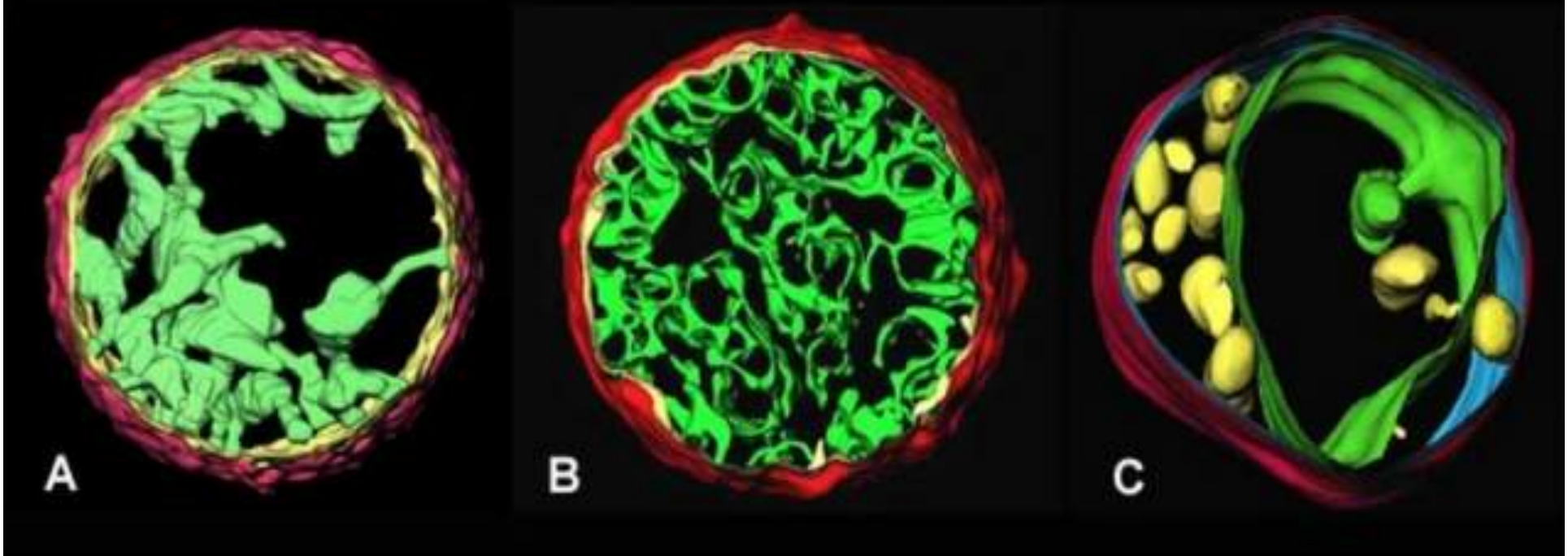
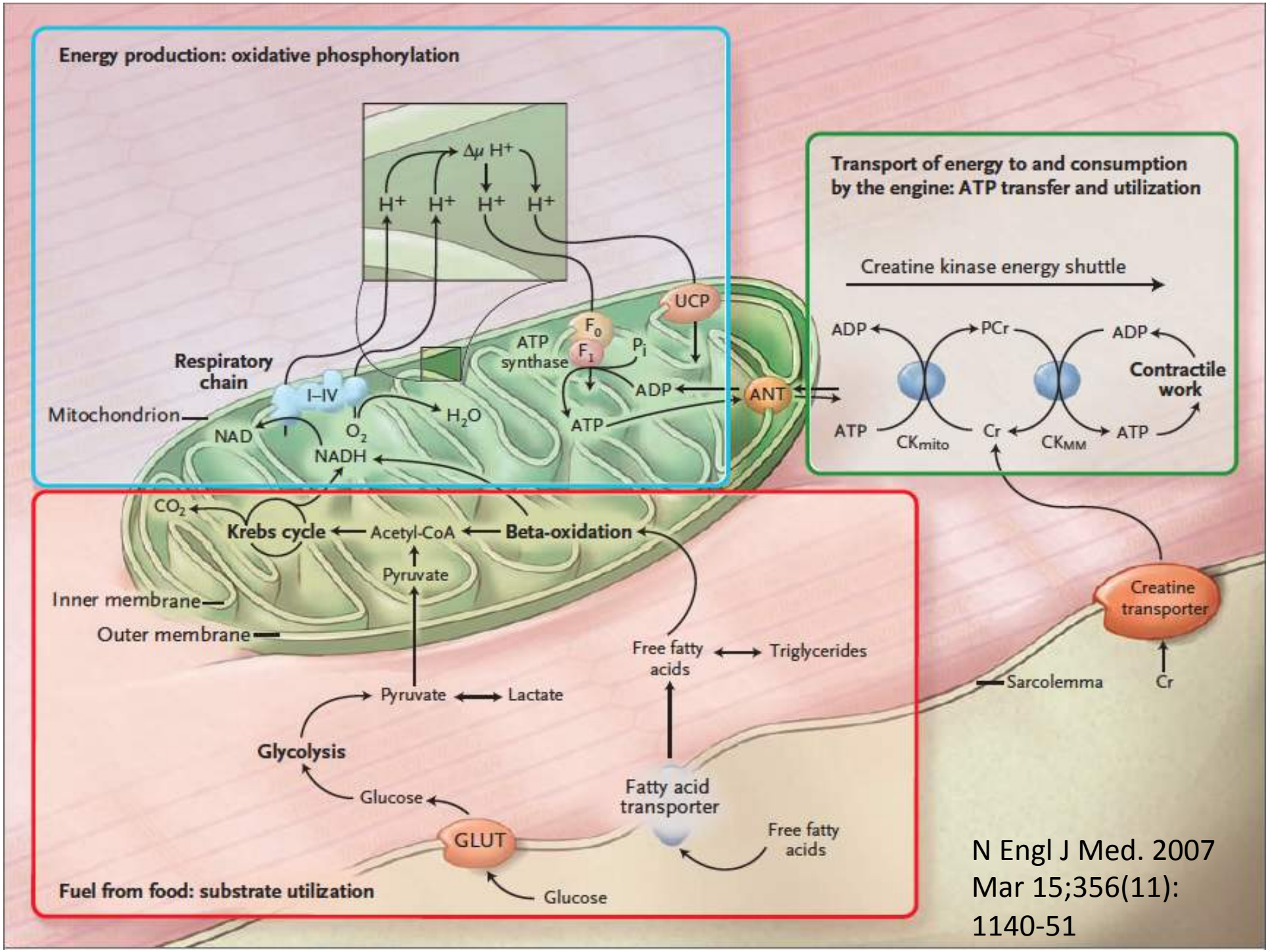
Brain Mitochondrial Metabolism and Psychiatric Illness



