The Emerging Role of the Immune System in Depression

Faculty Disclosure

• Dr. Raison: Speaker—Pamlab, Sunovion, Merck; Advisory Board—Lundbeck-Otsuka, Pamlab.

Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - The off-label use of infliximab, lipopolysaccharide, and non-steroidal anti-inflammatory drugs (celecoxib) for the treatment of major depressive disorder will be discussed.
• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
Immune-Brain Interactions: An Overview

Inflammatory Cytokines and MDD

MDD = major depressive disorder.

Interleukin (IL)-6
C-reactive protein (CRP)
Tumor necrosis factor (TNF)
Interleukin (IL)-1β

Practical Implications of the Brain-Immune Connection for MDD

- Both infectious and non-infectious dangers (e.g., stress) activate peripheral inflammation, which can signal the brain through several pathways. In the brain, this signal can activate microglia, the resident immune cells of the CNS.
- Peripheral inflammation can induce biochemical and functional changes in the brain that have been repeatedly associated with depression.
- As a group, medically-healthy depressed individuals demonstrate increased circulating levels of the inflammatory cytokines IL-6 and TNF, as well as the acute phase reactant CRP. However, not all patients with MDD demonstrate increased peripheral inflammation, and as we’ll see next this likely has treatment implications.

CNS = central nervous system.

The Evolutionary Imperative
Why Does Depression Exist?

- MDD has a genetic component
- MDD strikes early in life. It impairs social relationships, suppresses sexual drive, and reduces attractiveness so likely reduces reproductive success
- MDD reduces lifespan

SO:

*Why have the genes for MDD persisted in the human genome as opposed to being culled by natural and/or sexual selection?*


An Inflammatory Answer

- The genes that promote MDD evolved and persist because they help us manage our relationships

BUT:

- Not our relationships with other people …
- Our relationships with the world of microbes and parasites

Something is Wrong with the Immune System in the Modern World

*Incidence of Immune Disorders*

- Multiple Sclerosis
- Crohn’s Disease
- Type 1 Diabetes
- Asthma

The response of human beings to the conditions of the present is always conditioned by the biological remembrance of things past.

The Hygiene Hypothesis: Version II

Does the Modern World Contribute to the Immune-Depression Link?

Putting the Old Friends and Evolutionary Mismatch to the Test

- If separation from the “Old Friends” has produced an evolutionary mismatch that has promoted unrestrained inflammation in the modern world, then re-exposure to the Old Friends should reverse this and treat depression.

A Treasure in the Ugandan Mud

Mycobacterium vaccae


Examining Behavioral Effects of the Old Friend M vaccae

Single Housed Controls Chronic Subordinate Colony Housing

CSC = chronic subordinate colony.

Effects of Pretreatment with *M. vaccae* on Chronically Stressed Mice

- Blocked the development of intestinal inflammation
- Prevented stress-induced increases in peripheral inflammatory cytokines
- Increased in proactive behavior, i.e., they fought back more and because of this were left alone more by the “bully mouse”
- Prevented all measures of stress-induced increases in anxiety-like behavior
- Anti-anxiety and anti-inflammatory effects of *M. vaccae* erased when regulatory T cells were blocked


Design of an Animal Model of PTSD

PTSD = posttraumatic stress disorder.


Evidence that the Link between Depression and Inflammation is Ancient

- Until recently ~50% of individuals died prior to reproductive age due to infection, providing strong selective pressure for genetic alleles that enhance host defense
- As a result of strong selective pressure, microbial interactions have been primary drivers of human evolution
- Patterns of inflammation associated with depression enhance survival in high pathogen environments
- Many of the best-replicated risk alleles for depression have proinflammatory or anti-pathogen protective effects or are implicated in social behaviors that reduce risk of pathogen exposure
- Environmental risk factors for depression are uniformly proinflammatory
- Exposure to proinflammatory cytokines produces a sickness syndrome that overlaps considerably with MDD. Chronic cytokine exposure produces a combination of withdrawal and anxiety/hypervigilance that commonly co-exist in depression
- Symptoms shared by sickness and depression that have no social value possess potent anti-pathogen effects

