

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Jeffrey Moss, DDS, CNS, DACBN
jeffmoss@mossnutrition.com
413-530-0858 (cell)

1

Working hypotheses:

- What is generally referred to as low immune function is actually suboptimal adaptive immune function.
- Most supplemental approaches to optimizing immune function involve nutrients and/or herbs.
- Herbs tend to function in a pharmaceutical fashion to optimize immune function. However, the way they function leads to an important question:

2

Is the use of herbs as
“panaceas” to optimize
immune function equivalent to
“beating a dead horse?”

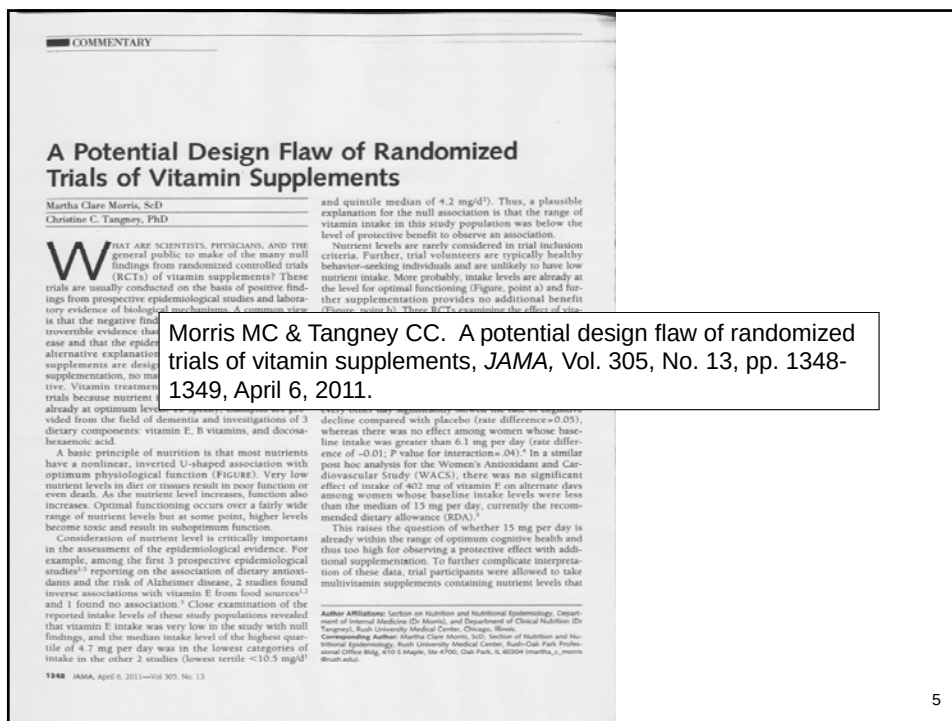
3

Nutrients as immune
enhancing panaceas

4

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss



- “A common view is that the negative findings from the randomized controlled trials (RCTs) offer inconvertible evidence that the nutrient is unrelated to disease and that the epidemiological studies are biased.”
- “An alternative explanation is that most RCTs of vitamin supplements are designed to test the hypothesis that supplementation, no matter what the nutrient status, is protective.”

“Vitamin treatment may not be effective in these trials because nutrient intake among the participants is already at optimum levels.”

7

How is “optimum level”
determined?

8

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss



312066 0290 7429 7

**Nestlé Nutrition Workshop Series
Clinical & Performance Program, Vol. 8**

**Nutrition and
Critical Care**

**Luc Cynober
Frederick A. Moore**




Baracos VE. Overview on metabolic adaptation to stress, pp. 1-13.

“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.”

9

Clinical Nutrition (2004) 23, 1256-1266



ELSEVIER

**Clinical
Nutrition**

www.elsevier.com/locate/clinu

REVIEW

Acute and “chronic” phase reaction—a mother of disease

Stig Bengmark

Department of Surgery and Liver Institute, UCL, London, UK

Received 23 July 2004

KEYWORDS

Acute phase response;
Chronic phase response;
Metabolic syndrome;
Cellular membranes;
Endothelial cells;
Abdominal obesity;
Insulin resistance;
Growth hormones;
Free fatty acids;
Alzheimer disease;
Parkinson disease;
Neurodegenerative disease;
Atherosclerosis;
Coronary-vascular disease;
Cancer;
Breast cancer;
Colorectal cancer;
Prostatic cancer;
Diabetes;
Crimson;
Fatty liver;
Gallbladder disease;
Chronic renal disease;

Summary The world is in diseases. Almost half of the mortality is due to these chronic diseases. And they are these diseases are associated consumption of calorie and also under-consumption of a function of the innate immune changes induced in response the subsequent development chronic diseases. The and importance, and the function of the underlying cells; their ability to obtain nutrients and antioxidants and to eliminate waste products. The abdominal adipocytes seem to play a key role, as they have the ability to in stressful situations release much of proinflammatory cytokines, PPAR-1 and free fatty acids compared to elsewhere in the body. The load on the liver of these various substances in often of greater magnitude than the liver can handle. Some of the most common chronic diseases and their potential association with acute and “chronic” phase responses and metabolic syndrome are discussed separately. The need for studies with lifestyle modifications is especially emphasized.

