THE NEURO-ENDOCRINOLOGY OF PTSD

A GLIMPSE INSIDE THE BRAIN

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Relevant anatomy

- Autonomic Nervous System
  - Sympathetic NS
  - Parasympathetic NS
- Endocrine system
- Immune system
- Anti-inflammatory – Pro-inflammatory balance...
**Stress and health**

- **Hypercortisolemia** - cortisol elevation
- **Hypocortisolemia** - cortisol depression
- PTSD, Cortisol & Cytokines (immuno-proteins).

**Medically Unexplained Symptoms (MUS)**

- Manifestations of hypocortisolemia
- Implications for treatment
- Focus on sensation and pain - somatoform trauma sx., and/or
- Referral to endocrinologists, oncologists, or immunologists...

**Medically Unexplained Symptoms (MUS) (Cont.)**

- Fibromyalgia
- Chronic Fatigue Syndrome
- Rheumatoid Arthritis
- Reflex Sympathetic Dystrophy.
- Hashimoto’s Thyroiditis
- Grave’s Disease
- Systemic Lupus Erythematosus
- Sjogren’s Syndrome
- Crohn’s Disease
- Type I Diabetes
- Multiple Sclerosis
Neural Pathways of PTSD

- Amygdala is activated...triggering...
- Hypothalamus for the production of CRF.
- Locus Ceruleus for increased Norepinephrine.
- Opioid centers for increased endorphins...

PTSD

- Flashbacks
  - Intrusive thoughts
    - Hyper-arousal
    - Hypervigilence
    - Numbing
    - Intrusive somatic sensations...

PTSD Is Associated With Increased Plasma Norepinephrine

Yehuda et al. Biol Psychiatry. 1998, 44:56-63
PTSD is associated with increased plasma norepinephrine.


PTSD is associated with decreased plasma cortisol levels.

Problems with Cortisol Studies

- Methodological details regarding the collection and processing of biologic samples,
- As well as details regarding how cortisol levels were determined,
- Are given surprisingly little attention in PTSD literature.
- Methodological inconsistencies,
  - single measures vs. measures across the day
  - venous puncture vs. indwelling catheter
  - blood, urine, saliva...


Solutions for Cortisol Studies

- Measurements to be taken across the day.
- The best medium considered to be blood.
  - Stable – can be thawed, frozen and re-thawed.
  - Only requires centrifugation.
  - Using an indwelling catheter.
- Saliva and urine require extraction procedures,
  - leading to increased potential for error.
- Saliva can be contaminated.
- Urine collection may not be properly done.


Hypothalmo-Pituitary-Adrenal (HPA) Axis
PTSD Is Associated With Decreased Plasma Cortisol Levels


The DST
If negative feedback is strong, cortisol levels will show a dramatic decline.

Enhanced Suppression

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Cortisol Studies – Evidencing Hypocortisolemia in PTSD

  - In PTSD – as compared to depression, stress, or controls
  - In PTSD
  - In Combat veterans
  - In child survivors of the Armenian earthquakes.


Cortisol Studies – Evidencing Hypocortisolemia in PTSD

  - Adult survivors of childhood sexual abuse.
  - Gulf-war soldiers on active duty.
  - Holocaust survivors
  - Combat veterans & mixed group of trauma survivors


STRESS & REGULATION

- The survival of living organisms depends upon the maintenance of a harmonious equilibrium or homeostasis in the face of constant challenge by intrinsic or extrinsic forces or stressors.
- Successful equilibrium is reflected by a rapid neurochemical response to these stimuli.
- Which is terminated at the appropriate time, or gives way to counter-regulatory measures to prevent an excessive reaction or energy expenditure...
Medically Unexplained Symptoms (MUS)

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- Sjogren’s Syndrome
- Crohn’s Disease
- Pelvic Inflammatory Disease
- Inflammatory Bowel Disease
- Type I Diabetes
- Hashimoto’s Thyroiditis
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Medically Unexplained Symptoms
Neuro-endochronology

Chronic PTSD Drives the Neuro-endochronology

Autonomic Nervous System

- Two branches of the ANS
- Act to maintain homeostatic balance.
  - Sympathetic NS
    - Parasympathetic NS
**Autonomic Nervous System**

**Sympathetic Nervous System**
- Energy Expanding – Arousal Mediating
- Mediating approach behavior (seeking, attachment)
- Fight or flight behavior
  - Catecholamine neurotransmitter mediated
    - Norepinephrine/Noradrenaline
    - aka Epinephrine/Adrenaline
    - Dopamine...

