enhanced cortisol suppression in response to dexamethasone administration in traumatized veterans with and without posttraumatic stress disorder


a Department of Military Psychiatry, Central Military Hospital, Utrecht, The Netherlands

b Rudolf Magnus Institute of Neurosciences, Department Psychiatry, University Medical Center Utrecht, The Netherlands

c Laboratory of Psychoneuroimmunology, University Medical Center Utrecht, The Netherlands

d Department of Clinical Chemistry and Haematology, Laboratory of Endocrinology Utrecht, The Netherlands

Volume 37, Issue 3, April 2007, Pages 215–226
Salivary Cortisol and PTSD Symptoms in Persian Gulf War Combatants

MICHAEL KELLNER, DEWLEEN G. BAKER, AND RACHEL YEHUDA

Department of Psychiatry
Mount Sinai School of Medicine
Bronx Veterans Affairs Medical Center
Bronx, New York 10468

Cincinnati Veterans Affairs Medical Center and
Department of Psychiatry
University of Cincinnati Medical Center
Cincinnati, Ohio 45220

Basal HPA axis activity: 24 hour cortisol levels in GWV and non-deployed veterans

- No group difference in cortisol level
- Diurnal variation maintained
- Differs from findings in depression in which there is consistent evidence of elevated plasma cortisol or PTSD in which there is evidence of reduced levels (Yehuda et al., 1993; Bremner et al., 2004)

Golier et al., Biol Psych, 2007
Basal HPA axis activity: 24 hour ACTH levels in GWV and non-deployed veterans

- Significant effect of group (F(2,43)=5.03, p=0.011); mean 24-hour ACTH levels in GWV PTSD- group < non-exposed group (17.5 (2.8) vs. 27.6 (2.1) pg/ml, p=0.021) and < GWV PTSD (+) group (28.3 (2.3) pg/ml, p=0.018).
- GWV < non-deployed subjects (F(1,42)=9.18, p=0.004) controlling for a diagnosis of PTSD and depression.
- Self-reported acute effects of pesticides and PB were associated with lower ACTH levels, controlling PTSD.

Why are ACTH levels significantly lower in Gulf War veterans?

- Is it due to enhanced negative feedback inhibition of cortisol on pituitary release of ACTH?
- Metyrapone stimulation test
  - Metyrapone inhibits 11-beta hydroxylase--an enzyme which converts 11-deoxycortisol into cortisol--resulting in increased 11-deoxycortisol levels and decreased cortisol synthesis and increased ACTH secretion.
Metyrapone Stimulation Test

ACTH → CRF → 11-deoxy cortisol → CORTISOL

- METYRAPONE

Metyrapone stimulation test in GWV and non-deployed subjects

- Group: F(1,40)=13.07, p=0.001 controlling for basal ACTH
- PTSD- < PTSD+ (p=0.007) and non-exposed (p=0.02)
- post-MET ACTH AUC was significantly associated six of the nine health symptom subscales: neurological (r=0.56, p=0.005), psychological (r=0.47, p=0.015), musculoskeletal (r=0.43, p=0.028), neuropsychological (r=0.42, p=0.03), pulmonary (r=0.39, df=24, p=0.046), and cardiac (r=0.39, df=24, p=0.048) as well as total PTSD (r=0.59, df=26, p=0.001) controlling for basal ACTH level
- Neither combat exposure nor environmental exposures were associated with the ACTH response to metyrapone

ACTH (pg/ml)
Non-deployed  (n=15)
GWV PTSD (-)  n=11
GWV PTSD (+)  n=18

- METYRAPONE 750 mg PO
Results of Metyrapone Stimulation Test

- Since ACTH levels increased less in the GWV deployed group without PTSD than in the GWV group with PTSD and the healthy non-deployed group the following metyrapone stimulation, rather than normalize or increase more, suggests that enhanced cortisol inhibition not driving the lower 24 hour ACTH, may be due to reduced central/hypothalamic drive to the HPA axis.