© 2004 Elsevier Ltd. All rights reserved.

Bengmark S. Acute and “chronic” phase reaction – a mother of disease, *Clin Nutr*, Vol. 23, pp. 1256-66, 2004

E-mail address: S.bengmark@ucl.ac.uk (S. Bengmark).

0261-5614/\$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.clnu.2004.07.016

10

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss

Considerations for the Catabolic Patient				
Signs & Symptoms	Consider	Treatment Plan	Monitor	Supplementation
Signs & Symptoms: - Feeling "lousy" - Fatigue - Cravings - Depression/anxiety - Poor quality sleep - Poor digestion/absorption/leaky gut - Chronic pain/infection Clinical Findings: - High % body fat - Low bone density - High fasting insulin - Heavy metal burden - Calcium to phosphorus ratio 3:1 - High normal globulin - Cholesterol (220-280) - High LDL, low HDL - High triglycerides - Low normal serum potassium, high normal serum sodium - High normal BUN with normal creatinine - Low urinary sulfate - Genomic variations	Optimize pH	Optimize fluid and electrolyte balance	Morning urinary pH -pH paper	Potassium bicarbonate -K Alkaline (Moss) Magnesium -Magnesium Glycinate (Vital Nutrients)
	Optimize muscle mass (reduce sarcopenia) and amino acid levels	Pay special attention to protein and amino acids	Body composition: -Bioelectric impedance scale Grip strength: -dynamometer	Amino acids -Custom Amino Base (Metabolic Maint.) Protein powders/bars -UltraLean products (Biogenesis) -Paleo products (DFH)
	Reducing inflammation	Reduce inflammation Address food allergies	Inflammatory biomarkers: -HS-CRP -Fibrinogen levels -WBC -Differential	Anti-inflammatory agents -Inflametric (Olympian) -D-Flame (Protocols) -Pain Guard (Perque) Fish Oils -Ultra Pure Fish oil (Vital Nutrients) Food allergy blends -AllerGzymes (DFH)
	Improving insulin sensitivity	Watch carbohydrate/protein ratio	Fasting glucose Fasting insulin Cravings	Metabolic Synergy (DFH)
	Optimize dietary carbohydrate/protein ratios	Replete protein deficiencies and reduce carbohydrate intake along with improvements in dietary quality	Diet diary Optimal protein intake -1.0 – 1.2 g/kg body weight	Protein powders/bars -Paleo products (DFH) -UltraLean (Biogenesis)
	Optimize GI function	Dietary changes, supplementation of digestive aids	Patient signs and symptoms	Betaine HCl (Vital Nutrients) Digestzymes (DFH) Intestinal Repair Complex (Biogenesis)
	Optimize micronutrient deficiencies/imbbalances	Supplementation of multis Possible emphasis on vitamin D, iodine, and zinc	Serum 25 OH vitamin D Fatigue/serum thyroid indicators Zinc taste test	Multi Nutrients (Vital Nutr) Vitamin D (Vital Nutr) Iosol (Moss) Zinc Supreme (DFH)
Presented by:  800-851-5444 mossnutrition.com Tools for True Healing™				

NEURO-SIGNALS

Invited Review

Neurosignals 2009;17:144-152
DOI: 10.1159/000188162

Received: April 26, 2009
Accepted after revision: June 4, 2009
Published online: February 4, 2009

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

Kuan-Pin Su

Department of General Psychiatry and Mind-Body Interface Laboratory (MBI-LAB), China Medical University and Hospital, Taichung, Taiwan; Stress, Psychiatry and Immunology Laboratory (SPI-Lab), Institute of Psychiatry, King's College London, London, UK

Key Words

Major depressive disorder · Depressive acid · Docosahexaenoic acid · Arachidonic acid · Prostaglandins · Thromboxanes · Lipid Phospholipase A2 · Cyclo-oxygenase

Abstract

The unsatisfactory results of monoamine-based antidepressant therapy and the high occurrence of somatic symptoms and physical illness in patients with depression imply that the serotonin hypothesis is insufficient to approach the aetiology of depression. Depressive disorders with somatic presentation are the most common form of depression. Somatization, the bodily symptoms without organic explanation, is similar to cytokine-induced sickness behaviour. Based on recent evidence, omega-3 polyunsaturated fatty acids (n-3 PUFAs, or n-3 fatty acids) are enlightening a promising path to discover the unsolved of depression, sickness behaviour and to link the connection of mind and body. The PUFAs are classified into n-3 (or omega-3) and n-6 (or omega-6) groups. Docosapentaenoic acid and docosahexaenoic acid, the major bioactive components of n-3 PUFAs, are not efficiently synthesized in humans and should therefore be obtained directly from the diet, particularly by consuming fish. Docosahexaenoic acid deficiency is associated with dysfunctions of neuronal membrane stability and transmission

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

prostaglandin E₂ synthesis, which might be linked to the somatic manifestations and physical comorbidity in depression. The role of n-3 PUFAs in immunity and mood function supports the promising hypothesis of psychoneuroimmunology of depression and provides an excellent interface between 'mind' and 'body'. This review is to provide an overview of the evidence about the role of n-3 PUFAs in depression and its common comorbid physical conditions and to propose mechanisms by which they may modulate molecular and cellular functions.

