Brain-Gut Connection

Dr. Matthew E. Worth, DC, DACNB, FACFN
Fellow, American College of Functional Neurology
Diplomate, American College of Chiropractic Neurology
Associate Professor of Clinical Neurology
The information enclosed in this lecture is protected by copyright. Unauthorized use, reproduction, or distribution of any portion of this presentation without written consent of the author is prohibited by law. Violator will be prosecuted.
FIGURE 4 | Brain–gut–microbe communication in health and disease. A stable gut microbiota is essential for normal gut physiology and contributes to appropriate signaling along the brain–gut axis and to the healthy status of the individual as shown on the left hand side of the diagram. Conversely, as shown on the right hand side of the diagram, intestinal dysbiosis can adversely influence gut physiology leading to inappropriate brain–gut axis signaling and associated consequences for CNS functions and disease states. Stress at the level of the CNS can also impact on gut function and lead to perturbations of the microbiota.
• The digestive tract is an important component of the body’s immune system. In fact, the intestines possess the largest mass of lymphoid tissues in the human body.

• GALT is made up of several types of lymphoid tissue that stores immune cells (T/B lymphocytes) that carry out attacks and defend against pathogens.
GALT (Gastrointestinal Associated Lymphatic Tissue)

- Tonsils
- Adenoids
- Peyer’s Patches
- Lymphoid aggregates in appendix & Large intestine
- Lymphoid tissue in stomach (age dependent)
- Small lymphoid aggregates in esophagus
(Dysbiosis) aka... Leaky Gut Syndrome

• Over the last 5 years there has been an overwhelming amount of evidence-based studies accumulating that dysbiosis is a **real** condition that affects the lining of the intestines.

• The theory is that dysbiosis (increased intestinal permeability), is the result of damage to the intestinal lining, making it less able to protect the internal environment, as well as to filter needed nutrients and other biological substances.
Food Allergy and Digestion
The Small Intestine

Food particles which have been broken down into small enough size for absorption.

These particles can either ferment or get absorbed across the intestinal mucosa.

Secretry IgG antibodies

Poorly digested food particles due to lack of HCL, pancreatic enzymes, bile salts, poor mastication and/or excessively rapid transit.

These larger particles may either get absorbed from the small intestine or fermented in the large intestine into various toxins which can either cause damage locally or can get absorbed into the bloodstream where they can cause many symptoms including fatigue, headaches, joint pain, etc.

Lumen
The absorptive surface of the small intestine covered over with mucus and secretory IgA antibodies.

When foreign substances, such as large unbroken down food particles, cross the intestinal membrane, the body’s immune system makes antibodies against them. These antibodies can attack the food particles, yeast proteins, and other foreign substances producing immune complexes which can cause inflammation and other problems.

Interstitial Fluid

Leaky Gut Syndrome can result from inflammation of the intestine, parasites, medications such as cortisone, and allergies. This allows larger particles of food or other proteins to cross the mucosa.

Bloodstream

Formation of food-specific IgA, IgG, or IgE antibodies (unbound)

Food-Immune Complexes
Composed of food-specific IgA, IgG and/or IgE antibodies, if not cleared from circulation, may deposit in tissues and initiate a host of allergic responses.

adapted from Nutritional Diagnostics: Perosval & Voska
As a consequence, some bacteria and their toxins, incompletely digested proteins and fats, and waste not normally absorbed may "leak through the intestinal barrier" out of the intestines into the blood stream. This triggers an autoimmune reaction, which can lead to:

- **Auto Immune Ds:**
  - Lupus (SLE)
  - Crohn's disease
  - Arthritis / RA
  - MS
  - Celiac Ds
  - Autism
- **Digestive disorders:**
  - Acid reflux
  - chronic giardiasis
  - Food allergies
  - Chronic intestinal candidosis
  - IBS, Bloating, constipation
- **Dysautonomia:**
  - Headaches / migraines
  - Raynaud's disease
- **Skin lesions:**
  - Eczema
  - Acne
  - Psoriasis
- **Behavioral, cognitive, attention changes**
### Association between Neural Antibodies and Different Neuroautoimmune Disorders

