Using organic acids to resolve chief complaints and improve quality of life in chronically ill patients

Part VIII
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Tryptophan metabolism and mood/behavioral disorders
Summer of work exposes medical students to system’s ills, The New York Times, September 9, 2009

"...a tidal wave of chronic illness..."

"An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors."

"All stresses may be presumed to be associated with characteristic modifications in the metabolism of lipids, carbohydrates, amino acids, and micronutrients."

Biological Mechanism of Antidepressant Effect of Omega-3 Fatty Acids: How Does Fish Oil Act as a ‘Mind-Body Interface’?

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Department of General Practice and Addiction Medicine, National Taiwan University Hospital, Taipei, Taiwan.

ABSTRACT
Omega-3 fatty acids have been widely used in the prevention and treatment of cardiovascular diseases and mental health problems. This review examines the potential mechanism of omega-3 fatty acids as a ‘mind-body interface’. The biochemical properties of omega-3 fatty acids can provide neuroprotective, anti-inflammatory, and antioxidant effects. Omega-3 fatty acids can also influence neurotransmitter systems, such as norepinephrine, dopamine, and serotonin, which are associated with the development and treatment of depression. However, the exact mechanism of omega-3 fatty acids as a ‘mind-body interface’ remains uncertain. Further research is needed to elucidate the precise role of omega-3 fatty acids in the prevention and treatment of depression.

Keywords: Omega-3 fatty acids, ‘Mind-Body Interface’, Neurotransmitters, Depression, Antidepressants

Introduction
Major depressive disorder (MDD) is a serious mood disorder that affects millions of people worldwide. Despite advancements in the treatment of depression, many patients still experience symptoms that do not respond to traditional therapies. Omega-3 fatty acids have gained interest as a potential adjunct therapy for depression due to their effects on brain function and neurotransmitter systems. This review aims to summarize the current evidence regarding the use of omega-3 fatty acids in the treatment of depression and explore their potential role as a ‘mind-body interface’.

Conclusions
Omega-3 fatty acids can exert antidepresant effects through various mechanisms, including modulation of inflammatory processes, neurotrophic effects, and improvement in mood and cognitive function. Further research is needed to fully understand the role of omega-3 fatty acids as a ‘mind-body interface’ and to determine their optimal use in the prevention and treatment of depression.
Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN-α therapy and the somatic symptoms in MDD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence in IFN-α therapy, %</th>
<th>Prevalence in MDD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/asthenia</td>
<td>39–90</td>
<td>73</td>
</tr>
<tr>
<td>Headache</td>
<td>27–67</td>
<td>33%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>50%–1</td>
<td>34–47%</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>40%</td>
<td>59–65%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>20–39%</td>
<td>63%</td>
</tr>
<tr>
<td>Irritability</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9–36</td>
<td>31%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26–32</td>
<td>62–80%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15–20</td>
<td>21%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13–19</td>
<td>40%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13–18%</td>
<td>57%</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>14%</td>
<td>51%</td>
</tr>
</tbody>
</table>

* [46], unless otherwise specified; † [99], unless otherwise specified; ‡ [100]; § [101]; † [102]; † [103]; † [104].
1 Nausea, vomiting, bowel problems.
2 Result from depressed inpatient population.

Modulation of tryptophan and serotonin: Diagnostic and treatment issues
Traditional allopathic approaches have primarily revolved around neurotransmitter modulation – particularly serotonin

• How well has it worked?

Neurotransmitter imbalances are byproducts of chronic inflammation!!
Chronic inflammation, inflammaging

Key deficiencies or excesses, i.e., Calories, macronutrients, B vitamins, zinc, selenium, iodine, sleep, psychological and chemical stress, movement against gravity, weight

Low calorie intake and excessive carbohydrate/protein ratio – Refeeding syndrome

Hyperinsulinemia/Insulin resistance

Sarcopenia/Loss of lean body mass

Low grade chronic metabolic acidosis/fluid electrolyte imbalance

Gut dysfunction/atrophy

THE CREATION OF THE EXCESSIVE CATABOLIC PHYSIOLOGY “RESPONSE”

Fig. 1. Catabolic pathways of tryptophan: tryptophan (5)-hydroxylase (TSH) initiates the production of 5-hydroxytryptamine (serotonin) whereas tryptophan (2,3)-dioxygenase (TDO) and indoleamine (3,4)-dioxygenase (IDO) catalyze the formation of kynurenine.