Copyright © 2009 S. Karger AG, Basel

Introduction

Major depressive disorder (MDD) is a serious psychiatric illness with a high lifetime prevalence rate [1]. However, the current treatment for this high burden disease is not satisfactory. Less than 50% of patients achieve full remission with optimized medication treatment [2] despite that more than 40 antidepressants with mechanisms related to serotonin, norepinephrine and/or dopamine

KARGER

Fax: +41 76 308 11 34

E-Mail: karger@karger.ch

www.karger.com

© 2009 S. Karger AG, Basel
1661-8747/09/17144-152\$30.00
Accessible online at:
www.karger.com

Dr. Kuan-Pin Su

Department of Psychiatry
China Medical University Hospital
No. 2, Yuh-Der Road, Taichung 40424 (Taiwan)
Tel.: +886 4 2256 2121, ext. 3076; Fax: +886 4 2256 1230; E-Mail: kalsu@cmu.edu.tw

12

Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39–90	73
Headache	27–67	33 ^e
Gastrointestinal symptoms	50 ^{c, 1}	34–47 ^f
Psychomotor slowing	40 ^c	59–65 ^f
Insomnia	20–39 ^d	63
Irritability	35 ^d	50
Arthralgia	9–36	31 ^e
Musculoskeletal pain	26–32	62–80 ^{g, 2}
Abdominal pain	15–20	21 ^e
Anorexia	13–19	40
Anxiety	13–18 ^d	57
Poor concentration	14 ^d	51

^a [46], unless otherwise specified; ^b [99], unless otherwise specified; ^c [100]; ^d [101]; ^e [102]; ^f [103]; ^g [104].

¹ Nausea, vomiting, bowel problems.

² Result from depressed inpatient population.

13

- ## 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

14

- “Certainly there is little debate that supraphysiologic supplementation is indicated for a brief period when a frank deficiency of a micronutrient is identified. As a general guideline, the provision of 5 to 10 times the RDA on a daily basis for 5-7 days, either enterally or parenterally, will suffice as a means of repletion.”

Mason JB. Vitamin and trace elements in the critically ill patient. In: Shikora SA et al, ed. *Nutritional Considerations in the Intensive Care Unit*. Dubuque, IA: Kendall/Hunt Publishing Co.; 2002:61-77.

Nutrition 26 (2010) 1070–1074
 Contents lists available at ScienceDirect
 Nutrition
 Journal homepage: www.elsevier.com/locate/nut

Applied nutritional investigation

Metabolic origin of hypovitaminosis C in acutely hospitalized patients

Rebecca Evans-Olders B.Sc.^a, Shaun Eintracht M.D.^b, L. John Hoffer M.D., Ph.D.^{a,*}

^a Lady Davis Institute for Medical Research, McGill University and Jewish General Hospital, Montreal, Quebec, Canada

^b Department of Diagnostic Medicine, Jewish General Hospital, Montreal, Quebec, Canada

ARTICLE INFO
 Article history:
 Received 3 April 2009
 Accepted 12 August 2009

Keywords:
 Acute phase response
 Ascorbic acid
 Blood
 Malnutrition
 Nutritional supplements
 Scurvy
 Vitamin C

ABSTRACT

Objective: Recent studies have indicated a high prevalence of hypovitaminosis C in acutely hospitalized patients. It is unclear whether hypovitaminosis C is due to severe response deficiency or tissue redistribution of the vitamin as part of the acute phase response.

Methods: We administered vitamin C for 1 wk to acutely hospitalized, but not critically ill patients.

Results: A significant increase in plasma C-reactive protein concentrations (P < 0.0001) was observed between plasma C-reactive protein and plasma vitamin C concentrations (P = 0.0001).

Conclusion: Although associated with systemic inflammation, the metabolic features of hypovitaminosis C in acutely hospitalized, non-critically ill patients are more consistent with deficiency than with tissue redistribution.

© 2010 Elsevier Inc. All rights reserved.

Introduction

Vitamin C deficiency, or scurvy, is a well-recognized clinical entity. It is characterized by a deficiency of ascorbic acid, which leads to a variety of clinical manifestations, including fatigue, weakness, and joint pain. In contrast, a high prevalence of hypovitaminosis C has recently been reported in acutely hospitalized patients in Brazil [1].

This work was supported by the Lady and John Hoffer Memorial Foundation, the Canadian Institutes of Health Research, and a medical student research award to R. Evans-Olders from the Faculty of Medicine, McGill University.

* Corresponding author. Tel.: +1 514 340-4200; fax: +1 514 340-7302.
 E-mail address: l.hoffer@mcgill.ca (L. Hoffer).

