The Gut-Brain Connection

The role of a healthy gut in healthy brain function

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Lecture in Brief

- The gut-brain connection – What’s involved:
  - Microbiota
  - Stress
  - The importance of SIgA
  - Barrier function
  - Fructose and the Western Diet
  - Lipopolysaccharides and endotoxemia
  - Tying it all to brain function
  - Therapeutic options
  - A case study

The Gut-Brain Connection

- A large body of evidence is accumulating to support a role between healthy gut function, neural development and function of the central nervous system.
- The microbiota present in the gut should be considered an inner organ with functions similar in importance to any other organ present in the body.
- Disruptions in this “organ” may alter many things including central nervous system function.

Gut-Brain Connection

- The human gut is sterile at birth, but is quickly colonized.
- By one year of age, it looks similar to that of an adult profile, although it is still unique to that child.
- Total adult load is estimated at 1,800 genes, 40,000 species, 1-2kg in weight, 100 trillion in number and possesses 100 times the genes found in the human genome.
- It is the equilibrium of the above that is important.

Gut-Brain Connection

- The gut-brain axis includes:
  - CNS
  - Neuroendocrine system
  - Neuroimmune system
  - Sympathetic nervous system
  - Parasympathetic system
  - Enteric nervous system
  - Intestinal microbiota

Gut-Brain Connection

- It is through this bidirectional relationship that signals from the brain can influence the gut and visceral messages from the gut can influence brain function.
- Established influences of the microbiota on the host include:
  - Regulation of the mucosal immune system
  - Gastrointestinal motility
  - Epithelial barrier function
  - Digestive and host metabolism support
  - Prevention of colonization by pathogens

References:
Gut-Brain Connection

- The effects of bacteria on the CNS is critical and begins very early in life.
- Germ-free mice demonstrate exaggerated HPA axis response (high corticosterone and ACTH secretion) to mild stress. This is corrected by colonization by pathogen free bacteria from other controls.
- This study showed that microbial content of the gut is critical to the development of an appropriate stress response later in life and that there is a critical window where colonization must occur to ensure proper HPA axis development.

Microbiota and its effects on the CNS

- The most obvious connection is in patients with hepatic encephalopathy.
- Patients in hepatic failure often develop:
  - Impaired cognition, tremors, dementia and even coma.
- Treatment is an oral, non-absorbed antibiotic which works to reduce urease producing bacteria and therefore ammonia production and other neurotoxins.

The “Gut” Feeling

How our GI tract can influence the CNS

Definitions

- Lipopolysaccharides (LPS) – molecules present on the surface of gram-negative bacteria that elicit a strong immune response.
- Cytokines – messengers used by the immune system to communicate with itself and other parts of the body including the CNS.
  - These may be inflammatory, anti-inflammatory or regulatory.

Barrier function

- Barrier function in the gut is extremely important.
- Because we put the outside world into our GI tract, there must not be open access to systemic circulation.
- An intact gut barrier is one factor that protects us.

Barrier function

- The intestinal epithelium is large – more than 2,000,000 cm²
  - This is just over 2,100 square feet!
- Tight junctions play a major role in regulating what is absorbed and what is excreted.
- Tight junctions control flow of particles between cells. This is called paracellular flow.
Barrier function

- Tight junctions are composed of at least 50 different membrane associated proteins.
- They are located between cells at the apical (top) and lateral portions of connected epithelial cells.
- Some actually extend into intercellular space as a function as a gate.
- Others are linked to cytoskeletal structures which serve to anchor membrane proteins.

Triggers for Gut Dysbiosis and Gut Dysfunction

- Stress
  - Physical (infection)
  - Mental
- Environmental
  - Chemical (medication, pollution)
- Dietary
  - Gluten
  - Dairy
  - Other food sensitivities
  - Alcohol
  - Generally poor diet

Stress

- Stress activates the autonomic nervous system.
- Stress primarily activates the sympathetic nervous system.
- While the SNS seems to display mild anti-inflammatory properties in the gut, the parasympathetic nervous system has powerful anti-inflammatory effects.
- With stress, sympathetic activity is dominant and parasympathetic activity is significantly reduced.

