Traditional nutritional/functional medicine viewpoint on the gut

- Somewhat isolated physiologic entity that, when functioning suboptimally, can have a systemic impact.
- Most dysfunction (which includes dysbiosis) is directly caused by environmental stressors and genetic propensity.
- Treatment generally consists of removal of environmental stressors and introducing supplements that directly address function, tissue repair, and/or microflora imbalances.
Entry Level Clinical Nutrition viewpoint of the gut

In addition to the preceding, the impact of systemic health on the gut needs to be addressed.
Quality of life issues are the major concerns more than ever now.

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'?

Su KP. Biological mechanism of antidepressant effect of omega-3 fatty acids: How does fish oil act as a 'mind-body interface'? Neurosignals, Vol. 17, pp. 144-152, 2009

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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.
Key metabolic imbalances seen with the acute phase response

- Metabolic acidosis
- Loss of lean body mass (sarcopenia)
- Insulin resistance
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Suboptimal caloric intake and carbohydrate:protein ratio (Refeeding syndrome)
- Gastrointestinal dysfunction/gut atrophy
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

Underlying hypotheses of Entry Level Clinical Nutrition:

- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.
Entry Level Clinical Nutrition:

A new model of functional medicine that incorporates allostatic load and the “chronic” acute phase response

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

Chronic inflammation, inflammaging, metainflamm.

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”
Systemic health and the gut

• “An exciting new observation is the finding that, in response to hypoglycemia, amino acids for gluconeogenesis are released from the gut not from muscle.”
• “It seemed most likely that amino acids are derived from the digestion and absorption of cells shed from the tip of the mucosal villus, although the possibility of a labile pool of amino acids within the mucosa was suggested by Dr. Soeters.”
• “It is clear that, whatever the details of the mechanism, the amino acids are derived from the mucosal rather than the smooth-muscle layer of the gut wall.”

• “The primary site of this proteolytic response is not skeletal muscle but primarily the gastrointestinal tract, resulting in an increased net release of both essential and nonessential amino acids across the extrahepatic splanchnic tissues.”

• “During this process, the majority of amino acids released by the gut are taken up by the liver, but a significant component, specifically that of branched-chain amino acids, is released into the systemic circulation and taken up by other organs, mainly skeletal muscle.”
• “Taken together with the human studies these investigations confirm that protein turnover responds to injury and infection in a manner that redistributes body protein to satisfy the body’s needs.”
• “The synthesis rate is decreased in ‘nonessential’ tissues (e.g., limb skeletal muscle or gut) and is maintained or enhanced in tissues where work is increased (respiratory and cardiac muscle, lung, liver, spleen).”
• “Data generally support the hypothesis that serious surgical illness stimulates enhanced protein turnover.”
• “We hypothesize that an important function of endocrine mediators released under conditions of acute stress may be to ensure that appropriate leukocytes are present in the right place and at the right time to respond to an immune challenge that might be initiated by the stress-inducing agent (e.g., attack by a predator, invasion by a pathogen, etc.).”

• “The modulation of immune cell distribution by acute stress may be an adaptive response designed to enhance immune vigilance and increase the capacity of the immune system to respond to challenge in immune compartments (such as the skin and epithelia of the lung, gastrointestinal and urogenital tracts), which serve as major defense barriers for the body.”
• “Thus, endocrine mediators released during stress may serve to enhance immune preparedness for potential (or ongoing) immune challenge.”

“To our surprise and in contrast to previous studies no effects of glutamine supplementation were found on plasma and mucosal concentrations, gut permeability and villus height.”

“Unchanged glutamine concentrations after supplementation in humans has been described before.”

• “In this limited population plasma and mucosal glutamine concentrations as well as gut permeability were consistently correlated with the presence and severity of inflammatory stress in contrast to standard parameters of nutritional depletion.”

• “Systemic inflammation profoundly affects (inter)organ glutamine metabolism, resulting in enhanced release by muscle and lung and increased consumption by other organs.”
• “Another attractive hypothesis is that in times of severe injury or inflammatory stress, decreases in membrane potential result in release of glutamine.”

• “Endotoxaemia and inflammatory mediators have been shown to decrease the resting membrane potential.”

• “This is the result of marked increases in intracellular sodium and chloride concentrations and a decrease in intracellular potassium.”

• “Since transport of glutamine into the cell depends on this membrane potential, this process can lead to a net efflux of glutamine out of the cell into the plasma compartment.”