**Parasympathetic Nervous System**
- Energy Conserving/Homeostatic
  - Calm Mediating
  - Mediating avoidant, freeze or immobilizing behavior
  - Acetylcholine or GABA mediated...

**Brain Stem Affect System**

- Ascending Reticular Activation System
  - A sympathetic system providing neural excitation and promotion of rapid mobilization for behaviors associated with fight and flight.
- Dorsal Vagal Complex
  - An inflexible parasympathetic system promoting an immobilized freeze in functioning in response to danger.
- Ventral Vagal Complex
  - A flexible parasympathetic system of inhibitory effect (a brake), promoting social engagement and increased calm.
Endocrine System

- **Glandular Mediating**
- **Hypothalamus >>> CRF/CRH**
- **Anterior Pituitary >>> ACTH**
- **Adrenal Cortex >>> Cortisol**

Nervous & Endocrine System

- **Join together**
- **form metabolic pathways or axes**
  - **Sympatho-Adreno-Medullary (SAM) Axis**
  - **Hypothalamo-Pituitary-Adrenocortical (HPA) Axis**
- **Both work together to prepare for fight or flight...**
The role of cortisol is to facilitate a healthy adaptation to a particular stressor.
- Cortisol mobilizes glucose to provide the fuel necessary for surviving a fearful event.
- Cortisol also counters the damaging physiologic response to stress by limiting inflammation and suppressing hyper-immunity.
- Cortisol reduces energy available to neurons.
CORTISOL

- Other symptoms of hypocortisolemia
  - Diarrhea with stress
  - Irritable bowel inflammation
  - Sore throat
  - Flu-like symptoms
  - Achy skin
  - Headaches
  - Trouble staying hydrated
  - Fatigue, more in afternoon
  - Autoimmune disorders

CORTISOL

- Cravings for:
  - Sweets
  - Pasta, bread
  - Salty food
  - Pickles, vinegar
  - Lemon
  - Spicy food...

Anti-inflammatory/Pro-inflammatory Balance

- The basic balance between
  - Cell survival/growth – Anti-inflammatory
  - Cell death – Pro-inflammatory
  - Therefore, the autoimmune balance.
- Cortisol
  - Mediates the balance.
    - Cortisol >>> anti-inflammatory
      - Immuno-suppressing.
    - Cortisol >>> pro-inflammatory
      - Immuno-enhancing...
Hypothalmo-Pituitary-Adrenocortical (HPA) Axis

Therefore,
1. If Anti-Inf balance needed
   >>> decreased negative feedback
   >>> + Cortisol
2. If Inf balance needed,
   >>> enhanced negative feedback
   >>> - Cortisol

Cytokines

- Proteins or glycoproteins.
- Mediate communication between
  - Nervous & endocrine systems, and
  - Immune system.
- Mediate immune function in both directions.
  - Immuno-suppressive – neuro-protective
  - Immuno-enhancing – neuro-toxic...

Examples of Cytokines
- Interlukins - ILs
- Interferons - IFs
- Tumor Necrosis Factors – TNFs.
- When pro inflammatory/immuno-enhancing (IL-1, IL-6, TNF)
  >>> NK T-Cells
  >>> T-Cells
  >>> Microphage
- When anti-inflammatory/immuno-suppressing (IL-1, IL-4, IL-10)
  >>> Reduction in NK T-Cells, T-Cells & Microphage...
Stress & Health

- Acute or prolonged stress increases cortisol production.
- Prolonged elevations of cortisol impair the immune system.
  - Anti-inflammatory.
  - Adaptive for acute trauma
  - Maladaptive for prolonged/chronic stress.
- Impaired healing
- Gastro-intestinal illness
- Heart Disease
- Diabetes
- Cancer

PTSD & Health

- Neurobiology of PTSD
  - Abnormalities of the HPA Axis.
  - Acute/Chronic Stress, Anxiety & Depression
    - Cortisol levels are increased
  - In PTSD
    - Cortisol levels are chronically decreased
    - In excess of 50 years after initial trauma
    - In children – in utero, during trauma...