Corticotropin Releasing Factor (CRF) Stimulation Test

- Corticotropin releasing factor (CRF) is a hypothalamic peptide that stimulates the release of beta-endorphin and ACTH from the anterior lobe of the pituitary gland.

- The CRF stimulation is used in the differential diagnosis of Cushing's syndrome, an endocrinologic disorder characterized by hypercortisolism, and of adrenal insufficiency.

- Used in clinical research to examine the integrity of the HPA axis and provide information about the central drive to the HPA axis.
CRF stimulation test procedures

- Subjects admitted to the outpatient general CRC
- Instructed to have a light breakfast at 8 am
- After a 90-min period of accommodation, plasma samples drawn for basal cortisol and ACTH levels
- 1 ug/kg of o-CRF (corticorelin ovine triflutate, Acthrel®, Pferring Laboratories, Suffern, NY) administered as an i.v. bolus at 2 pm
- Plasma samples drawn at 15, 30, 60, 90 and 120 minutes

CRF stimulation test performed in Vietnam, Gulf War and OIF/OEF veterans

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>PTSD+ (n=15)</th>
<th>PTSD- (n=24)</th>
<th>PTSD- (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.3 (12.9)</td>
<td>46.5 (12.9)</td>
<td>45.3 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>12.6 (2.8)</td>
<td>14.4 (2.5)</td>
<td>14.7 (2.8)</td>
</tr>
<tr>
<td>Military Rank</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlisted</td>
<td>73.3% (n=11)</td>
<td>41.7% (n=10)</td>
<td>50.0% (n=5)</td>
</tr>
<tr>
<td>NCO</td>
<td>20.0% (n=3)</td>
<td>45.8% (n=11)</td>
<td>40.0% (n=4)</td>
</tr>
<tr>
<td>Officer</td>
<td>6.7% (n=1)</td>
<td>12.5% (n=3)</td>
<td>10.0% (n=4)</td>
</tr>
<tr>
<td>Service Era</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>46.7% (n=7)</td>
<td>41.7% (n=10)</td>
<td>40.0% (n=4)</td>
</tr>
<tr>
<td>Gulf War</td>
<td>33.3% (n=5)</td>
<td>33.3% (n=8)</td>
<td>30.0% (n=3)</td>
</tr>
<tr>
<td>OIF/OEF</td>
<td>20.0% (n=3)</td>
<td>25.0% (n=6)</td>
<td>30.0% (n=3)</td>
</tr>
</tbody>
</table>
ACTH response to o-CRF in veterans with and w/o PTSD and non-deployed veterans: 3 eras combined

Time F=8.97, p<0.0005
Group =5.10, p=0.01; (PTSD+ and PTSD- > non-exposed)
Group by era: (F)=4.84, p=0.003

Vietnam
Gulf War Cohort:
Group x time F(10,50)=3.30, p=0.005
Group (F(2,10)=4.96, p=0.03)
PTSD+ group > non-exposed (p=0.036), PTSD- (p=0.011)
Peak ACTH response to o-CRF by group and era

- Exposure to PB was variable significantly associated with the peak change in ACTH (F(1,19)=5.30, p=0.033) and was marginally associated with ACTH AUC (F(1,19)=4.16, p=0.055).
- PTSD group scored significantly higher than other group on nine categories of health sx.
- CRF results were not associated with physical health symptoms.

Cortisol response to o-CRF in veterans with and w/o PTSD and non-deployed veterans: 3 eras combined

- Significant main effect of group (F(2,38)=5.30, p=0.009, no main effect of era or group by era interaction.
- PTSD+ group (adj. mean (S.E.) 17.01 (0.95)) and PTSD- group (17.16 (0.66)) had higher levels than the non-exposed group (13.45 (1.01)) (p=0.023 and p=0.003, respectively).
ACTH stimulation test performed in Vietnam, Gulf War and OIF/OEF veterans