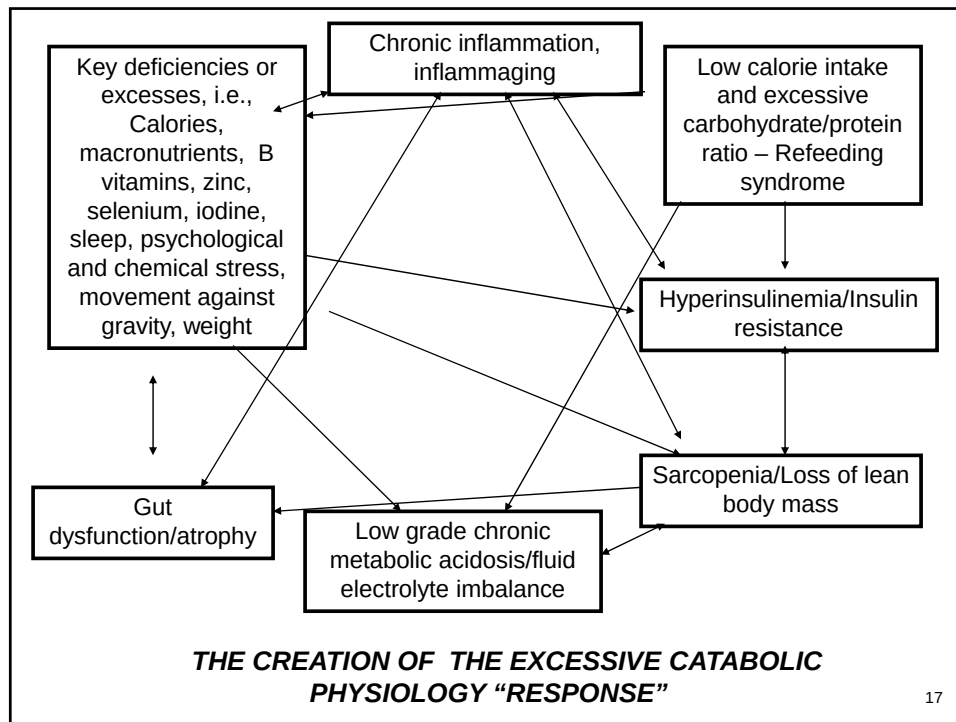
0899-9007/\$ – see front matter © 2010 Elsevier Inc. All rights reserved.
 doi:10.1016/j.nut.2009.08.015

Evans-Olders R et al. Metabolic origin of hypovitaminosis C in acutely hospitalized patients, *Nutrition*, Vol. 26, pp. 1070-1074, 2010

“Hypovitaminosis C usually implies vitamin C deficiency, but it could also occur as part of the acute phase response.”

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss



17

Effects of Stress on Immune Cell Distribution
Dynamics and Hormonal Mechanisms¹

Firdaus S. Dhabhar,^{1*} Andrew H. Miller,^{2*} Bruce S. McEwen,^{2*} and Robert L. Spencer^{2*}

¹Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10021, and the ²Department of Psychiatry, Mt. Sinai School of Medicine, New York, NY 10029

Immune cell trafficking is crucial to the performance of the surveillance as well as effector functions of the immune system. Because immune cells travel between tissues through the bloodstream, the numbers and proportions of leukocytes in the circulation provide an important representation of the state of leukocyte distribution in the body. The studies described here examine significant and selective changes in numbers and percentages of peripheral blood leukocyte subpopulations in the rat. These changes were rapidly induced under conditions of mild acute stress. Stress-induced increases in plasma corticosterone were accompanied by a significant decrease in numbers and percentages of lymphocytes, and by an increase in numbers and percentages of neutrophils. Flow cytometric analysis revealed that B cell, NK cell, and monocyte numbers showed a greater stress-induced decrease than did T cells. All stress-induced changes were observed during the light (inactive) as well as the dark (active) period of the animal's diurnal cycle. Importantly, the stress-induced changes in leukocyte numbers and percentages were rapidly reversed upon the cessation of stress. Furthermore, the effects of stress were largely dependent on adrenal hormones, because the magnitude of the stress-induced changes was significantly reduced in adrenalectomized animals. Moreover, administration of corticosterone to adrenalectomized animals resulted in a close replication of stress-induced changes observed in adrenalectomized animals. These results suggest that endocrine factors released during stress modulate leukocyte trafficking and result in the redistribution of leukocytes between the blood and other immune compartments. Such a redistribution may significantly affect the ability of the immune system to respond to potential or ongoing immune challenges. *The Journal of Immunology*, 1995, 154: 5511-5527.

The appropriate distribution of immune cells between different tissues in the body is crucial to the performance of the surveillance as well as the effector functions of the immune system. The continuous circulation of immune cells from the blood, into various immune compartments, and back into the blood, is essential for the maintenance of an effective immune defense mechanism (1). The numbers and proportions of leukocytes in the blood provide an important representation of the state of distribution of leukocytes in the body and of the state of activation of the immune system. We have established a model in which relatively mild acute stress produces rapid and selective changes in numbers and percentages of blood leukocyte subpopulations (2). The magnitude and specificity of these changes make this a very useful model for studying the kinetics, hormone dependency, and consequences of an effect regulated by the immune system in response to acute stress.