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Disease Occurences</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Myelin Basic Protein (MBP)</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>● Myelin Oligodendrocyte Glycoprotein (MOG)</td>
<td></td>
</tr>
<tr>
<td>● α-B-Crystallin</td>
<td></td>
</tr>
<tr>
<td>● Transaldolase</td>
<td></td>
</tr>
<tr>
<td>● Myelin Associated Glycoprotein (MAG – GM₁, LM₁, GD₁b, GQ₁b)</td>
<td>Demyelinating Sensorimotor Neuropathies</td>
</tr>
<tr>
<td>● Sulfatide</td>
<td></td>
</tr>
<tr>
<td>● Campylobacter Jejunii</td>
<td>Guillian-Barre Syndrome</td>
</tr>
<tr>
<td>● Sulatide and Chondroitin Sulfate</td>
<td>Chronic Sensory Neuropathy</td>
</tr>
<tr>
<td>● Glutamate Receptors</td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td>● Ion Channel</td>
<td>Or Lou Gehrig’s Disease</td>
</tr>
<tr>
<td>● Cerebellar Purkinje Cells</td>
<td>Rassmussen’s Encephalitis</td>
</tr>
<tr>
<td>● MBP</td>
<td>Paraneoplastic Cerebellar Degeneration</td>
</tr>
<tr>
<td>● Neuron-Axon Filament Protein (NFP)</td>
<td></td>
</tr>
<tr>
<td>● Glial Fibrillary Acidic Protein (GFAP)</td>
<td></td>
</tr>
<tr>
<td>● Tubulin</td>
<td></td>
</tr>
<tr>
<td>● S-100 Protein, NFP, GFAP</td>
<td>Neurotoxicity, Autism</td>
</tr>
<tr>
<td>● Muscarinic Acetylcholine Receptor</td>
<td></td>
</tr>
<tr>
<td>● Acetylcholine Receptor</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>● Acetylcholine Receptor</td>
<td>Myasthenia Gravis</td>
</tr>
</tbody>
</table>
The Damaged Brain
What to consider

Cerebral Blood Flow
- Nitric Oxide
- Autonomics
- Tissue Perfusion
- Blood Pressure

Phospholipid Morphology
- Essential Fatty Acids
- Choline
- Partially Hydrogenated Fats

Neurotransmitter Functional Systems
- Acetylcholine Pathways
- Dopamine Pathways
- Serotonin Pathways
- GABA Pathways

Neuroinflammation
- Glia Activity
- Gut-Brain Axis
- Trauma
- Autoimmunity
- Blood-Brain Barrier

Neuron Oxidative Phosphorylation
- Environmental Toxicity
- Systemic Inflammation
- Medications

Methylation

↓ Neuronal Growth Factor Activity
↑ Microglia Neuroinflammation
↓ Neuronal ATP Activity

Accelerated Brain Aging
AUTISM is a Neuroimmune Disorder induced by:

- Infections
- Dietary Proteins & Peptides
- Toxic Chemicals

It starts in the gastrointestinal tract, affects the immune system, and manifests itself in the brain.

Induction of neuroimmune disorders by infections, toxic chemicals and dietary proteins or peptides in autism.
• Pathways involved in bidirectional communication between the gut microbiota and the brain.

• Multiple potential direct and indirect pathways exist through which the gut microbiota can modulate the gut–brain axis.
  • endocrine (cortisol)
  • immune (cytokines)
  • neural (vagus and enteric nervous system) pathways.

The brain recruits these same mechanisms to influence the composition of the gut microbiota, for example, under conditions of stress.

The hypothalamus–pituitary–adrenal axis regulates cortisol secretion, and cortisol can affect immune cells (including cytokine secretion) both locally in the gut and systemically.

Cortisol can also alter gut permeability and barrier function, and change gut microbiota composition.

Conversely, the gut microbiota and probiotic agents can alter the levels of circulating cytokines, and this can have a marked effect on brain function.
From mucosal immune abnormalities to neuroinflammation and neurodegeneration.
What is Autoimmunity?