Fig. 2. Th1-type cytokine interferon-γ (IFN-γ), which is released within innate and adaptive immune response, induces enzyme indoleamine (2,3)-dioxygenase (IDO) in macrophages, dendritic cells and various other cells.
Table 1
Relationship between tryptophan metabolic changes and immune activation

<table>
<thead>
<tr>
<th>Changes of blood levels</th>
<th>Tryptophan</th>
<th>Kynurenine</th>
<th>Kyn/trp</th>
<th>Immune activation markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient dietary intake</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDO</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDO</td>
<td>↓↓</td>
<td>↑↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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5-Hydroxyinoleacetate (5-HIAA)
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• “Catabolic breakdown of serotonin leads to excretion of 5-hydroxyindoleacetate (5-HIAA).”
• “Abnormally high levels of this metabolite result from the use of serotonin-specific reuptake inhibitor (SSRI) drugs, 5-hydroxytryptophan supplementation, or increased release of serotonin from any of three primary sites: central nervous system, intestinal argentaffin cells, or platelets.”

• “The effect of an SSRI can cause strong elevations of 5-HIAA.”
• “We have found that patients who show no elevation of urinary 5-HIAA in response to SSRIs concurrently often report poor antidepressive responses to the drug.”
• “The drugs with greater serotonin selectiveness are more likely to cause urinary 5-HIAA elevation.”
• “A principal reason for difficulty with interpretation of urinary 5-HIAA is the lack of tissue-specific knowledge of its origin.”
• “Although serotonergic neurons in the brain have been most intensely studied, they also are abundant in the spinal cord and other tissues, notably the gastrointestinal tract.”
• “Carcinoid tumors composed of chromaffin tissue can release large amounts of serotonin.”
• “Urinary 5-HIAA has been recommended for diagnosis of some types of carcinoid tumor cases.”

“Because of the magnitude of total body serotonin synthesis, increased rates of serotonin turnover indicated by elevated urinary 5-HIAA can lead to depletion of the essential amino acid precursor, L-tryptophan.”
• “Since several commonly consumed foods contain appreciable concentrations of serotonin, patients should be advised to eliminate those food for at least 12 hours before gathering specimens for urinary 5-HIAA testing.”

<table>
<thead>
<tr>
<th>Food</th>
<th>Serotonin mg/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butternuts</td>
<td>398</td>
</tr>
<tr>
<td>Black Walnuts</td>
<td>304</td>
</tr>
<tr>
<td>English Walnuts</td>
<td>87</td>
</tr>
<tr>
<td>Plantain</td>
<td>30</td>
</tr>
<tr>
<td>Pecans</td>
<td>29</td>
</tr>
<tr>
<td>Pineapple</td>
<td>17</td>
</tr>
<tr>
<td>Banana</td>
<td>15</td>
</tr>
<tr>
<td>Kiwi fruit</td>
<td>5.8</td>
</tr>
<tr>
<td>Plums</td>
<td>4.7</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>3.2</td>
</tr>
<tr>
<td>Haas Avocado</td>
<td>1.6</td>
</tr>
<tr>
<td>Dates</td>
<td>1.3</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>0.9</td>
</tr>
</tbody>
</table>

• “Serotonin is required for control of gut motility as it activates smooth muscle activity.”

• “Inadequate serotonergic activity contributes to constipation. However, increased serotonin output in response to constipation is the dominant effect that has been reported.”

• “Ethanol consumption also causes lowered 5-HIAA excretion, due to serotonin metabolism interference.”
• “When 5-HIAA levels are low, increased consumption of foods high in tryptophan, including chicken, red meat, dairy products, nuts, seeds, bananas, soybeans and soy products, tuna, shellfish, and turkey can minimize the need for oral tryptophan or 5-hydroxytryptophan.”

• “Oxidation products of dopamine, epinephrine, norepinephrine, serotonin and melatonin may act as cumulative neurotoxins.”
• “The toxic effects of such products may interfere with one-carbon metabolism.”
• “Such metabolic toxicant effects add potential significance to findings of elevated VMA, HVA, and 5-HIAA, which are the oxidized products of neurotransmitters.”
“Since stress is an important part of depression, studies have measured both urinary HVA and 5-HIAA and found them to have strong positive correlation with depression.”

“Because of the prevalence of enterochromaffin cells in the transitional gut, there is considerable capacity of serotonin output in response to stress.”

“Various lines of evidence from animal studies suggest gastrointestinal microbial origins for elevated 5-HIAA.”