Numerous studies have investigated the effects of environmental and psychologic stress on alterations in immune parameters, and in susceptibility to disease (3, 4). However, the majority of these studies have focused on stress-induced changes in immune cell function as opposed to changes in immune cell distribution as a possible mechanism for the effects of stress on the immune system. We have previously hypothesized that an important effect of acute stress may be the regulation of immune cell distribution between different body compartments and that such a redistribution may have significant consequences for the immune response (2). Support for this hypothesis also

Dhabhar FS et al. Effects of stress on immune cell distribution, *J Immunol*, Vol. 154, pp. 5511-5527, 1995.

18

- “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.).”

19

- “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.”

20

What is the net result?

- Increased innate immunity
- Decreased adaptive immunity

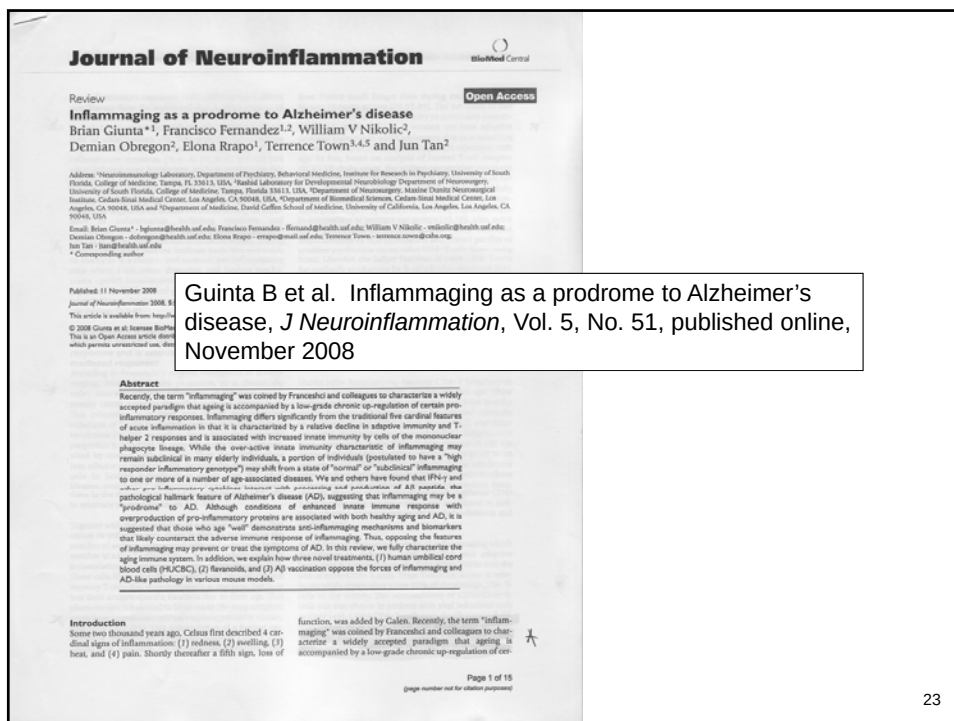
21

Inflammaging

22

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss



- **“According to Franceschi’s original description of inflammaging, innate immunity progresses to a chronically active state secondary to exhaustion of the more evolutionary recent adaptive (specific) immune system. This exhaustion is in large part due to age-associated reduction of T-cells for various reasons including thymic involution, as well as fewer bone marrow early progenitor B cells.”**
- **“The net result of this is (1) to reduce adaptive immunity to previously encountered pathogens, and (2) to weaken the host adaptive immune response to novel pathogens due to a reduction in the diversity of the antigen-recognition repertoire with age.”**

Amino acids and immune function

25

Immunonutrition: Role of Sulfur Amino Acids, Related Amino Acids, and Polyamines

ROBERT F. GRIMBLE, PHD,* AND GEORGE K. GRIMBLE, PHD†

From the *Institute of Human Nutrition, Medical and Biological Sciences Building, University of Southampton, Southampton, and †Addictive Behaviour Unit, The Roehampton Institute, London, UK

ABSTRACT

Pro-inflammatory cytokines mediate widespread changes in protein metabolism. Amino acids released from peripheral tissues fulfill a number of functions. They act as substrate for acute phase proteins and immunoglobulin synthesis and, together with polyamines, in the replication of immune cells. Demand for specific amino acids may outstrip the supply from endogenous sources. A number of strands of evidence suggest that sulphur amino acids, and amino acids that are metabolically related to them, may be required in increased amounts. Tissue deficiency impairs the acute phase response. However, sulfur amino acid insufficiency compromises glutathione synthesis, to a greater extent than hepatic protein synthesis. In the presence of increased inflammatory stimulus, the resulting effect may be compounded antioxidant deficiency. Functioning of T cells is dependent of an inflammatory stimulus. The resulting effect may be compounded antioxidant deficiency. Functioning of T cells is dependent of an inflammatory stimulus. The resulting effect may be compounded antioxidant deficiency. It has been suggested

Grimble RF & Grimble GK. Immunonutrition: Role of sulfur amino acids, related amino acids, and polyamines, *Nutrition*, Vol. 14, No. 7/8, pp. 605-610, 1998.