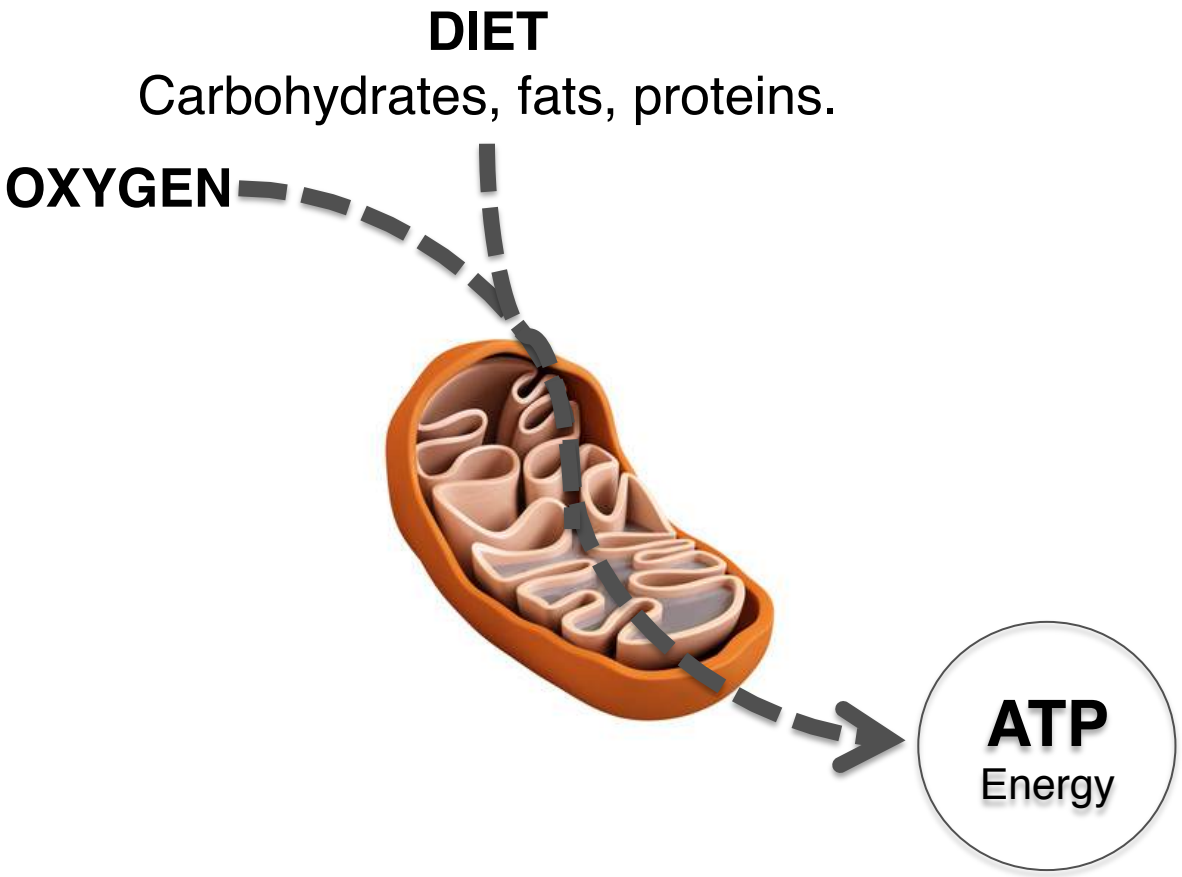
Benjamin Brown, ND

timeforwellness.org



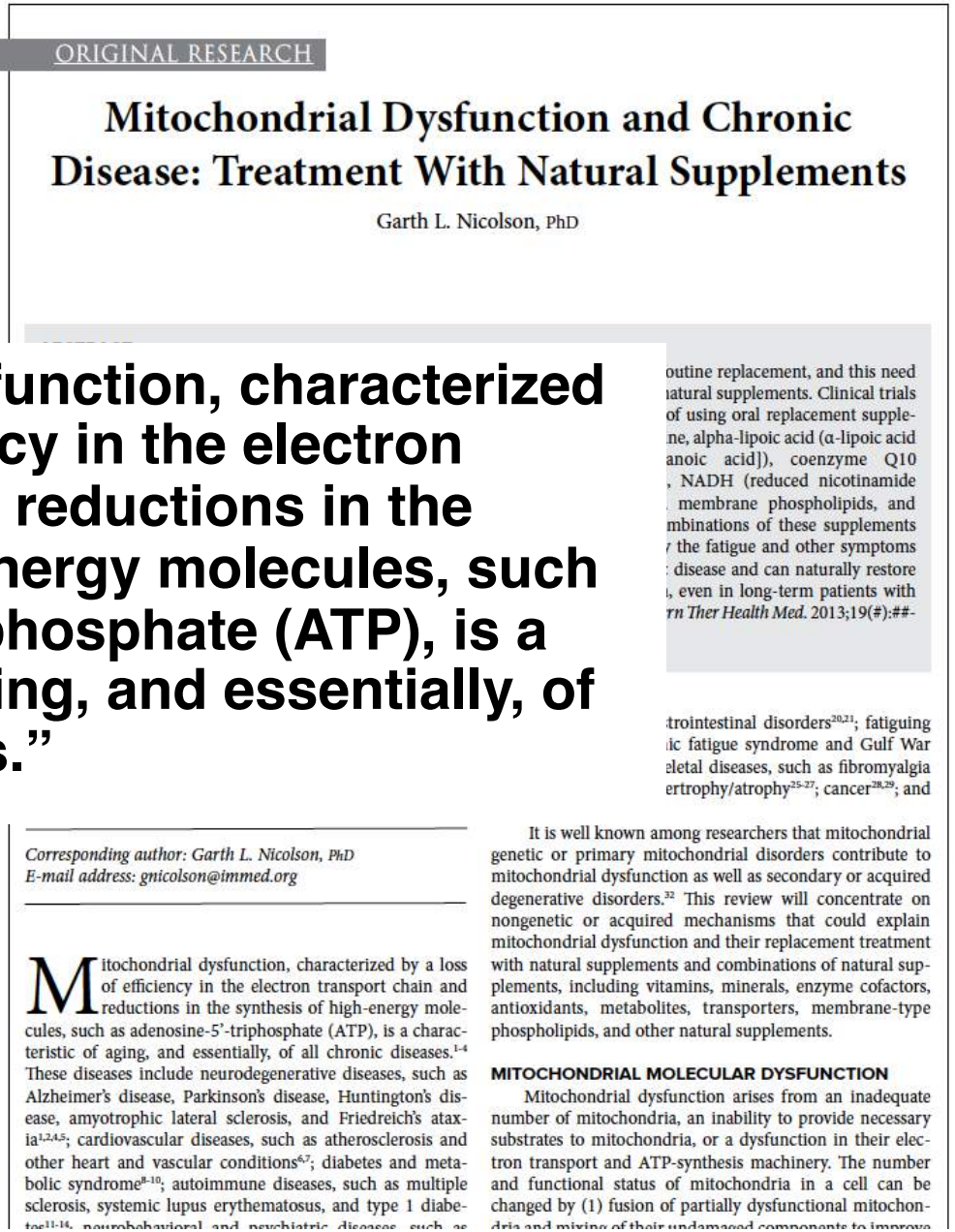
N Engl J Med. 2007 Mar 15;356(11): 1140-51

Energy Production



No more ‘Qi’

“Mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high-energy molecules, such as adenosine-5’-triphosphate (ATP), is a characteristic of aging, and essentially, of all chronic diseases.”