Stress

- Parasympathetic activation and anti-inflammatory effects on the gut:
  - Functional evidence shows that the vagus regulates the intestinal immune system.1
  - Stimulation of the vagus nerve has been shown in laboratory animals to prevent endotoxin-induced shock by reducing pro-inflammatory cytokine production.2

1ISRN Gastroenterol. 2013 Apr 4;2013:630159.
Stress – the importance of SIgA

• SIgA or secretory IgA is an antibody produced in mucosal linings and plays a major role in host immunity.\(^1\)

• SIgA helps prevent antigens in the gut from being able to stick to the walls of the intestines.\(^1\)

• SIgA promotes the clearance of antigens and pathogenic microorganisms from the intestinal lumen by blocking their access to epithelial receptors, entrapping them in mucus, and facilitating their removal by peristaltic and mucociliary activities.\(^2\)

• If these antigens are not excreted they are able to produce an inflammatory response that may break down the gut barrier.\(^1\)

\(^1\) Front Integr Neurosci. 2013; 7: 86.
\(^2\) Mucosal Immunology (2011) 4, 603–611.

• Additionally, SIgA has an anti-inflammatory role by neutralizing pro-inflammatory antigens.

• Together with the intestinal microflora, it contributes to maintaining intestinal inflammatory response within physiological limits.

Stress – the importance of SIgA

• Down regulation of SIgA is associated with stress and can have negative repercussions on intestinal function and integrity.

• This can take the form of increased adhesion of pathogenic agents to the intestinal epithelium and/or an altered balance of inflammation leading to greater intestinal permeability.

Front Integr Neurosci. 2013; 7: 86.

• The modulation of SIgA in response to stress is determined by the duration and intensity of the stress.

• Acute stress upregulates immune response and SIgA.

• Chronic stress down regulates immune response and SIgA.

• Chronic stress also decreases the number of lymphoid cells in Peyer’s patches within the intestinal epithelium.

Front Integr Neurosci. 2013; 7: 86.

• Interestingly, the immunosuppressive effects of stress on SIgA can be attenuated by activating peroxisome proliferator activated receptors (PPAR).

• This can be done through polyunsaturated fatty acids and exercise.

Front Integr Neurosci. 2013; 7: 86.
Dietary Considerations

- Dietary factors affecting gut barrier function, gut microbiota and systemic inflammation:
  - High Fructose diet
  - The “Western Diet”
  - Nutrient deficiencies

High Fructose Diet

- Fructose has been implicated in insulin resistance, fatty liver and metabolic syndrome.
- Some studies have shown that fructose, but not glucose, could induce liver damage directly through increasing intestinal LPS translocation and endotoxemia.\(^1\)
  - Fructose combined with antibiotics reduced endotoxemia and fatty liver.

Fructose

1. Fructose consumed
2. Increased LPS translocation
3. LPS binds immune cells via toll-like receptors
4. Immune cells generate inflammatory cytokines
5. Inflammatory cytokines alter systemic inflammatory load

High Fructose Diet

- This fructose-mediated change in endotoxemia, and subsequent amelioration with antibiotics, means the type of carbohydrate consumed is important and fructose may alter intestinal permeability through dysbiosis and activation of the immune system.\(^1\)
- In mice who have been genetically modified not to have a specific receptor for endotoxins called a toll-like receptor (and therefore cannot generate an inflammatory response) fructose exposure does not cause fatty liver or insulin resistance.\(^2\)
- This means processes like fatty liver and insulin resistance may be mediated by gut microbiota and are inflammatory in nature.

High Fructose Diet

- Additionally, patients with depression have been shown to have abnormal hydrogen breath profiles after consumption of fructose and other sugars.\(^1\)
- Elimination of fructose resulted in improved depression.\(^2\)

High Fructose Diet

- Other studies have shown fructose malabsorption is associated with a reduction of plasma tryptophan.\(^3\)
- Fructose malabsorption also provides a substrate for bacterial fermentation that can alter:
  - GI motility
  - Mucosal biofilm
  - Profile of microbiota

References:
The Western Diet

- It has been shown that diets high in calories are associated with higher levels of plasma LPS.¹
- It has also been shown that excessive fat and carbohydrate intake can increase transport of LPS from the gut to the bloodstream although fat seems to be more efficient.²
- However, the type of fat also has an impact on the level of endotoxemia with saturated fat being the biggest offender.