- Subjects admitted to the outpatient CRC at Mt. Sinai
- Light breakfast at 8 am and then refrain from eating
- After a 60-min period of accommodation, a plasma sample will be drawn for basal cortisol and ACTH
- Low-dose (1 µg) of cosyntropin (1-24 corticotropin; Cortrosyn®, Organon) administered by i.v. bolus at 2 pm by an MD
- Blood for hormonal determinations drawn at intervals through T+90

Cortisol response to ACTH in veterans with and w/o PTSD and non-deployed veterans: 3 eras combined
Peak cortisol response to ACTH: no significant group by era interaction

- Evidence of dysregulation of the HPA axis at baseline and in response to challenges in relation to Gulf War deployment and/or health symptoms.
- Despite dysregulation at multiple points in the axis, and dynamic/sensitized response to stress signals (DEX, CRF, ACTH) basal 24 hour cortisol levels are normal and diurnal variation maintained.
HPA Axis in Gulf War veterans

- Data suggest the presence of overlapping/co-occurring alterations in GWV
  - Enhanced glucocorticoid sensitivity (DST) is present Gulf War deployment, but finding not unique to this population.
  - Low basal ACTH, blunted ACTH response to metyrapone and exaggerated ACTH response to o-CRF
    - Profile not previously described, appears unique to GWV
  - Constellation suggests reduced central drive to the HPA axis
    - Distinctly different from increased CRF drive in stress-related psychiatric disorders
    - Consistent with animal model of role of neurotoxicity secondary to environmental exposures (e.g., PB)

Could PB exposure account for HPA axis dysregulation in GWV?

- Self reported exposure to PB is the one environmental exposure associated with HPA axis measures in different samples: greater percent cortisol suppression to DEX, lower basal ACTH AUC, and increased ACTH to o-CRF
- Mixed results re: central effects of PB in animal models; however:
  - Exposure to PB, DEET, and permethrin in rats associated with neuronal cell death in cingulate cortex, dentate gyrus, thalamus and hypothalamus (Abdel-Rahman et al., 2002).
  - Exposure to PB and stress associated with learning dysfunction and exposure to PB increases expression of mineralocorticoid receptor (MR) with no effect on glucocorticoid receptor in hypothalamus (Barbier et al, 2008)
What are the treatment implications of HPA axis dysregulation in GWV?

Rationale for Mifepristone Trial

- Selective type II glucocorticoid receptor (GR) antagonist
- Diminishes the negative feedback effects of cortisol on the HPA axis
- Compensatory increase in ACTH levels and cortisol production in may increase central glucocorticoid signalling
- Net effect of mifepristone is to reset hypothalamic-pituitary-adrenal axis
Relevant effects of mifepristone

Preclinical

- Protects against glucocorticoid-induced impairments in hippocampal function and neurogenesis (Haynes et al., 2001; Mayer et al., 2006)
- Reverses deleterious effects of stress on hippocampal synapses (Krugers et al., 2006)
- Improves spatial memory in stressed animals (Oitzl et al., 1998)
- Conceptualized as neuroprotective

Clinical

- Preliminary evidence it Improves symptoms in other endocrine and neuropsychiatric conditions
  - Cushing’s disease
  - Psychotic Major Depression
  - Primary insomnia

Specific Aims

1. To determine the efficacy of mifepristone on physical health in veterans of the 1991 Gulf War with chronic multisymptom illness (CMI)
2. To examine the efficacy of mifepristone on cognitive functioning in Gulf War veterans with CMI
3. To determine the efficacy of mifepristone on mental health in Gulf War veterans with CMI
4. To determine whether screening levels of HPA axis activity (glucocorticoid sensitivity, cortisol and ACTH levels) or changes in HPA axis activity predict treatment outcome
**Overall Crossover Study Design**

**Primary Outcomes**
- Improvement in physical health components score of SF-36

**Secondary Outcomes**
- Improvement in mental health components score of SF-36
- Improvement in fatigue, cognitive impairment, depression
- Improvement in cognition using MATRICS test battery