Autoimmunity is the failure of an organism to recognize its own constituent parts as self, which results in an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease.
The gut-brain barrier in major depression: Intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression

Michael Maes 1, Marta Kubera 2 and Jean-Claude Leunis 3

1. MCare4U Outpatient Clinics, Belgium;
2. Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland;
3. Laboratory Ategias, Waver, Belgium.

Correspondence to: Prof. Dr. M. Maes, M.D., Ph.D. Director: M-Care4U Outpatient Clinics, Olmenlaan 9, 2610 Antwerp, Belgium. Tel.: +32-3-4809282 Fax: +32-3-2889185 www.michaelmaes.com E-mail: ccmh@telenet.be

Submitted: 2008-01-06 Accepted: 2008-01-27 Published online: 2008-02-22

Key words: major depression; chronic fatigue syndrome; inflammation; enterobacteria; leaky gut; gut permeability; cytokines; LPS; oxidative stress

Abstract

There is now evidence that major depression (MDD) is accompanied by an activation of the inflammatory response system (IRS) and that pro-inflammatory cytokines and lipopolysaccharide (LPS) may induce depressive symptoms. The aim of the present study was to examine whether an increased gastrointestinal permeability with an increased translocation of LPS from gram negative bacteria may play a role in the pathophysiology of MDD. Toward this end, the present study examines the serum concentrations of IgM and IgA against LPS of the gram-negative enterobacteria, Hafnia Alvei, Pseudomonas Aeruginosa, Morganella Morganii, Pseudomonas Putida, Citrobacter Koserti, and Klebsielle Pneumoniae in MDD patients and normal controls. We found that the prevalences and median values for serum IgM and IgA against LPS of enterobacteria are significantly greater in patients with MDD than in normal volunteers. These differences are significant to the extent that a significant diagnostic performance is obtained, i.e. the area under the ROC curve is 90.1%. The symptom profiles of increased IgM and IgA levels are fatigue, autonomic and gastro-intestinal symptoms and a subjective feeling of infection. The results show that intestinal mucosal dysfunction characterized by an increased translocation of gram-negative bacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. It is suggested that the increased LPS translocation may mount an immune response and thus IRS activation in some patients with MDD and may induce specific “sickness behaviour” symptoms. It is suggested that patients with MDD should be checked for leaky gut by means of the IgM and IgA panel used in the present study and accordingly should be treated for leaky gut.
FIGURE 2 | Function of the intestinal microbiome. Commensal bacteria exert a miscellany of protective, structural, and metabolic effects on the intestinal mucosa.
Factors affecting mucosal immune system resulting in intestinal barrier dysfunction, autoimmunity and nervous system abnormalities

INTESTINAL BARRIER DYSFUNCTION

FOOD ALLERGY & INTOLERANCE

IMMUNE SYSTEM ABNORMALITIES

AUTOIMMUNITY

INFLUENCE ON THE BLOOD-BRAIN BARRIER AND NEUROAUTOIMMUNITY

Dietary Proteins & Peptides
Antibodies
Drugs & Xenobiotics
Stress
Infections
Cytokines
Neurotransmitters
Enzymes

Lamina propria

Breakdown of mucosa IgA and tight junction proteins
Permeability increase

copyright Aristo Vojdani, Ph.D., M.Sc., C.L.S.

Depiction of immunological mechanisms underlying gluten intolerance and its immunopathological consequences
Hidden Sources of Gluten

- Soy sauce
- Food starches
- Food emulsifiers
- Food stabilizers
- Artificial food coloring
- Malt extract, flavor, syrup
- Dextrin
Gluten Sensitivity vs. Celiac Disease

Gluten Sensitivity + Intestinal Damage = Celiac Disease

Gluten Sensitivity + No Intestinal Damage = Sensitivity

Damage to Other Tissues: Myelin, Cartilage, Skin, Vascular Endothelium, Liver, Kidney, etc.
Celiac Disease
• Antigliadin Antibodies +
• HLA–DQ +
• Transglutaminase +
• Small Intestine Biopsy +
• Endomysial Antibodies +
• Fecal Fat Microscopy +