Key words: immune function, sulfur amino acids, polyamines

INTRODUCTION

The metabolic response to infection and injury, described previously, is mediated by a range of secondary messengers and cell signaling mechanisms, which offer broad scope for nutritional modulation.

Nutritional modulation acts at three main levels. First, by changing the composition of macromolecules of cells that respond to, and produce, pro-inflammatory cytokines. This form of modulation is exclusively due to dietary fat and has been reviewed elsewhere. Second, by changing the redox state of cells either by enhancing the production of oxidant molecules, or by altering the strength of antioxidant defenses. This form of modulation involves antioxidant components of the diet and sulphur amino acids. Third, modulation may occur by provision of substrate to support the enhanced metabolic flows and cellular synthesis that occur during the inflammatory and immune responses. This form of modulation, which involves amino acids and polyamines, is discussed.

INFLUENCE OF PROTEIN INTAKE ON THE RESPONSE TO INFECTION AND INJURY

Nutritional support, in the form of protein and individual amino acids, may alter the availability of substrate for the synthesis of proteins and peptides important in the inflammatory process and its regulation. Likewise, amino acids and polyamines may increase DNA and protein synthesis during lymphocyte replication and antibody synthesis.

The biochemical changes which occur during inflammation exert a large metabolic demand on amino acid metabolism. The loss of urinary N, which increases with the severity of the inflammatory insult, is a reflection of this phenomenon. The pro-inflammatory cytokines, interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF) are the main mediators that alter protein and amino acid metabolism to support the immune and inflammatory responses. Amino acids are released from peripheral tissues for nutrition of cells of the immune system and the synthesis of acute phase proteins and glutathione by liver.¹⁻⁴

Correspondence to: Robert F. Grimble, PhD, Institute of Human Nutrition, University of Southampton, Southampton, SO16 7PX UK.

Nutrition 14:605-610, 1998
© Elsevier Science Inc. 1998
Printed in the USA. All rights reserved.



0899-5067/98/1407-0000\$10.00
PII: S0899-5067(98)00011-2

26

- “The biochemical changes which occur during inflammation exert a large metabolic demand on amino acid metabolism.”
- “The loss of urinary N, which increases the severity of the inflammatory insult, is a reflection of this phenomenon.”
- “The pro-inflammatory cytokines, interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF) are the main initiators that alter protein and amino acid metabolism to support the immune and inflammatory responses.”
- “Amino acids are released from peripheral tissues for nutrition of cells of the immune system and the synthesis of acute phase proteins and glutathione by the liver.”

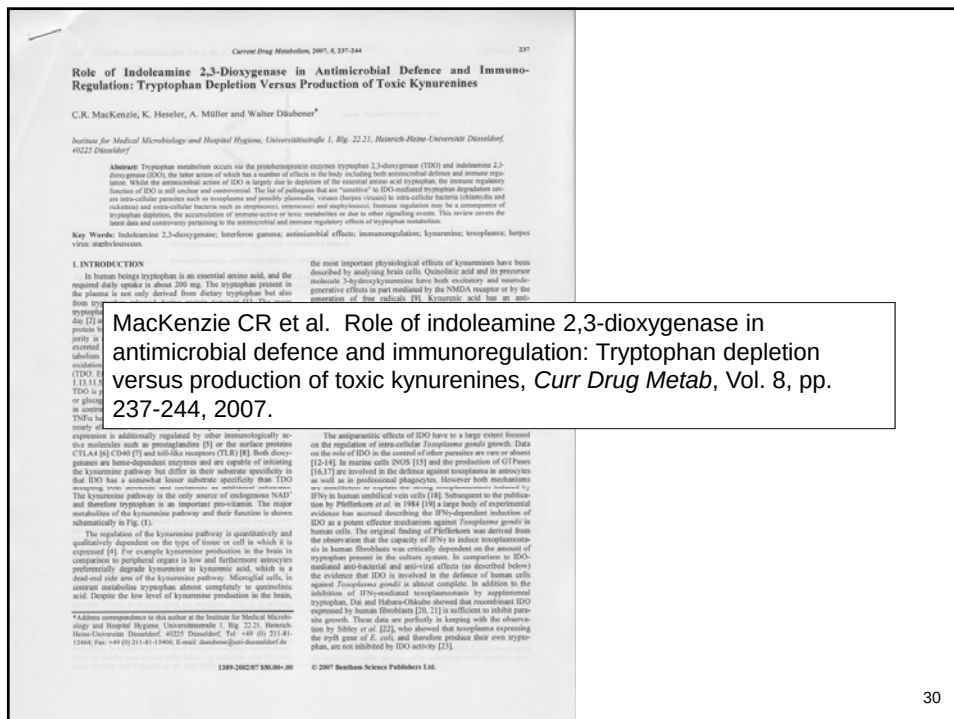
27

- “It has been estimated that during major infections in humans, the amount of protein required to produce and maintain an increase in circulating white blood cells and acute phase proteins is approximately 45 g/d.”
- “However, the supply from the peripheral tissues may not always match demands due to previous dietary intake.”