PTSD, Cortisol & Cytokines

- Cortisol suppression >>> Immuno-enhancement
- Pro-inflammatory/immune-enhancing (IL-1, IL-6, TNF)
  - NK T-Cells
  - T-Cells
  - Microphage
- Since this is not in reaction to bacteria, viruses or tumors,
  - Which are responded to by immune cells as “non-self”
  - Various systems in the body are now responded to as “non-self” and attacked.
- Antibodies that attack the “self” become “auto-antibodies”
  - >>> Autoimmune neuropathies...
MEDICALLY UNEXPLAINED SYMPTOMS (MUS)

In the absence of methodological flaws,

Consistent hypo-cortisolemia findings.

Therefore, immuno-enhancement...


Sjogren’s Syndrome

Immuno destruction, initially, of glands that secrete tears and saliva.

Can progress to kidneys, lungs and skin.

Fibromyalgia

Diffuse auto-antibody attack by inflammatory Cytokines (IL-6, IL-8).

>>> Hyperalgesia and fatigue...

Rheumatoid Arthritis

Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies attack joints >>> inflammation and cartilage damage.

Reflex Sympathetic Dystrophy

Immuno anti-body attack of nerve proteins, normally hidden,

Which are exposed due to minor myelin sheath damage

Responded to by immune cells as “non-self”...
**MEDICALLY UNEXPLAINED SYMPTOMS (MUS)**

- Hashimoto's Thyroiditis
  - Autoantibodies & autoantigens infiltrate the thyroid gland >>> functional depletion & hypothyroidism.

- Graves Disease
  - Auto-antibodies attach to receptors on thyroid
  - >>> over-production of Thyroid Hormone >>> Goiter.

**MEDICALLY UNEXPLAINED SYMPTOMS (MUS)**

- Systemic Lupus Erythematosus
  - Auto-antibodies attack DNA, blood, neurons and tissue.
  - When cells die, immune complexes form and deposit
    - Under skin, joints, kidneys, blood & CNS
    - >>> inflammation and kidney damage...

**MEDICALLY UNEXPLAINED SYMPTOMS (MUS)**

- Crohn's Disease - Inflammatory Bowel Disease
  - Attack of autoantibodies of the GI tract,
  - >>> Inflammation.

- Type I Diabetes
  - Autoantibody destruction of insulin-secreting pancreatic cells by T-cells...
**MEDICALLY UNEXPLAINED SYMPTOMS (MUS)**

- Multiple Sclerosis
  - Autoantibody attack of neural fiber and myelin sheathing.
- Chronic Fatigue Syndrome
  - Hypocortisolemia >>> generalized systemic autoimmune attack
  - Or, a generic reaction to the other MUS and/or the energy depletion of -Cortisol...

**IMPLICATIONS FOR TREATMENT**

- If symptoms are not consistent with MUS syndromes,
  - Focus on sensation and pain
    - Somatoform symptom trauma sx.,
    - The “trauma expressed in the body”
  - Utilizing somatic targets within EMDR Tx...

**IMPLICATIONS FOR TREATMENT**

- If MUS is present, or
  - Patient presents only with MUS
    - and no trauma or psychological problems,
    - Referral to endocrinologists, oncologists, or immunologists...
IMPLICATIONS FOR TREATMENT

- Medically Unexplained Symptoms
- Neuro-endochronology
  - Hydrocortisone tx.
  - Anti-inflammatories
  - ILs, Ifs, TNFs
  - Alemtuzumab
- If indicated...
- Treatment of PTSD That Drives the Neuro-endochronology

QUESTIONS TO BE ANSWERED

- Why do some patients respond to symptomatic tx.?
- Hydrocortisone
- Anti-inflammatory ILs, Ifs, TNFs
- Alemtuzumab
- Do they evidence PTSD?
  - Yehuda – Hypocortisolemia in utero
  - Maybe they don’t evidence PTSD
- Maybe, in the absence of PTSD, sx. tx. works?