ORIGINAL RESEARCH

Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements

Garth L. Nicolson, PhD

outine replacement, and this need
natural supplements. Clinical trials
of using oral replacement supple-
ne, alpha-lipoic acid (α-lipoic acid
anoic acid]), coenzyme Q10
, NADH (reduced nicotinamide
membrane phospholipids, and
mbinations of these supplements
the fatigue and other symptoms
disease and can naturally restore
, even in long-term patients with
rn Ther Health Med. 2013;19(#):##-

trointestinal disorders[20,21]; fatiguing
ic fatigue syndrome and Gulf War
eletal diseases, such as fibromyalgia
ertrophy/atrophy[25-27]; cancer[28,29]; and

Corresponding author: Garth L. Nicolson, PhD
E-mail address: gnicolson@immed.org

Mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high-energy molecules, such as adenosine-5’-triphosphate (ATP), is a characteristic of aging, and essentially, of all chronic diseases.[1-4] These diseases include neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and Friedreich’s ataxia[1,2,4,5]; cardiovascular diseases, such as atherosclerosis and other heart and vascular conditions[6,7]; diabetes and metabolic syndrome[8-10]; autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes[11-14]; neurobehavioral and psychiatric diseases, such as

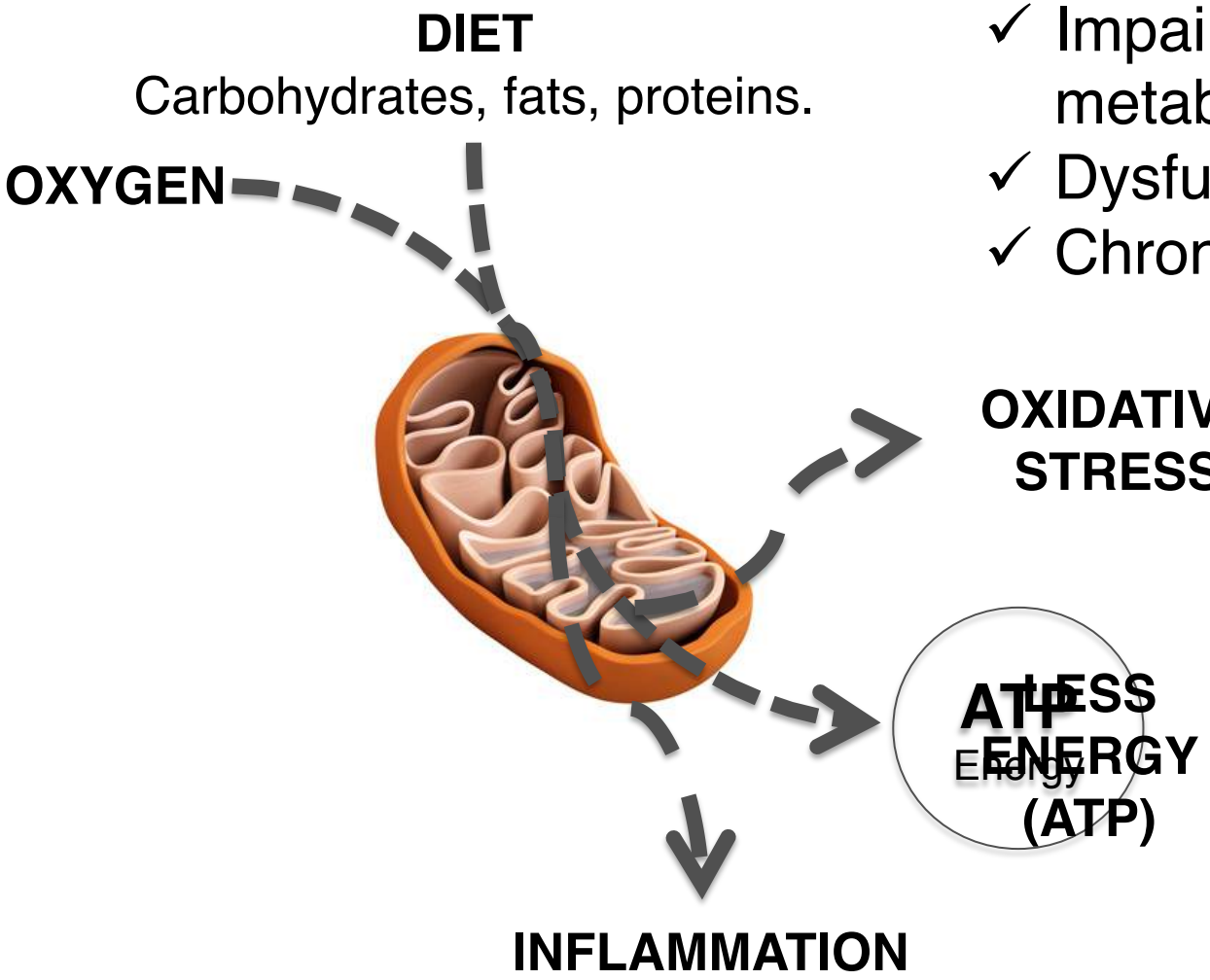
It is well known among researchers that mitochondrial genetic or primary mitochondrial disorders contribute to mitochondrial dysfunction as well as secondary or acquired degenerative disorders.[32] This review will concentrate on nongenetic or acquired mechanisms that could explain mitochondrial dysfunction and their replacement treatment with natural supplements and combinations of natural supplements, including vitamins, minerals, enzyme cofactors, antioxidants, metabolites, transporters, membrane-type phospholipids, and other natural supplements.

MITOCHONDRIAL MOLECULAR DYSFUNCTION

Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and ATP-synthesis machinery. The number and functional status of mitochondria in a cell can be changed by (1) fusion of partially dysfunctional mitochon-
dria and mixing of their undamaged components to improve

Altern Ther Health Med. 2014 Winter;20 Suppl 1:18-25.

Dysfunctional and deadly



- ✓ Impaired metabolism
- ✓ Dysfunction
- ✓ Chronic disease

Cellular burnout

"At the cellular level, moderate to severe fatigue is related to loss of mitochondrial function and diminished production of ATP.."

ORIGINAL RESEARCH

Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements

Garth L. Nicolson, PhD

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rn Ther Health Med. 2013;19(#):##-

of adenosine-5'-triphosphate (ATP). Several components ##.)

Garth L. Nicolson, PhD, is founder, president, and research professor in the Department of Molecular Pathology at The Institute for Molecular Medicine in Huntington Beach, California.