28

Tryptophan and Immune function

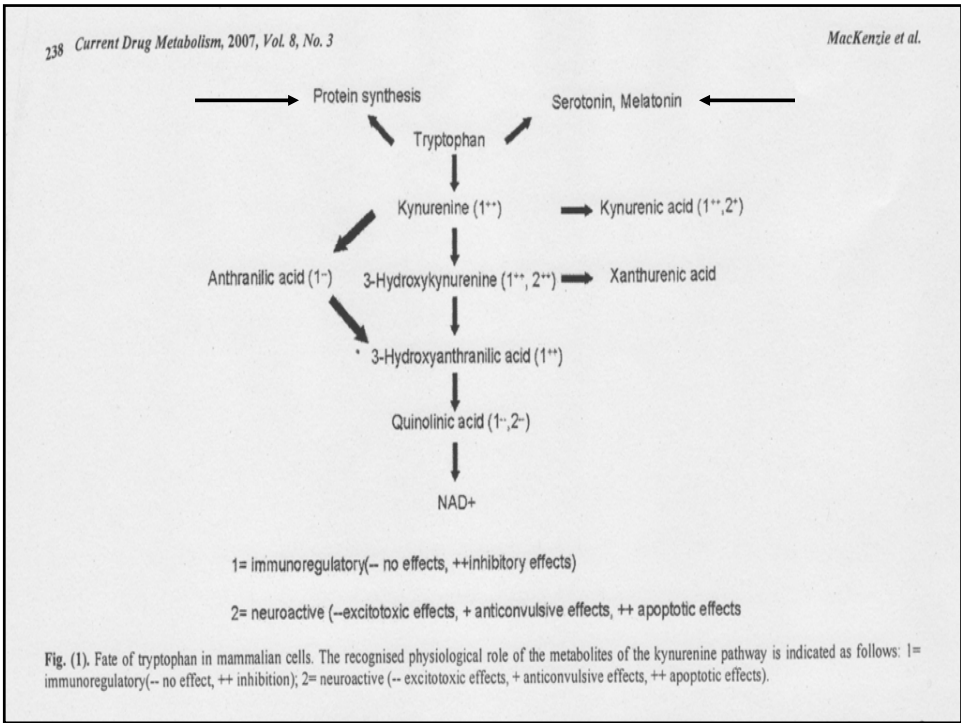
29



30

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss



Available online at www.sciencedirect.com

SCIENCE @ DIRECT[®]

Biochemical and Biophysical Research Communications 338 (2005) 12–19

BBRC

www.elsevier.com/locate/ybbr

Review

Biochemical and medical aspects of the indoleamine
2,3-dioxygenase-initiated L-tryptophan metabolism[☆]

Osamu Takikawa^{*}

^{*}National Institute for Languey Sciences, National Center for Geriatrics and Gerontology, Obu, Aichi 474-8522, Japan

Received 11 August 2005

Available online 12 September 2005

Abstract

Indoleamine
major path
abolic path
unique con
metabolism
12 By try
tryptophan
quinolonic
tophatic di
© 2005 Else

Keywords: Heme-containing dioxygenase; Tryptophan; Interferon- γ ; Immunosuppression; Dendritic cells; Quinolonic acid; Alzheimer's disease; Age-related diseases; Kynureninase; Neurotrans; Metabolism; Indoleamine dioxygenase

Although it is not easy to evaluate individual scientific achievements without bias, nobody doubts that one of the biggest breakthroughs in understanding of biological oxidation is the discovery of "Oxygenase" by Prof. Hayashi [1] and Matsuo [2] in 1922. 1 means to use uncertainty, we now know that many different varieties of living matters can transform diverse biological constituents into appropriate materials by the direct incorporation of either one or two oxygen atoms of atmospheric dioxygen into the substrates of such biological constituents. In mammals, oxygenases are involved in the synthesis of vital compounds including prostaglandins, leukotrienes, steroid hor-

mones, and nitric oxide. They also work in the synthesis of neurotransmitters (i.e., serotonin and catecholamine). In this tribute to the celebration of the discovery of oxygenases 50 years ago, I will highlight indoleamine 2,3-dioxygenase (IDO) discovered by Prof. Hayashi and his co-workers in 1967. In the last decade, the IDO-initiated tryptophan metabolism has been attracting much interest because of its great potential for understanding, treating, and preventing human diseases, as pointed out by Prof. Raymond Brown in the closing remarks in the 10th meeting of the International Study Group for Tryptophan Research (ISTRY) held at Padova in Italy in 2002 [3]. I quote his words to explain why IDO is so important in human diseases as stated below.