The Association of Inflammation with Depression is Ancient


Evidence for the Role of Inflammation in the Evolution of Depression

Asymptomatic (No) Symptomatic (Yes) Comorbidity (No) Comorbidity (Yes)

Values are odds ratios (ORs) and their 95% CIs per 1-SD increase in log-transformed C-reactive protein. Filled squares denote statistically significant ORs (< .05) and empty squares statistically nonsignificant ORs. Single associations with depression symptoms are adjusted for age, sex, and race/ethnicity. Mutually adjusted associations are further adjusted for the sum of all the other depression symptoms besides the outcome symptom.

Evolutionary Imperatives and Mismatches in MDD


Inflammation as a Treatment Target for Major Depressive Disorder

Goods and Bads of Anti-Inflammatory Treatment for MDD

CGI = Clinical Global Impression; HAM-D = Hamilton Rating Scale for Depression; INFLIX = infliximab; TRD = treatment-resistant depression.


Depressed? A Little Inflammation Might Be a Good Thing

Therapeutic Approach 1: Blockade of stress-induced microglial activation and subsequent apoptosis
Therapeutic Approach 2: Blockade of chronic stress-induced microglial decline by microglial stimulation


Inflammation May (Sometimes) Treat Depression

In a small study of 7 severely depressed inpatients, the administration of LPS at 5 pm produced a significant reduction in depressive symptoms the next day (P = .018). The improvement was maintained in 2 of the 7 participants, whereas the other 5 relapsed following a night of recovery sleep. LPS increased IL-6 and TNF-alpha and suppressed REM sleep. Reductions in depressive symptoms were highly correlated with increased IL-6 after LPS administration (r₁ = .95, P < .001).

The Double-Edged Sword of Microglia in Depression

Guidelines for Anti-Inflammatory Trials in MDD

• Inflammation only occurs in sub-groups of depressed patients. Clinical trials should be enriched for high-inflammation participants
• Anti-inflammatory agents may harm depressed patients without increased inflammation
• In addition to classic “sickness symptoms”, behavioral outcomes should focus on anhedonia and anxiety
• Drugs that specifically target inflammatory cytokines without “off-target” effects are preferable agents
• Target engagement must be established in the periphery and ultimately the CNS

Above All Do No Harm

• Approximately 107,000 patients are hospitalized each year from complications of NSAID use
• Close to 17,000 patients with rheumatoid arthritis alone die from GI complications from NSAIDs each year
• The addition of NSAIDs to SSRIs significantly increases bleeding risk
• Celecoxib increases the risk of myocardial infarction by 226%. All NSAIDs increase risk of vascular complications
• TNF-α antagonists increase the risk of tuberculosis and other infections and have been rarely associated with rare T-cell cancers

GI = gastrointestinal; 2009 = selective serotonin reuptake inhibitor.
Safer Ways to Reduce Inflammation
*(Incomplete List)*

- Develop a sense of reverence and awe
- Eat a Mediterranean diet
- Exercise
- Don’t live a sedentary lifestyle
- Get adequate sleep
- Practice meditation
- Stay thin
- Work to reduce early life trauma/neglect


Conclusions

- We now know that immune-brain interactions can produce a syndrome indistinguishable from MDD, which likely explains—at least in part—why populations of depressed patients have elevated peripheral inflammation
- The “inflammatory perspective” casts new light on why depression exists and how it evolved. This perspective has important treatment implications
- Evidence increasingly suggest that only a sub-group of depressed patients—those with elevated inflammation—are likely to benefit from anti-inflammatory treatment modalities
- Anti-inflammatory strategies—either in the periphery or CNS (ie, microglia suppression)—may actually worsen depressive symptoms in some patients, whereas a little inflammatory stimulus might help