“Although the depressed patients in the current study showed increase in cortisol and a decrease in HVA levels, which are well documented phenomena in depressive states, the same patients exhibited an increase in 5-HIAA concentrations....”

“Therefore, it could be that increased plasma 5-HIAA levels are a compensatory phenomenon to protect the patient against stress or the effects of antidepressants.”
The kynurenine pathway

Entry of tryptophan into the kynurenine pathway is governed by tryptophan-2,3-dioxygenase that is subject to regulation by tryptophan, NADPH, kynurenine and cellular hormones. When all enzymes are properly formed and cofactor status is good, the pathway leads to either quinolinate or nicotine, depending on tissue location as shown in Figure 6.14. The critical point for vitamin B6, functional assessment is the pyridoxal-5-phosphate requiring kynurenine step. Cofactor inefficiency is the enzyme activity causes diversion of 3-hydroxymethylpyruvate to alternative pathways leading to production of nicotinamide and quinolinate. Omega-3 polyunsaturated fatty acids suppress transcription of ALA522, decreasing palmitate production.
The kynurenine/vitamin B6 connection

- “Elevated kynurenate provides biochemical confirmatory evidence of B₆ insufficiency, especially when quinolinate is not high.”

Quinolinate

- “Quinolinic acid (QUIN) provides a critical link between the immune system and the brain.”
- “Stimulation of the inflammatory response causes release of interferon-gamma (IFN-γ) by macrophages.”
- “QUIN interacts with NMDA receptors of glutamatergic neurons that respond to pain and other peripheral signals.”
Quinolinate

- “This is biochemical event is the origin of the typical pain symptoms of viral infections.”
- “If they are overstimulated, the neurons can degenerate with permanent loss of brain function known as glutamate excitotoxicity.”

Conditions related to quinolinate toxicity

- Stroke
- HIV infection
- Alzheimer’s disease
Quinolinate and toxicity

- “Toxicants can enhance sensitization of NMDA receptors, decreasing the threshold for QUIN-induced neuronal loss.”
- “Rats exposed to methyl mercury at gestational day 8 show significant increases in brain QUIN at day 21, suggesting that kynurenine pathway alterations may mediate mercury effects on brain development.”

Quinolinate and toxicity

- “The widespread exposure to phthalates in plastic products has also been shown to have potential for enhancing quinolinate production by inhibition of an alternative tryptophan pathway in rats.”
Quinolinate and vaccinations

“Vaccination with measles virus induces INF-γ stimulation of the gate keeper enzyme, indolamine-2,3-dioxygenase (IDO), for viral clearance.”


“A dysfunctional synergism with other predisposing and contributing factors may contribute to autism spectrum disorders by provoking innate and adaptive immune reactions to cause and perpetuate effects in susceptible individuals that result in inflammation, molecular mimicry, kynurenine pathway changes, increased quinoleneic acid and decreased serotonin, oxidative stress, mitochondrial dysfunction and excitotoxicity that impair development of the amygdala and other neural structures and neural networks…”

Quinolinate and sources of inflammation

- “Since the gut is frequently a source of chronic inflammatory signal induction via INF-γ, there is reason to suspect that QUIN elevation may indicate both inflammatory bowel conditions and neuronal degeneration.”
More on quinolinate and autism

• “Because modulation of glutaminergic activity affects firing patterns of dopaminergic neurons, there is potential for QUIN excursions to disrupt the primary learning system.”
• “These responses suggest that QUIN elevation following episodes such as viral infections is a metabolic event with potential for precipitating brain developmental disruption of the type seen with regressive autism.”

Quinolinate and chronic fatigue syndrome

• “Because of the tight, positive association between QUIN and IFN-γ, immune stimulation and increased QUIN production may also be a key feature in the progression of events that lead to chronic fatigue syndrome.”
Kynurenic acid, quinolinate, and multiple sclerosis

- KYNA (kynurenic acid), a biochemical precursor to QUIN, is frequently found to be simultaneously elevated by inflammatory responses.”
- “KYNA production via the kynurenin pathway is characteristically altered in relapsing-onset multiple sclerosis.”

Glucocorticoids and kynurenine

- “Early work showed that the gateway enzyme for the hepatic kynurenin pathway, tryptophan-2,3-dioxygenase, is highly inducible by corticosteroids, and urinary kynurenin excretion increases in direct proportion to activity of this enzyme in the liver.”
Glucocorticoids and kynurenine

- “Patients with diseases like rheumatoid arthritis that are characterized by chronic corticosteroid stimulation or those under hydrocortisone therapy may show patterns of elevated kynurenate with normal or low quinolinate.”