Corresponding author: Garth L. Nicolson, PhD
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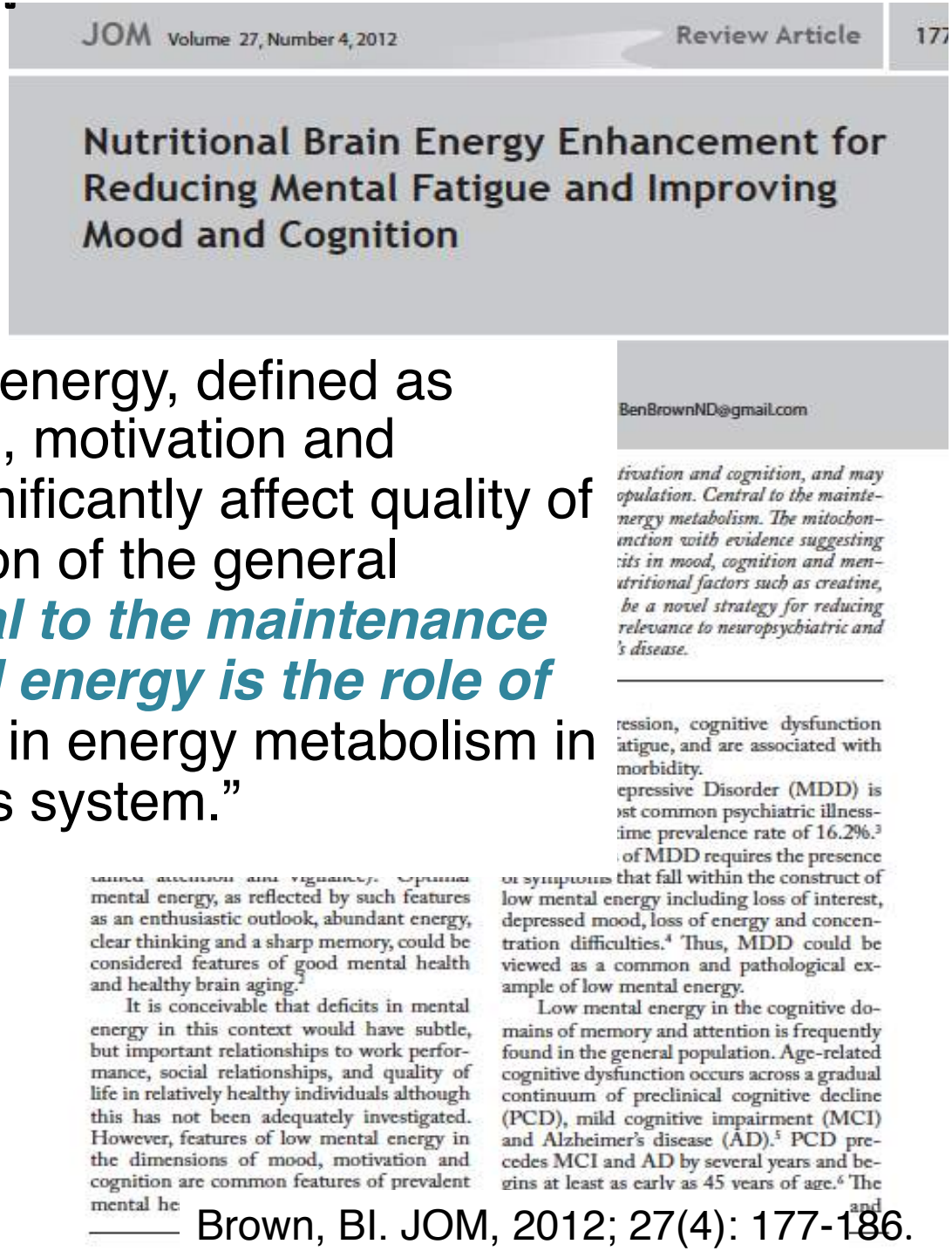
Brain burnout



JOM Volume 27, Number 4, 2012 Review Article 177

Nutritional Brain Energy Enhancement for Reducing Mental Fatigue and Improving Mood and Cognition

BenBrownND@gmail.com

tivation and cognition, and may opulation. Central to the mainte- nergy metabolism. The mitochon- nction with evidence suggesting its in mood, cognition and men- utritional factors such as creatine, be a novel strategy for reducing relevance to neuropsychiatric and 's disease.

ression, cognitive dysfunction atigue, and are associated with morbidity.
epressive Disorder (MDD) is ost common psychiatric illness- ime prevalence rate of 16.2%.[3] of MDD requires the presence of symptoms that fall within the construct of low mental energy including loss of interest, depressed mood, loss of energy and concentration difficulties.[4] Thus, MDD could be viewed as a common and pathological example of low mental energy.

Low mental energy in the cognitive domains of memory and attention is frequently found in the general population. Age-related cognitive dysfunction occurs across a gradual continuum of preclinical cognitive decline (PCD), mild cognitive impairment (MCI) and Alzheimer's disease (AD).[5] PCD precedes MCI and AD by several years and begins at least as early as 45 years of age.[6] The

mental energy, as reflected by such features as an enthusiastic outlook, abundant energy, clear thinking and a sharp memory, could be considered features of good mental health and healthy brain aging.[2]

It is conceivable that deficits in mental energy in this context would have subtle, but important relationships to work performance, social relationships, and quality of life in relatively healthy individuals although this has not been adequately investigated. However, features of low mental energy in the dimensions of mood, motivation and cognition are common features of prevalent mental he

and

Brown, BI. JOM, 2012; 27(4): 177-186.

- "Deficits in mental energy, defined as measures of mood, motivation and cognition, may significantly affect quality of life in a large portion of the general population. ***Central to the maintenance of optimal mental energy is the role of the mitochondria*** in energy metabolism in the central nervous system."

Mitochondrial psychiatry

"Brain mitochondria are essential for neurotransmission, short- and long-term neuronal plasticity, cellular resilience to stress and behavioural adaptation. ***Dysfunction in these metabolic processes contributes to a wide variety of diseases, including psychiatric disorders.***"

BJP British Journal of Pharmacology

DOI:10.1111/bph.12531
www.brjpharmacol.org

Themed Issue: Mitochondrial Pharmacology: Energy, Injury & Beyond

REVIEW

Changes in mitochondrial function are pivotal in neurodegenerative and psychiatric disorders:

DNF?