Nutrient Deficiencies

- Nutrients to consider include vitamin A, magnesium, zinc, and vitamin D.
- It is through these nutrients’ ability to change cytoskeletal structure or expression of tight junction proteins that they may be involved in changes in gut barrier function.

Vitamin A and Magnesium

- Retinoic acid plays a major role in the expression of genes related to epithelial barrier and tight junctions.
- Vitamin A status regulates the cellular availability of retinoic acid.
- It has been shown that reduction in vitamin A adversely affects barrier function and tight junction expression.¹
- Magnesium deficiency has also been reported to reduce tight junction expression and reduce bifidobacteria content in the gut.


Zinc

- In animal models, zinc deficiency has been shown to directly breakdown tight junctions and/or sensitize barrier cells to external stressors capable of increasing gut permeability like alcohol.¹
- Eventually, this results in the breakdown of the gut barrier through zinc dyshomeostasis.¹
- Additionally, changes in zinc homeostasis are associated with subclinical enteropathy and subsequent altered intestinal permeability in children.

Vitamin D

- The vitamin D receptor (VDR) is hugely important in mucosal barrier function.
- It preserves junctional complexes and stimulates epithelial cell renewal.
- It modulates the immune function associated with mucosal barriers.
- Administration of vitamin D to experimental animals increases colonic epithelial cell resistance to injury.


GI Induced Inflammation and the CNS

- Many mental health disorders are associated with low-grade inflammation, oxidative stress and an elevation of inflammatory cytokines.¹
- In fact, mood disturbance and fatigue can be induced by injecting LPS.²

¹Gut Pathog 2013, 5:3
²Arch Gen Psychiatry 2003, 58:445–452.

Lipopolysaccharides

- Miniscule amounts of LPS are found in the blood of healthy controls signifying an intact gastrointestinal barrier is efficient in preventing entrance into circulation.
- Other disorders with known inflammatory connections and connections with depression and anxiety have been shown to be associated with higher circulating LPS levels.
- This includes:
  - Obesity
  - High insulin, triglycerides, and cholesterol
  - Diabetes.

GI Induced Inflammation and the CNS

- Further supporting healthy GI microbiota and general health are studies showing oral probiotics favorably impact.¹³
  - Systemic cytokine levels
  - Oxidative stress
  - Inflammatory markers
  - Mental outlook
  - Cognition


Inflammatory Cytokines

- Systemic inflammatory cytokines can induce the production of inflammatory cytokines in the CNS via microglial activation.¹
- While microglia are very important in neuronal survival, chronic activation compromises neuronal function through a cascade of inflammation and oxidative stress.¹
- Eventually this results in abnormal intracellular and extracellular communication, abnormal function and possibly neurodegeneration.
Lipopolysaccharides

- This systemic inflammation (and eventual glial activation) is increasingly being recognized as being stimulated by LPS.
- As a matter of fact, LPS at low levels have been shown to cause acute anxiety, depressive symptoms, cognitive deficits and decreased visceral pain tolerance.\(^1\)\(^4\)

1. Neuroimmune Pharmacol 2013, 8:42–50
2. PLoS One 2011, 6:e28330

Indoleamine-2,3-dioxygenase (IDO) and Tryptophan-2,3-dioxygenase (TDO)

- The vast majority of circulating tryptophan is metabolized using these two enzymes into kynurenine.
- Less than 1% is available to be converted to serotonin in the brain.\(^1\)
- TDO is usually the dominant enzyme but under immune stimulation, IDO is further activated.
- When this occurs, the combination of the activity of TDO + IDO makes tryptophan far less available for conversion to serotonin.
- As a matter of fact, serum tryptophan may be reduced 25-50%.\(^1\)\(^4\)


IDO and TDO

Altered Cytokines = Altered Neurochemistry

- Quick Review:
  - Altered cytokine levels can be brought about by:
    - Stress
    - High fructose diet
    - Western diet
    - Endotoxemia (LPS stimulation)
- All of this is complicated by changes to intestinal barrier function also from the above mechanisms but also some documented nutrient deficiencies.
Evidence supports a connection between altered cytokine levels and altered neurochemistry.
- Neurochemical changes have been noted to various cytokine changes and compared to changes that occur with influenza infection.