Quinolinate/kynurenine ratio

- “Because QUIN is a powerful agonist of the NMDA receptors, and KYNA antagonized this effect, the relative amounts of the two metabolites should related to the potential for neuronal degeneration.”

- “In inflammatory diseases, the ratio of QUIN/KYNA is frequently found elevated, so that neurotoxicity must be suspected.”
Quinolinate and niacin

• “A useful outcome of the conversion of tryptophan to QUIN is the ultimate production of nicotinic acid to supply its cofactor form, NAD.”
“High-protein diets induce large increases in ACMSD activity through a mechanism unrelated to increased tryptophan in the diets.”

“Thus, high-protein intake shifts the processing of tryptophan away from nicotinate production to picolinate.”

“Polyunsaturated fatty acids, on the other hand, divert flow through the kynurenin pathway from picolinate to quinolinate by inhibiting ACMSD.”
Picolinate

- “Picolinate is potent activator of inflammatory chemokines.”
- “Picolinate and QUIN are thought to act in a concerted way to regulate leukocyte recruitment and distribution into damaged tissues during inflammatory responses.”

Treatment strategies to divert tryptophan away from the kynurenine pathway
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Considerations for the Catabolic Patient

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Consider</th>
<th>Treatment Plan</th>
<th>Monitor</th>
<th>Supplementation</th>
</tr>
</thead>
</table>
| Optimize pH      | Optimize fluid and electrolyte balance | Monitoring urinary pH paper | Potassium Neutrate, 
|                  |          |                | Magnesium Citrate, 
|                  |          |                | Vitamin B6, 
| Optimize muscle mass (reduce sarcopenia) and amino acid levels | Pay special attention to protein and amino acids | Body composition | Anti-inflammatory agents, 
|                  |          |                | Inflammation blockers (e.g., ibuprofen), 
| Reducing inflammation | Reduce inflammation | Address food allergies | Pain Guard (Fenamate), 
|                  |          |                | Prednisone, 
| Improving insulin sensitivity | Watch carbohydrate/protein ratio | Fasting glucose, Fasting insulin, Cravings | Bodybuilder Synergy (D97), 
|                  |          |                | Optimal protein intake 1.0–1.3 g/kg body weight, 
| Optimize dietary carbohydrate/protein ratios | Watch carbohydrate/protein ratio | Fasting glucose, Fasting insulin, Cravings | Bodybuilder Synergy (D97), 
|                  |          |                | Optimal protein intake 1.0–1.3 g/kg body weight, 
| Optimizing GI function | Dietary changes, supplementation of digestive aids | Patient signs and symptoms | Reduce H2 and/or Pepsin, 
|                  |          |                | Digestive enzymes, 
| Optimizing micronutrient deficiencies/imbalance | Supplementation of minerals | Folate, vitamin B6, vitamin C, vitamin D, and iron | Multi-Vitamin (Vital Nutrients), 

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• “Supplementation [of tryptophan] in patients with accelerated tryptophan catabolism is, however, hampered by increased production of potentially harmful products such as quinolinic acid.”
• “Tryptophan supplementation also circumvents the antiproliferative strategy of the immune system and it is unclear whether tryptophan supplementation would up-regulate malignant cell growth in cancer patients.”
• “On the other hand, immunoresponse could be improved.”

• “An alternative strategy is to increase the tryptophan pool via supplementation with nicotinamide to suppress IDO activity.”
• “In patients with HIV infection, treatment with nicotinamide was found to increase plasma tryptophan concentration by 40% with no major side effects.”
• “As such, administration of nicotinamide might provide a valuable strategy to counteract tryptophan depletion by IFN-γ stimulated IDO in cells.”
“Any cure of the underlying disease process would also correct tryptophan concentration in the long term.”

- “It is interesting to note that the non-steroidal anti-inflammatory drug aspirin is capable of slowing tryptophan degradation at least in vitro.”
- “Extracts of *Hypericum perforatum* appear to act in similar way and are used as herbal remedy with antidepressant activity.”
- “Antioxidant compounds appear important for the observed suppressant activity.”
What about 5-HTP?

A final, “big picture” thought

"The findings of this pilot study suggest that increased tryptophan degradation may occur in women with early-stage breast cancer."


“It is argued that the coupling of peripheral tryptophan levels and cerebral serotonin levels has physiological significance.”

Thank you!!