"In these several sessions we heard exciting new data which indicate the critical role of induced IDO activity in several important areas. The activation of dendritic cells (macrophages, astrocytes, etc.) results in IDO induction with the depletion of tryptophan levels locally

[☆] Corresponding author. E-mail address: osamu@nigms.ac.jp.
Keywords: IDO; indoleamine 2,3-dioxygenase; TDO; L-tryptophan; 2,3-dioxygenase; IDO; indoleamine; Kyn; L-kynurenine; 3HKG; 3-hydroxy-L-kynurenine; 3HKG; 3-hydroxy-L-kynurenine glucoside; AHHG; 4C2-amine; 3-hydroxyphenyl-4-methylamine; acid glucoside; XA; senhime; acid; QA; quinolonic acid; DC; dendritic cells.
Fax: +81 562 44 4440.
E-mail address: osamu@nigms.ac.jp.

0006-2952/\$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2005.09.052

32

- “These findings suggested first that the degradation of tryptophan (TRP) by IDO thus plays a role in the defense mechanism against bacterial and viral infections.”
- “...the anti-parasitic or antiviral activity of IFN- γ against various pathogens has been shown to be explained by the same mechanism, namely, the IDO-mediated TRP depletion from human cultured host cells.”

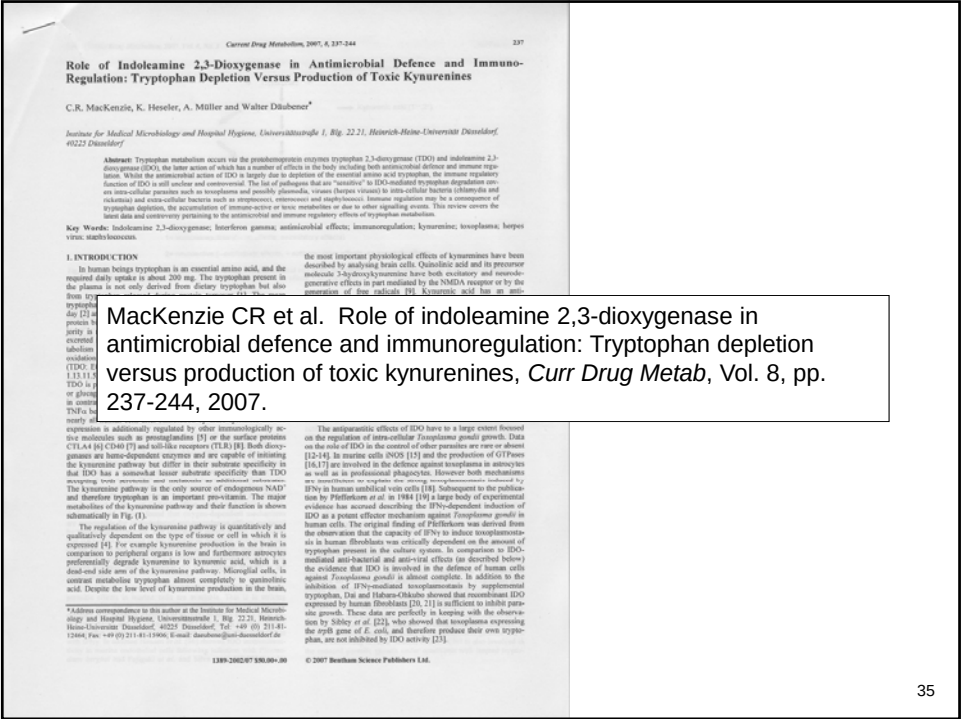
33

- “The pathogens sensitive to intracellular Trp depletion in human cells in vitro are *Chlamydia*, *psittaci*, *trachomatis*, *C. pneumoniae*, group B *Streptococci* and *Enterococci*, *Staphylococcus aureus*, herpes simplex virus, cytomegalovirus, and measles virus.”
- “These results indicate that one of the physiological functions of IDO is the suppression of various intracellular pathogens through Trp depletion.”

34

An Entry Level Clinical Nutrition Perspective on Immune Deficiency

Dr. Jeff Moss



- “The down regulation of the immune system (T-cell proliferation) by tryptophan metabolism would appear to be in direct conflict with its anti-microbial function.”
- “On the one hand this IFN γ -induced system protects against invading pathogens while on the other inhibiting the production of the same IFN γ by T-cells.”

- “We can therefore construct a theory in which the IDO-mediated tryptophan depletion in the first instance leads to an inhibition in the growth of the pathogen and then, at lower concentrations, acts as a negative feedback loop by down regulating the T-cell proliferation and hence IFN γ production.”
- “This would in effect prevent an overshoot of the immune response and thus protect the host tissue from possibly damaging tryptophan starvation.”

37

Why does this system cause problems in chronically ill patients?

Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).

38

A final thought

39

It's OK to give some herbs to
stimulate the immune system

MAKE SURE YOU'RE NOT WHIPPING
A DEAD HORSE!!

40

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

41



An Entry Level Clinical Nutrition Perspective on Immune Deficiency
Dr. Jeff Moss



Thank you!!

43