### Altered Cytokines = Altered Neurochemistry

- The known mechanisms by which this occurs are:
  - Cytokines act on central sites where the blood brain barrier is weak or cause breakdown of the blood brain barrier themselves.
  - Cytokines may be transported in by selective transporters, bypassing the BBB.
  - Cytokines may act on peripheral nerves that send information into the central nervous system.
  - Cytokines can affect the secretion of molecules who are not limited by the BBB but can themselves affect neurochemistry.
  - Cytokines can be synthesized by immune cells that have infiltrated the CNS through a compromised BBB.

### Altered Cytokines = Altered Neurochemistry = Altered Mood, Behavior and Cognition

- Eventually, altered neurochemistry changes behavior, mood and cognition with resultant symptomatology.
- To control this process, cytokine levels must be kept in appropriate ranges and barrier function optimized.
- This involves:
  - Reducing small intestinal bacterial overgrowth (SIBO)
  - Reducing endotoxemia
  - Reducing inflammatory cytokine production
  - Improving intestinal barrier function
  - Improving BBB integrity

Options for care: The Basics

- Exercise is one of the most successful treatment strategies for those who have altered neurochemistry.
  - It has multiple effects:
    - Weight loss (which is inherently anti-inflammatory).
    - Reduces inflammation by other mechanisms.
    - Increases fuel delivery and waste removal in the brain.
    - Increases neural feedback to the brain.
  - Exercise should be 30-60 minutes at least four times per week.

Options for care: The Basics

- A test of current allergies is warranted in patients suspected brain dysfunction from altered gut physiology.
- Removing all allergens will reduce immune drive and reduce pro-inflammatory cytokine production.
- Major triggers include casein, gluten and soy.
- Using other methods like IgG testing or ALCAT testing to identify other allergies is helpful.
- All moderate and severe allergies should be removed and mild intolerances should be rotated.

Optimizing Gut Health

- In addition to removing potential allergens/sensitivities as briefly mentioned earlier, optimizing the bacterial profile is critical.
- Parasites and fungal/yeast load should be considered as well.
- Stool tests using DNA analysis are the most sensitive and accurate way to assess a patient’s gastrointestinal balance.
- Tests through specialty labs are available to check for predominant, or “beneficial,” bacterial load, opportunistic bacteria, pathogenic bacteria, parasites, and fungus/yeast.
- They will also often measure digestive, absorptive, and inflammatory parameters which may also be of value.

Optimizing Gut Health

- Oregano is a potent antimicrobial showing the ability to destroy or inhibit the growth of *Escherichia coli* O157:H7, *Staphylococcus aureus*, *Listeria innocua*, *Saccharomyces cerevisiae* and *Aspergillus niger* in addition to a variety of parasites.\(^1\)
- Emulsification and time release of the product is key. If not emulsified and time released, distribution of the oil of oregano is too quick and the distal GI tract is left untreated.
- Dose is 600mg daily for 6 weeks.\(^2\)

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\(^1\)International Journal of Food Microbiology. Volume 146, Issue 2, 30 March 2011, Pages 144–150
Optimizing Gut Health

- Other naturally sourced ingredients shown to be effective as antimicrobials include:
  - Thyme\textsuperscript{1,2}
  - Clove\textsuperscript{3}
  - Anise\textsuperscript{4}
  - Buchu/Betulina\textsuperscript{5}
  - Dill\textsuperscript{6}
  - 
  - Buchu/Betulina\textsuperscript{5}
  - Dill\textsuperscript{6}
  - 
  - Brueca javanica\textsuperscript{7,10}
  - Acacia catechu\textsuperscript{7,11}

\textsuperscript{2} Fabio et al. New Microbiol. 2003 Jan.
\textsuperscript{9} J Ethnopharmacol. 2005 Apr 8;98(1-2):67-72.

Dysbiocide

- Supplies a proprietary blend of Stemona sessilifolia, Artemisia absinthium, Brueca javanica, Pulantill chinensis, Picrasma excelsa, Acacia catechu, Hedysora diffusa, Yarrow and Dill.

- Great adjunct to A.D.P. for parasites and SIBO.

- 2-3 capsules, twice per day with food.

Bio-HPF

- I've found this product very effective for H. pylori overgrowth if it is identified.

- 3 capsules, 3x per day for 20-40 days taken with meals.

