IMMUNE DYSFUNCTION AND DEPRESSION

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Why is depression increasingly problematic in the modern world?


Who: The study was conducted in the United States.
Method: The study was a retrospective analysis of data from national surveys. The sample included adults aged 18-64 years.
Results: The prevalence of major depression increased from 6.2% in 1991-1992 to 7.7% in 2001-2002. The prevalence of substance use disorders also increased, with an increase in the co-occurrence of depression and substance use disorders.

Why is depression increasingly problematic in the modern world?

- Increased stress levels due to urbanization and fast-paced lifestyles.
- Availability of mental health resources and awareness campaigns.
- Changes in social norms and increased acceptance of mental health issues.

Cytokines sing the blues

- Cytokines, proteins produced by the immune system, have been implicated in the development of depression.
- Elevated levels of cytokines have been found in individuals with depression.
- The relationship between cytokines and depression may be mediated by the hypothalamic-pituitary-adrenal (HPA) axis.

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Psychosocial Stress

Danger Circuits

PVN: CRF, AVP

LOCUS CERULEUS: Norepinephrine (NE)

PITUITARY: ACTH

ADRENAL: Cortisol

ADRENAL: NE, Epi

HPA Axis

ANS

FLIGHT RESPONSE: Production, mobilization, and direction of energy. Shut down of all nonessential bodily, vegetative, and cognitive functions. Narrowing of attentional focus to perceived danger.

INNATE IMMUNE RESPONSE: Activation of systemic inflammatory response to prime the immune system for tissue damage from danger situation.

Chronic Stress, Depression and the Stress System

HPA Axis

Increased activity
Develop resistance
Loss of circadian variation

ANS

Increased SNS
Decreased cholinergic activity
Reduced HRV

How do We Know Stress Activates Inflammation?

Psychosocial Stress Activates Inflammation: Effects of Depression

The majority of the depressed patients in this sample also experienced significant early life stress, as measured by the CTQ.

Interleukin-6 and Depression

C-reactive protein and Depression

Depression is Associated with Increased Peripheral Inflammation


Inflammation is Increased in Behavioral Distress and with Neurovegetative/Somatic Symptoms and is not a Specific Marker for MDD

Raison et al. BBI 2009;23:327-337.

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Evidence That Inflammation Can Cause Depression, Pain, and Fatigue

A Picture is worth a thousand words.....
**Sickness**
- Loss of pleasure
- Loss of appetite
- Weight loss
- Cognitive disturbance
- Decreased sexual energy
- Fatigue
- Physical sloveness
- Sleep disturbance
- Social isolation
- Increased pain
- Fever
- Sad mood
- Suicidal ideation
- Worthlessness/guilt

**Depression**
- Loss of pleasure
- Loss of appetite
- Weight loss
- Cognitive disturbance
- Decreased sexual energy
- Fatigue
- Physical sloveness
- Sleep disturbance
- Social isolation
- Increased pain complaints
- Increased body temperature
- Sad mood
- Suicidal ideation
- Worthlessness/guilt

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**Depression Is Associated With Elevated Body Temperature in Medically Healthy Patients**

![Graph showing body temperature over time for depression and no depression](image)

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**Lessons from Interferon-alpha**
**SSRI Pretreatment Reduces IFN-alpha–Induced Depression**

Weeks on IFN-alpha vs. Placebo vs. Paroxetine

- **Survival Free of Major Depression (%)**
  - Placebo
  - Paroxetine

**Phenomenology and Pathophysiology of Interferon-a-induced Behavioral Change**

**IFN**-Induced CORTISOL and ACTH Response to the First Infusion of IFN-alpha

**HPA Axis Response to the First Infusion of IFN-alpha is Higher in Patients Who Later Develop MDD**

*Initial Visit*

- **ACTH**
- **CORTISOL**
- **IL-6**

**Time post-IFN Injection**

MDD vs. Non-depressed

- **Capuron, Raison et al., Am J Psychiatry 2003;160(7):1342-5**
Cortisol Responses to Psychosocial Stress Prior to IFN-alpha Predict Depression Following 12 Weeks of Treatment

IL-6 Responses to Psychosocial Stress Prior to IFN-alpha Predict Depression Following 12 Weeks of Treatment

First Dose of IFN-alpha Activates p-p38 Which Predicts Development of Depression and Fatigue
INF-alpha Increases Peripheral TNF-alpha Signaling

Increases in TNF-a associated with increased depression and fatigue

Flattened Cortisol Slope in Major Depression

Fig. 13.3 Mean hourly plasma cortisol concentrations in 12 hypomanic endogenous depressed patients (mean 24 hour cortisol = 4.4 LogU and 6 normal premenopausal women. Asterisks indicate significant differences between groups for each hourly period.

Paykel, Handbook of Affective Disorders, p. 181, 1982
Flattening of Diurnal Cortisol, Stress, Sickness and Survival

Associated with presence of cancer, metabolic syndrome, HTN and other medical illnesses
Associated with repression and high anxiety in women with breast cancer
Associated with presence of fatigue in breast cancer in remission
Predicts decreased survival in women with metastatic breast cancer
Increased IL-6 cross-sectionally associated with flattened cortisol rhythm in patients with metastatic colon cancer

Abercrombie et al, 2003; Giese-Davis et al., 2004; Bower et al. 2004; Sephton et al., 2000; Rich et al., 2005

IFN-alpha is associated with flattening of the cortisol slope which correlates with fatigue

MFI - Multidimensional Fatigue Inventory

IFN-alpha Reduces Glucocorticoid Sensitivity

Raison et al. in preparation
Decrease in Glucocorticoid Sensitivity is Correlated with Flattening of the Cortisol Slope

\[ r = 0.56, n=22, p<0.01 \]

IFN-alpha Administration is Associated with Increased Time Spent Awake and Poor Sleep Efficiency but not Sleepiness

\[ \Delta \text{Sleep Efficiency (12 week-Baseline)} \]

\[ \Delta \text{Sleep Efficiency} \]

\[ \Delta \text{Fatigue (MFI)} \]

\[ \Delta \text{Sleepiness (Epworth)} \]

\[ \Delta \text{Fatigue (total MFI)} \]

Clinical Implications of the Link Between Inflammation and Mood Disorders
Celecoxib, a COX-2 Inhibitor, Has Therapeutic Effects in MDD And Aspirin might augment Lithium

Figure 1: Comparison of HAM-D scores during therapy with celecoxib (pCOX), aspirin (pAS), and placebo (pP).

618 subjects were randomized to etanercept or placebo. Although rates of depression were low at baseline, subjects randomized to etanercept demonstrated larger reductions in depressive symptoms than subjects randomized to placebo. Depressive changes did not correlate with improvements in psoriasis symptoms.

TNF-alpha Antagonism as an Antidepressant Strategy

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Why Study Compassion Meditation in Particular?

According to Shan Deva, enemies are really good for us as we can learn a lot from them and build our inner strength.

Effect of Meditation Practice on IL-6 Responses to the TSST when Compared to Control Subjects

Effect of Meditation Practice on Distress Responses to the TSST when Compared to Control Subjects