Correspondence
Professor Anthony Markham, Department of Pharmacy, Health & Well Being, Faculty of Applied Sciences, University of Sunderland, Wharncliffe Street, Sunderland SR1 3SD, UK. E-mail: tony.markham@sunderland.ac.uk

Keywords
mitochondria; BDNF; calcium; glucocorticoids; neurogenesis; plasticity; neurodegenerative diseases; psychiatric disorders

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11 November 2013

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evolved specific means of adapting function to energy supply, of inflammatory processes may not only have opposite effects on ıondrial oxidative phosphorylation and glycolytic processes, ch also have marked effects on mood. Neurodegenerative processes in areas, sometimes decades before symptoms appear (Parkinson's urotrophic factor couples activity to changes in respiratory efficiency nes, a key factor in neurodegenerative processes.

rmacology: Energy, Injury & Beyond. To view the other articles in ue-8

ild stress; ETC, electron transport chain; GRs, glucocorticoid receptors; IMM, mitochondrial inner membrane; IMS, intermembrane space; IMS, mitochondrial inner membrane space; MRs, mineralocorticoid receptors; mtPTP, mitochondrial permeability transition pore; NT, neurotrophins; OMM, outer membrane mitochondrial

Mitochondria

The brain is at the absolute limit of its energy supply

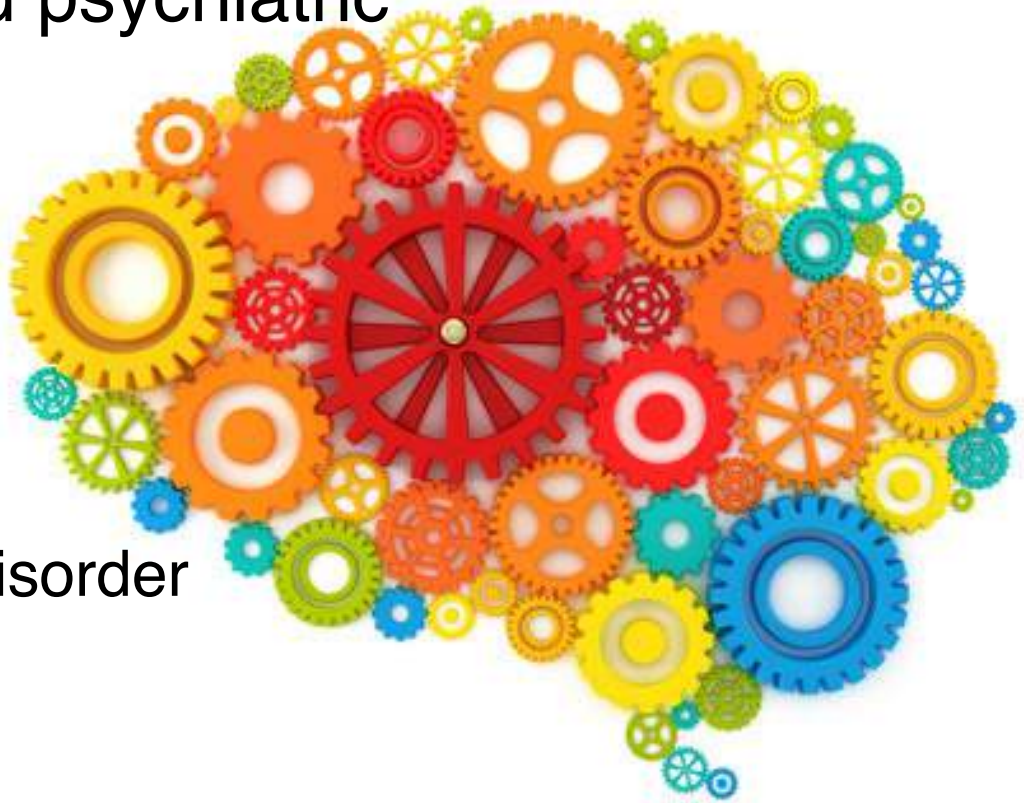
The human brain receives ~15% of cardiac output at rest and has only a few minutes autonomy. Table 1 shows some of the strategies used to optimize oxygen use. In the heart, McCormack and Denton (1990) showed that calcium coupled cardiac work to metabolism by activating the three rate-limiting Krebs cycle enzymes: pyruvate, NAD^+-isocitrate and 2-oxoglutarate dehydrogenases. Energy production is therefore tightly coupled to work requirements, without depleting ATP. This also occurs in the brain, but here the main use-dependent neurotrophin, brain-derived neurotrophic factor (BDNF), also has a role in changing mitochondrial efficiency, but these effects may be countered by inflammatory cytokines.

Mitochondrial electron transfer chain

Brain mitochondria are essential for neurotransmission, short- and long-term neuronal plasticity, cellular resilience to stress and behavioural adaptation (Mattson *et al.*, 2008). Dysfunction in these metabolic processes contributes to a wide variety of diseases, including psychiatric disorders (Table 1; Quiroz *et al.*, 2008; Cheng *et al.*, 2010a). The electron transport chain (ETC) produces energy and is organized in five protein complexes located in the mitochondrial inner membrane (IMM). Three of these complexes (I, II and III) pump protons (H^+) across the inner membrane, establishing the electrochemical gradient, which is then used by complex V

Br J Pharmacol. 2014 Apr;171(8):2206-

Mitochondrial-related neurodegenerative and psychiatric disorders:

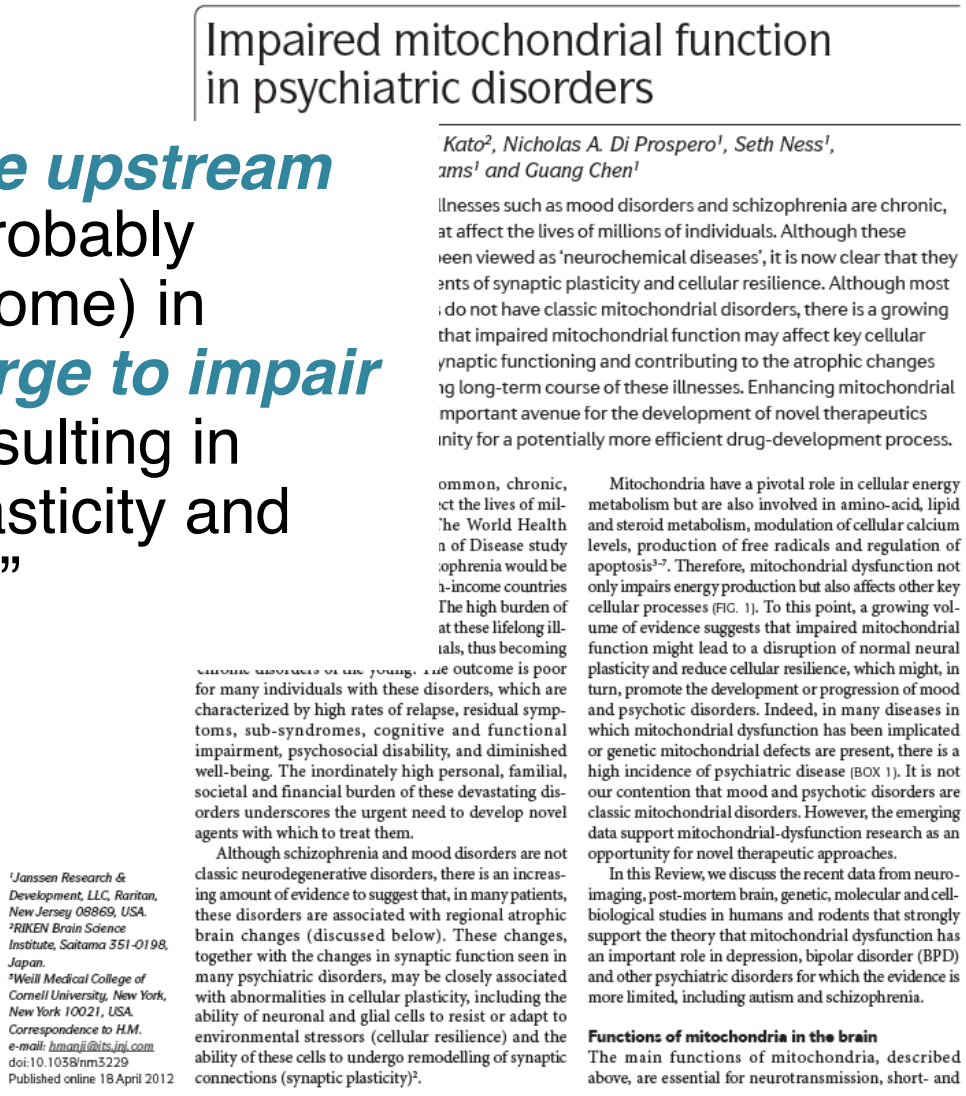


- ✓ Autism
- ✓ Depression
- ✓ Bipolar disorder
- ✓ Anxiety disorders,
- ✓ Obsessive-compulsive disorder
- ✓ Schizophrenia
- ✓ Ageing and senescence
- ✓ Alzheimer's disease

Manji H, et al. Nat Rev Neurosci. 2012 Apr 18;13(5):293-307. Markham A, et al. Br J Pharmacol. 2014 Apr;171(8):2206-29. Streck EL, et al. Rev Bras Psiquiatr. 2014 Apr-

Convergence

"…we think that ***many of the upstream abnormalities*** (which are probably encoded by the nuclear genome) in psychiatric disorders ***converge to impair mitochondrial function***, resulting in abnormalities in synaptic plasticity and long-term cellular resilience."



REVIEWS

Impaired mitochondrial function in psychiatric disorders

Kato², Nicholas A. Di Prospero¹, Seth Ness¹, ams¹ and Guang Chen¹

llnesses such as mood disorders and schizophrenia are chronic, at affect the lives of millions of individuals. Although these been viewed as 'neurochemical diseases', it is now clear that they ents of synaptic plasticity and cellular resilience. Although most do not have classic mitochondrial disorders, there is a growing that impaired mitochondrial function may affect key cellular ynaptic functioning and contributing to the atrophic changes ng long-term course of these illnesses. Enhancing mitochondrial mportant avenue for the development of novel therapeutics inity for a potentially more efficient drug-development process.

ommon, chronic, ct the lives of mil- The World Health n of Disease study ophrenia would be n-income countries The high burden of at these lifelong ill- uals, thus becoming chronic disorders of the young. The outcome is poor for many individuals with these disorders, which are characterized by high rates of relapse, residual symptoms, sub-syndromes, cognitive and functional impairment, psychosocial disability, and diminished well-being. The inordinately high personal, familial, societal and financial burden of these devastating disorders underscores the urgent need to develop novel agents with which to treat them.

Although schizophrenia and mood disorders are not classic neurodegenerative disorders, there is an increasing amount of evidence to suggest that, in many patients, these disorders are associated with regional atrophic brain changes (discussed below). These changes, together with the changes in synaptic function seen in many psychiatric disorders, may be closely associated with abnormalities in cellular plasticity, including the ability of neuronal and glial cells to resist or adapt to environmental stressors (cellular resilience) and the ability of these cells to undergo remodelling of synaptic connections (synaptic plasticity)².

Mitochondria have a pivotal role in cellular energy metabolism but are also involved in amino-acid, lipid and steroid metabolism, modulation of cellular calcium levels, production of free radicals and regulation of apoptosis³⁻⁷. Therefore, mitochondrial dysfunction not only impairs energy production but also affects other key cellular processes (FIG. 1). To this point, a growing volume of evidence suggests that impaired mitochondrial function might lead to a disruption of normal neural plasticity and reduce cellular resilience, which might, in turn, promote the development or progression of mood and psychotic disorders. Indeed, in many diseases in which mitochondrial dysfunction has been implicated or genetic mitochondrial defects are present, there is a high incidence of psychiatric disease (BOX 1). It is not our contention that mood and psychotic disorders are classic mitochondrial disorders. However, the emerging data support mitochondrial-dysfunction research as an opportunity for novel therapeutic approaches.

In this Review, we discuss the recent data from neuroimaging, post-mortem brain, genetic, molecular and cell-biological studies in humans and rodents that strongly support the theory that mitochondrial dysfunction has an important role in depression, bipolar disorder (BPD) and other psychiatric disorders for which the evidence is more limited, including autism and schizophrenia.

Functions of mitochondria in the brain

The main functions of mitochondria, described above, are essential for neurotransmission, short- and

¹Janssen Research & Development, LLC, Raritan, New Jersey 08869, USA.
²RIKEN Brain Science Institute, Saitama 351-0198, Japan.
³Weill Medical College of Cornell University, New York, New York 10021, USA.
Correspondence to H.M.
e-mail: hmanji@its.jnj.com
doi:10.1038/nrn3229
Published online 18 April 2012

Nat Rev Neurosci. 2012 Apr 18;13(5):293-3

Opportunity

"…***the ability to modulate mitochondrial function may have an important role*** in regulating synaptic strength and cellular resilience in neuronal circuits that mediate complex, high-order brain functions such as cognition, affect, perception and behaviour."