- May require more for stubborn infections.

BioDoph-7 Plus

- Contains a proprietary blend of seven different prebiotics and probiotics with each capsule containing 20 billion viable organisms at the time of manufacture.

- For use after antimicrobials have been used.

- Dose is 2-4 capsules daily.

Optimizing Gut Function

- After the elimination of dysbiosis, re-inoculation with probiotics is critical.

- A probiotic is defined as:
  - "A preparation of, or a product containing viable, defined microorganisms in sufficient numbers, which alter the microbiota (typically by colonization) in a compartment of the host, and by that, exert beneficial health effects in this host."

- A balanced probiotic containing prebiotic compounds is best.

- Dose of 40-80 billion live organisms is appropriate.

IPS

- Reducing gut permeability is also critical.

- Dietary changes are necessary, but IPS is a great addition.

- Designed to stimulate growth and repair of the intestinal mucosa as well as aiding in gut detoxification.

- Dose is 2 capsules twice per day on empty stomach.
Cytokine and Immune Modulation

- Options to consider:
  - Vitamin D
  - Superoxide dismutase
  - Omega-3s
  - Lipic Acid

Vitamin D and Depression

- Current guidelines for vitamin D intake of 400 – 800IU daily are far too low.
- Daily requirements are between 3,000 – 5,000IU per day.¹
- Low serum vitamin D is associated with an increased production of pro-inflammatory cytokines.²³

Vitamin D, Immunity and Cytokines

- High dose vitamin D supplementation (140,000IU) in a single dose or a monthly dose significantly increases circulating regulatory T-cells in healthy human subjects.¹²
- Vitamin D receptor agonists promote Treg cells that are able to mediate transplantation tolerance and to arrest the development of autoimmune diseases.³

Vitamin D, Immunity and Cytokines

- Vitamin D inhibits the production of the pro-inflammatory cytokines IL-6 and TNFα in vascular smooth muscle cells in a model of atherosclerosis.
- In this model, vitamin D also induced the activity of superoxide dismutase, another potent regulator of the immune system.

Vitamin D

- Bio-D Mulsion Forte is an emulsified highly absorbable liquid vitamin D providing 2000 IUs per drop.
- 5 drops per day for a total of 10,000 IUs per day.

SOD – Superoxide Dismutase

- SOD has immunomodulatory effects, likely through its properties as an antioxidant.¹
- It is also possible that through the ability of ROS to promote white cell adhesion to vascular walls it promotes immune activation.² (A process SOD would inhibit).
- Reactive oxygen species also promote T-cell polarization and pro-inflammatory cytokine secretion.³

¹Antioxid Redox Signal. 2012 Jan 20
²Hypertension. 2011;57:132-140

¹J Am Clin Nutr. 2003;77:204–10
³QJM. 2002;95:787-796
⁵Am J Clin Nutr. 2003;77:204–10
⁷QJM. 2002;95:787-796
SOD

- It has also been found that the reduction of extracellular SOD promotes T-cell activation and vascular inflammation. 1
- Diets low in antioxidants are likely to promote low levels of SOD and potentiate immune system dysfunction.

Omega-3s

- There is evidence that omega-3 fatty acids can positively affect T-cell function, cytokine production and antigen presentation by the immune system. 1,2
- Increased consumption of omega-3 fatty acids results in increased incorporation of omega-3s in immune cell phospholipids at the expense of arachidonic acid.
- This occurs in a dose-response fashion and influences immune function and inflammation. 3-6

Omega-3s and the BBB

- Omega-3s may also help to stabilize the blood brain barrier.
- This mechanism may be through their anti-inflammatory properties, reduction in cytokine levels or another unknown pathway.

Omega-3s

- Further, in vitro studies have shown decreased T-cell activation in response to EPA and DHA. 1-4
- Studies in rodents and humans have shown that supplementation of fish oil reduces T-cell proliferation and the production of T-helper cell cytokines IL-2 and IFN-γ. 5-11

Omega-3s

- Biomega-3 Liquid provides high dose EPA and DHA which are not only anti-inflammatory but also critical for brain health.
- A tablespoon once per day is a good dose.
- Per tablespoon, the patient will receive 2.220mg of EPA and 1.380mg of DHA.
**Omega-3s**

- **Biomega-3** is available in capsule as well.
- Each capsule provides 180mg of EPA and 120mg of DHA.
- An effective dose would be 4 capsules, twice per day.
- Note: The liquid is more cost effective.