• “This phenomenon can explain the sudden and unalterable decrease of intracellular glutamine seen during conditions of severe inflammatory stress.”
Therapeutics:
Protein and amino acids

Although the intestine in the prandial phase receives amino acids both from the small intestinal luminal side and via the systemic circulation, it has been observed that the intestine preferentially utilizes amino acids from the diet for its own metabolism.”

“Feeding is known to rapidly stimulate protein synthesis in the intestine as reflected by the large intestinal extraction during enteral feeding.”

Approximately 50% of dietary amino acid intake is used by the portal-drained viscera, but this percentage varies between different amino acids and diets.”

“Stimulation of overall protein anabolism by protein meals is reflected by the rapid stimulation of intestinal protein synthesis.”
“This means that the protein synthesizing capacity of the intestine depends on the same factors as whole body anabolism like the quality of the dietary protein source and the presence of carbohydrates in the protein meal.”

• “We postulated that a high-quality dietary protein source stimulates amino acids utilization in the intestine for protein synthesis.”
• “A low quality protein meal is defined as a meal containing a normal amount of macronutrients and a protein source with low digestibility or a deficient/low amount of essential (indispensable) amino acids (EAA).”
“In disease states, a meal with a low amount of functional and/or conditional EAA is also considered as low quality.”

What happens with a low quality protein meal?

• “In the present study, we examined the effects of a low quality protein meal (gelatin protein in a protein carbohydrate meal) on intestinal metabolism, and whether improving the biological value of this meal (by adding tryptophan) would affect intestinal, hepatic metabolism and systemic availability of nutrients.”
• “We observed that after intake of a low protein quality meal (Gel), the healthy intestine released into the portal vein an equivalent amount of amino acids that was given with the meal together with a substantial amount of the deficient tryptophan.”
• “We also observed a tendency that more EAAs were released to the portal system than consumed.”

“It is likely that the intestine responds to such a meal by net breakdown of endogenous (labile) gut protein.”
• “…adding the deficient amino acid tryptophan to the meal resulted in normalized intestinal net balance but not the systemic EAA and urea levels, suggesting improved intestinal metabolism without improved whole body response.”

Conclusions

• “After a low quality protein meal, the healthy gut is not able to generate an anabolic response.”
• “Our data suggest that in this situation, the intestine breaks down its own labile protein pool to fulfill the increased systemic amino acid demand.”
• “Supplementation of the deficient essential amino acid does improve intestinal metabolism, but the next limiting amino acid will determine the quality of the ingested protein for the remainder of the body.”

• “It is likely that chronic intake of low quality proteins can lead to exhaustion of the labile intestinal protein pool, possibly resulting in reduced function of the gut and susceptibility to intestinal and other disease states.”

• “These data…support the hypothesis that the total amino acid profile of a protein meal determines the biological value of the meal for the intestine and is independent of the sources of the proteins.”

• “Therefore, it is important particularly in vegetarian diets that a meal contains different protein sources to prevent that a complete meal becomes of very low quality because of one deficient EAA.”

**Animal study**

- **Protein source** – Whey protein isolate
- **Carbohydrate source** - Maltodextrin

- “Utilisation of dietary protein is affected not only by the quality of the protein, but is also dependent on the amount and type of carbohydrate present.”
- “…the results of this study indicate that the inclusion of digestible carbohydrate in the diet increases the net retention of meal-derived amino acids in the portal-drained viscera.”
"The lower liver amino-acid uptake and lower urea efflux suggest less nitrogen wastage."

"The gut appears to be an important site for nitrogen retention induced by the addition of carbohydrates to a protein meal."

"Changes in insulin levels may play an important role in the phenomenon."

• “…consensus exists that indeed after the meal there is a net accumulation of protein, whereas in the post-absorptive state a net loss of protein takes place.”

• “It has been assumed that this ‘labile protein pool’ predominantly resides in muscle, probably because of intuitive viewpoint, that muscle is a large organ and therefore is the most likely organ, in which this protein is temporarily stored and from which it is subsequently released.”

• “The logic of this feeling is weak, because the fractional synthesis rate of muscle, i.e. the percentage of the total muscle protein pool that is newly synthesized per day, is very low.”

• “As a consequence it can be calculated, that the protein accumulated during and after a meal, can only be present in muscle to a limited degree.”

• Much more likely, is the suggestion that protein accumulation takes place in the splanchnic area, as protein turnover in this area can change very rapidly and substantially, because the fractional synthesis rate is much higher than in muscle, and because changes in protein synthetic rate can occur within hours.”
TUT TUT...
'NUF SAID!
SIDDOWN...
RELAX...

Thank you!!