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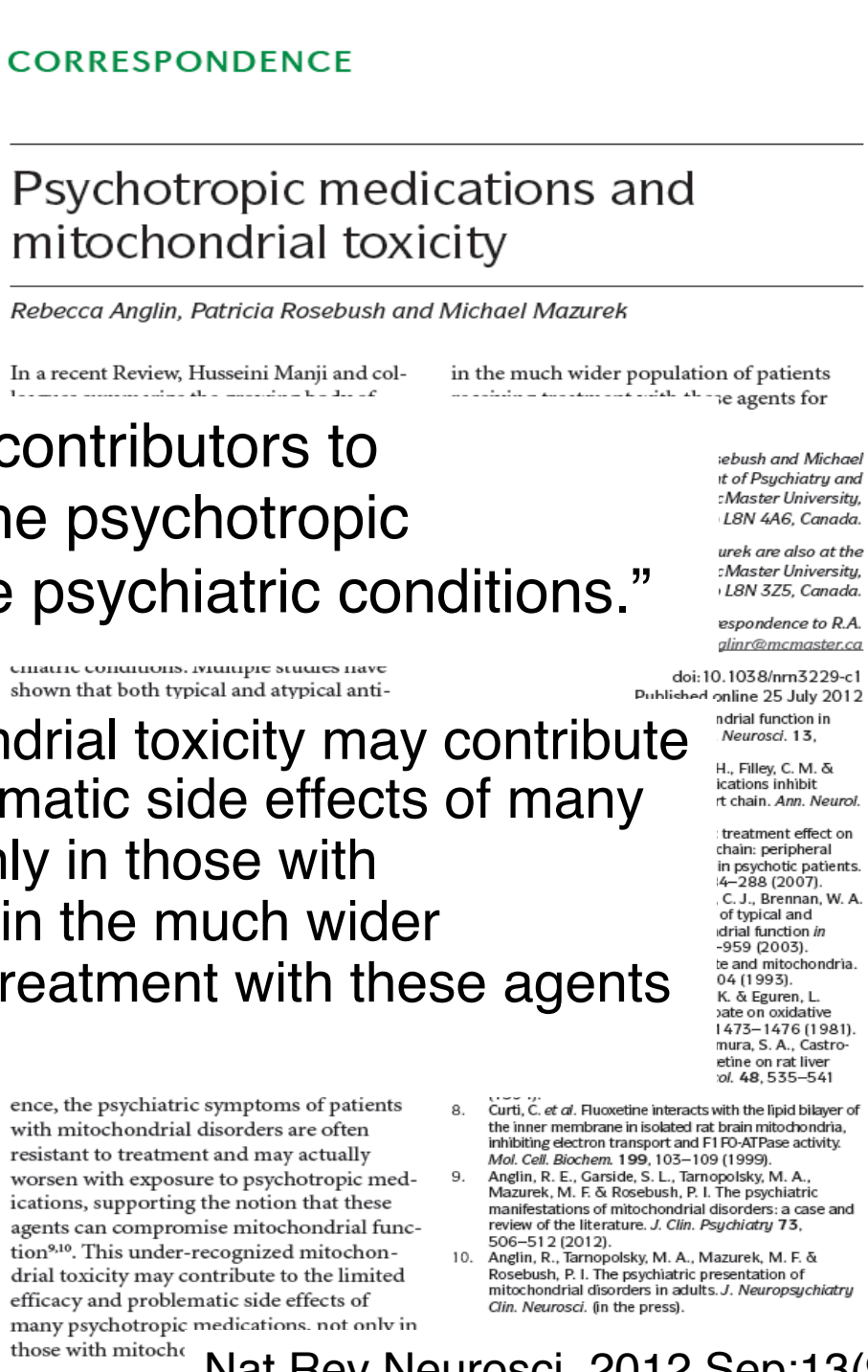
NATURE REVIE Nat Rev Neurosci. 2012 Apr 18;13(5):293-3

Missed opportunity

“One of the often-overlooked contributors to mitochondrial dysfunction is the psychotropic medication used to treat these psychiatric conditions.”

“This under-recognized mitochondrial toxicity may contribute to the limited efficacy and problematic side effects of many psychotropic medications, not only in those with mitochondrial disorders but also in the much wider population of patients receiving treatment with these agents for psychiatric illness.”



CORRESPONDENCE

Psychotropic medications and mitochondrial toxicity

Rebecca Anglin, Patricia Rosebush and Michael Mazurek

In a recent Review, Husseini Manji and col-

in the much wider population of patients

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Master University,
L8N 4A6, Canada.

urek are also at the
Master University,
L8N 3Z5, Canada.

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glinr@mcmaster.ca

doi:10.1038/nrn3229-c1
Published online 25 July 2012

shown that both typical and atypical anti-

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Neurosci. **13**,

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mura, S. A., Castro-
etine on rat liver
ol. **48**, 535–541

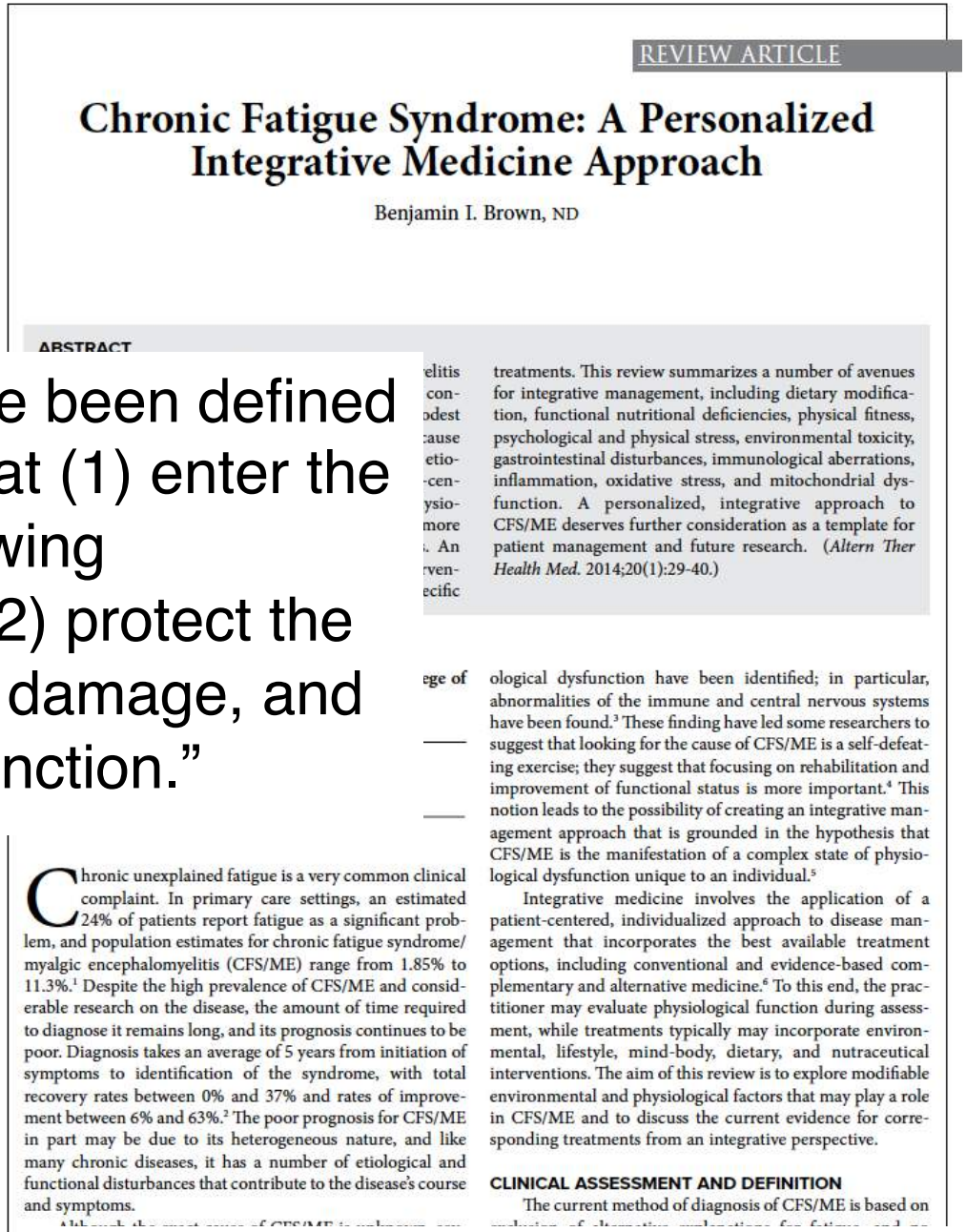
ence, the psychiatric symptoms of patients with mitochondrial disorders are often resistant to treatment and may actually worsen with exposure to psychotropic medications, supporting the notion that these agents can compromise mitochondrial function[9,10]. This under-recognized mitochondrial toxicity may contribute to the limited efficacy and problematic side effects of many psychotropic medications, not only in those with mitoch