**Lipoic Acid – Maintaining the BBB**

- Lipoic acid can attenuate increases in blood brain barrier permeability in experimental subarachnoid hemorrhage.1
- In the rat model of MS, lipoic acid showed a dose-dependent ability to reduce monocyte infiltration into the CNS and increase stability of the BBB.2
- Lipoic acid has also demonstrated the ability to repair the blood brain barrier after infection.3

1 Neurochem Res. 2010 Mar;35(3):418-28
3 Evid Based Complement Alternat Med. 2011;2011:984965

**Lipoic acid**

- **Lipoic Acid** provides 100mg of alpha-lipoic acid per capsule.
- 2 capsules twice per day

**Case Study - Heather**

- Heather is a 41 year old massage therapist who presented to my office with a 4-5 year history of:
  - Chronic yeast infections
  - Chronic bacterial vaginosis
  - Brain fog
  - Debilitating depression
  - Anxiety
  - Interrupted sleep pattern
  - Daily headaches

**Case Study - Heather**

- History:
  - Positive antibody titer for gluten and casein.
  - High thyroperoxidase antibody.
  - Mildly elevated lead level.
  - Low ferritin with elevated red cell distribution width.
  - Low normal immunoglobin A level.

Low ferritin and elevated RDW is another stressor and probably produces altered fuel delivery to the CNS. Borderline immunoglobin A production signifies long standing immune challenges and imbalances.
Case Study – Heather

Significant Stool Test Findings

- Relatively low “good” bacteria
- Combined with high level of pathogenic bacteria creates immune imbalance
- High lactoferrin indicates inflammation and explains the low ferritin as lactoferrin is an iron-binding protein

Treatment Protocol

- Although she’d been told before to remove gluten and dairy, she was not gluten and dairy free.
- The importance was stressed and she complied.
- A very low glycemic diet was also recommended.
- Regular exercise of 30-60 minutes at least 4 times per week was recommended.

Treatment Protocol

- Supplement recommendations:
  - Bio-D Mulsion Forte – 5 drops per day (10,000IU)
  - A.D.P. – 4 tablets, 3x per day for 20 days (2 bottles)
  - NAC – 3 capsules, 2x per day
  - Dismuzyme Plus 5000 – 1 tablet twice per day
  - Bio-HPF – 3 capsules, 3x per day (2 bottles)
- After one month her yeast infections and bacterial vaginosis were “a lot better.”
- Brain fog and depression unchanged.

Treatment Protocol

- At our one month follow-up the following was added:
  - Bio A4 Muision Forte - 4 drops per day
  - POA Phytolens – 1 per day
  - Neutrophil plus – 1 capsule twice per day
  - Folate – 5 – Plus – 5 capsules twice per day
  - St. John’s Forte - 1 capsule twice per day
- At the next month’s follow up she reported a 20% improvement in brain fog and depression. All yeast/bacterial symptoms gone.
- We continued to monitor her symptoms and make small changes in her supplement program for another two months.
  - BioDoph -7 Plus was added at 2 capsules twice per day
- In this time she reported sleep was great, headaches gone, anxiety improving and depression progressing slowly, but surely.

Treatment Protocol

- Last communication from patient:
  - “I feel amazing! The brain fog is almost 100% gone and whatever was in my gut is leaving. Been decreasing sertraline and I feel very good! Thank you sooooo much!”
  - From the start of treatment to her current status was approximately 8 months.

Suggested Reading

- A Clinician’s View of Biotics’ Products by Harry O. Eidenier, Jr.
- Functional Neurology for Practitioners of Manual Therapy by Randy Beck.
- Neurobehavioral Disorders of Childhood – An Evolutionary Perspective by Robert Melillo and Gary Leisman.
- The Human Brain by John Nolte.
Suggested Reading

- *Neurological Differential Diagnosis 2nd ed.* By John Patten.
- *Basic Neurochemistry 7th ed.* By Siegel, Albers, Brady and Price.
- *Introduction to Neuropsychopharmacology* by Iversen, Iversen, Bloom and Roth.

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