Gluten Sensitivity
• Antigliadin Antibodies +
• HLA–DQ +
• Transglutaminase -
• Small Intestine Biopsy -
• Endomysial Antibodies -
• Fecal Fat Microscopy -
DECREASED ACTIVITY OF BRAIN

- Decreased projection and activation of the vagal nuclei
- Decreased intestinal motility
- Suppressed intestinal immune activation

DECREASED INTESTINAL BLOOD FLOW

DECREASED INTESTINAL MOTILITY

INTESTINAL PERMIABILITY

- Intestinal yeast overgrowth
- Intestinal bacteria overgrowth

INTESTINAL INFLAMMATION

CYTOKINE ACTIVATION OF THE BRAIN MICROGLIA

GUT-BRAIN AXIS INFLAMMATION AND DISREGULATION
Neutrophils
Monocytes (Macrophages)
Basophils
Eosinophils
Lymphocytes → Natural Killer Cells

↓

B-Cells

T-Cells

↓

Cytotoxic T-Cells

↓

T-Suppressor

↓

Regulatory T Cells

↓

T-Helper

---------------------- BLOOD-BRAIN BARRIER ----------------------

Myeloid Progenitor Cells → Microglia

---
VI. CD4+ T helper Subsets
Th1/Th2 Cytokine Bias

• CD4+ T_{helper} cells can be divided into subsets based on their cytokine production.

• T_{h1} cells produce IL-2, IFN-\(\gamma\), TNF-\(\beta\) CKs which activate cell mediated immunity

• T_{h2} cells activate IL-4, IL-6, IL-10 CKs that activate humoral immunity

These Th subsets were originally identified using mouse T cell clones.
Mechanism responsible for induction of autoimmunity and tissue damage by $T_{H1}$ cells
Proposed effect of artificially increased dietary hapten on oral tolerance.

Modified from McFadden et al., Trends in Immunology, 30(2):67-74, 2009
Proposed effect of artificially increased dietary hapten on oral tolerance.

Modified from McFadden et al., Trends in Immunology, 30(2):67-74, 2009
Mechanism responsible for induction of autoimmunity and tissue damage in the brain. Under conditions of hyperexcitability, circulating $T_H1$ adhere to endothelial cells in brain blood vessels via interaction of endothelial adhesion molecules. $T_H1$ cells then roll along the internal vessel walls and extravasate through the BBB, where they produce local inflammation and neural cell destruction.
Brain-Blood Barrier

Degrade
• Elevated Homocysteine
• Increased Oxidative Stress
• Physiological Stress Response
• HPA Axis Dysregulation
• Alcohol
• Glycosylated End Products

Enhance
• Methylation Physiology
• Modulate Stress Physiology
• HPA Axis Regulation
• Alpha-Lipoic Acid
• Glutathione
• Antioxidants
• Brain Neuronal Activity
• Prostaglandin Balance
Neurodegeneration

Increased Sympathetic Activity

Decreased Cerebral Blood Flow

Energy-Linked Excitotoxic Activity

Neuronal Death and Microglial Activation
Insulin Surges

- Spikes of Serotonin
- Spikes of Dopamine
- Spikes of Epinephrine
- Leptin Elevations
- Elevation of Cortisol
- Cytokine Inflammation
- Increased Glycosylated End Products
- Brain Degeneration
Chronic Neuroinflammation

Activated Microglia

→

Produce Neurotoxic Mediators

→

Microglia Remain Activated for an Extended Period of Time

→

Increase Production of Neurotoxic Mediators is Sustained After Activation

→

Contributes to Surrounding Neuronal Death

→

Neurodegeneration
Figure 1: Hierarchy of the Pediatric Acute on set Neuropsychiatric Syndrome.
Drawings that Demonstrate Loss of Fine Motor Skills During Acute Illness.

Before symptom onset

During acute episode

Figure 3: Handwriting samples documenting dysgraphia during acute illness.