**Additional Outcomes**
- Cortisol and ACTH levels
- Measures of glucocorticoid sensitivity (low-dose dexamethasone suppression test and lysozyme IC$_{50}$-DEX)

---

**Descriptive Data**

**DST Results in GWV with CMI**

- Mean (SD) % cortisol suppression: $85.7 (16.8)$
- (N=33)

---

*Chronic multisymptom illness, Kansas definition*
Mean MATRICS Scores in GWV with CMI (T Scores)

Cognitive Domains
- Speed of Processing
  1. TMT
  2. BACS SC
  3. Fluency
- Attention/Vigilance
  - CPT-IIP scores
- Working Memory
  1. WMS-III SS
  2. LNS
- Verbal Learning
  1. HVLT-R scores
- Verbal Learning
  2. (HVLT-R scores)
- Reasoning and Problem Solving
  - NAB Mazes scores
- Social Cognition
  - MSCEIT ME scores

What are the medical implications of HPA axis dysregulation in GWV?
**Prevalence of Medical Conditions Found in GWV with and without CMI**

![Bar chart showing prevalence differences](chart.png)

Blanchard et al. 2005


<table>
<thead>
<tr>
<th>Chronic Disease*</th>
<th>Deployed (n=5,469)</th>
<th>Nondeployed (n=3,353)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence in 1995, %</td>
<td>Prevalence in 2005, %</td>
</tr>
<tr>
<td>Arthritis</td>
<td>25.7</td>
<td>28.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.9</td>
<td>19.4</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.3</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PD, prevalence difference
* P < 0.05
* Chronic diseases are listed in order of 1995 prevalence among deployed personnel.
* Excess prevalence in 2005 vs. 1995. The PD underestimates the excess prevalence of chronic diseases in 2005 over 1995 because the time period queried about in the 2005 survey was 4 weeks, as opposed to 12 months in the 1995 survey.

Li, Mahan, Kang, Eisen, and Engel, Am J Epidemiol, 2011
The HPA Axis and Metabolic Outcomes in Gulf War Veterans

Specific Aim 1
- To investigate the associations of CMI in Gulf War veterans and Gulf War deployment with HPA axis parameters, particularly with glucocorticoid activity and related functional impairments in the stress response

Specific Aim 2
- To investigate the associations of CMI in Gulf War veterans and Gulf War deployment with metabolic outcomes

Specific Aim 3
- To determine the associations between glucocorticoid activity and metabolic outcomes and whether the associations differ by subgroup
- To examine whether the associations of CMI with metabolic outcomes are direct or indirect, reflecting their associations with glucocorticoid activity

Visit 1
- Description of study and informed consent
- Self-report questionnaires
- Medical and psychiatric assessment
- Description of caloric intake prior to OGTT

Visit 2
- OGTT at the GCRC
- Complete medical evaluation for metabolic syndrome
- Educate subject on 24-hour urine collection and provide necessary containers

Visit 3
- Subject brings in completed 24-hour urine collection examine cortisol metabolism
- Blood draw for day 1 of the low-dose DST and for the lysozyme IC50-DEX
- Dispense 0.5 mg dexamethasone for subject to ingest at 11 p.m. with reminder from coordinator

Visit 4
- Blood draw for day 2 of the DST

Visit 5
- Neuropsychological testing
- Review pertinent clinical data with veteran
- Finalize psychiatric, medical or primary care referrals
- Collect data for subject payment
- Study termination

DoD W81XWH—07-1-0602
Study Population

- 120 eligible male and female Gulf War and Gulf War era veterans
  - 40 Gulf War veterans with CMI (CMI+)
  - 40 Gulf War veterans without CMI (CMI-)
  - 40 non-deployed Gulf War era veterans without CMI (GW Era)

- Gulf War veteran will be defined as a veteran who served with the United States Army, Marines, Navy, or Air Force between August 1, 1990 and December 30, 1991 and was deployed to the Persian Gulf during that time

- CMI case status will be based on the criteria from the Kansas Gulf War Study (Steele, 2000)