8. Curti, C. *et al.* Fluoxetine interacts with the lipid bilayer of the inner membrane in isolated rat brain mitochondria, inhibiting electron transport and F1 FO-ATPase activity. *Mol. Cell. Biochem.* **199**, 103–109 (1999).
9. Anglin, R. E., Garside, S. L., Tarnopolsky, M. A., Mazurek, M. F. & Rosebush, P. I. The psychiatric manifestations of mitochondrial disorders: a case and review of the literature. *J. Clin. Psychiatry* **73**, 506–512 (2012).
10. Anglin, R., Tarnopolsky, M. A., Mazurek, M. F. & Rosebush, P. I. The psychiatric presentation of mitochondrial disorders in adults. *J. Neuropsychiatry Clin. Neurosci.* (in the press).

Nat Rev Neurosci. 2012 Sep;13(9):6

Energy restoration

"Mitochondrial nutrients have been defined as nutritional compounds that (1) enter the cells and mitochondria following exogenous administration, (2) protect the mitochondria from oxidative damage, and (3) improve mitochondrial function."



REVIEW ARTICLE

Chronic Fatigue Syndrome: A Personalized Integrative Medicine Approach

Benjamin I. Brown, ND

ABSTRACT

treatments. This review summarizes a number of avenues for integrative management, including dietary modification, functional nutritional deficiencies, physical fitness, psychological and physical stress, environmental toxicity, gastrointestinal disturbances, immunological aberrations, inflammation, oxidative stress, and mitochondrial dysfunction. A personalized, integrative approach to CFS/ME deserves further consideration as a template for patient management and future research. (*Altern Ther Health Med.* 2014;20(1):29-40.)

Chronic unexplained fatigue is a very common clinical complaint. In primary care settings, an estimated 24% of patients report fatigue as a significant problem, and population estimates for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) range from 1.85% to 11.3%.[1] Despite the high prevalence of CFS/ME and considerable research on the disease, the amount of time required to diagnose it remains long, and its prognosis continues to be poor. Diagnosis takes an average of 5 years from initiation of symptoms to identification of the syndrome, with total recovery rates between 0% and 37% and rates of improvement between 6% and 63%.[2] The poor prognosis for CFS/ME in part may be due to its heterogeneous nature, and like many chronic diseases, it has a number of etiological and functional disturbances that contribute to the disease's course and symptoms.

ological dysfunction have been identified; in particular, abnormalities of the immune and central nervous systems have been found.[3] These finding have led some researchers to suggest that looking for the cause of CFS/ME is a self-defeating exercise; they suggest that focusing on rehabilitation and improvement of functional status is more important.[4] This notion leads to the possibility of creating an integrative management approach that is grounded in the hypothesis that CFS/ME is the manifestation of a complex state of physiological dysfunction unique to an individual.[5]

Integrative medicine involves the application of a patient-centered, individualized approach to disease management that incorporates the best available treatment options, including conventional and evidence-based complementary and alternative medicine.[6] To this end, the practitioner may evaluate physiological function during assessment, while treatments typically may incorporate environmental, lifestyle, mind-body, dietary, and nutraceutical interventions. The aim of this review is to explore modifiable environmental and physiological factors that may play a role in CFS/ME and to discuss the current evidence for corresponding treatments from an integrative perspective.

CLINICAL ASSESSMENT AND DEFINITION

The current method of diagnosis of CFS/ME is based on

Altern Ther Health Med. 2014 Jan-Feb;20(1):29-40.

Whole-of-diet

Public Health Nutrition: page 1 of 20 doi:10.1017/S1368980014002614

Review Article

The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials

Rachelle S Opie[1,*], Adrienne O'Neil[2,3], Catherine Itsiopoulos[1] and Felice N Jacka[2,4]
[1]Department of Dietetics and Human Nutrition, Faculty of Health Sciences, La Trobe University, Melbourne, VIC 3086, Australia: [2]IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Victoria, Australia: [3]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia: [4]Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia

"***Non-pharmacological approaches to the treatment of depression and anxiety are of increasing importance***, with emerging evidence supporting a role for lifestyle factors in the development of these disorders. ***Observational evidence supports a relationship between habitual diet quality and depression***."

Keywords
Diet
Diet intervention
Depression
Mental health

…erged to support
…ality and the risk
…s have suggested

economic burden they impose. Major depressive disorders and anxiety disorders are among the leading causes of years lived with disability[1]; in 2010, the global cost of these conditions was estimated to be $US 2·5 trillion[2]. Although pharmacotherapy and psychotherapy are considered first-line treatments for depression, fewer than half

that a healthy dietary pattern including fruits, vegetables, fish, olive oil, nuts and legumes is protective against depression[4,5]. Conversely, a dietary pattern that comprises a high consumption of processed foods and sugary products may increase the risk of depression[4,6]. While the observational evidence generated to date is suggestive

Public Health Nutr. 2014 Dec 3:1-20. [Epub ahead of print].

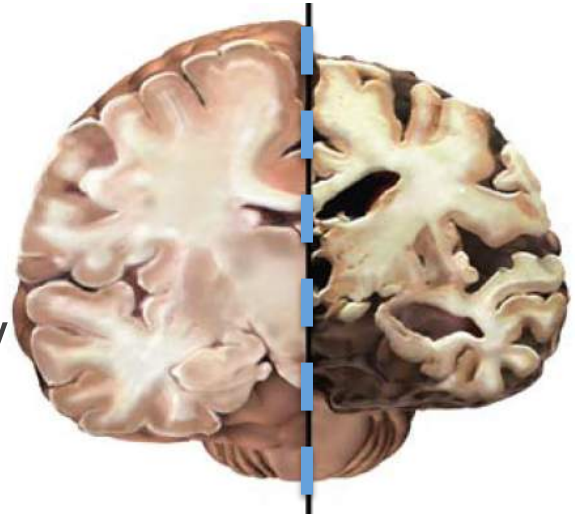
Brain Food: Diet and Mental Health

Natural Diet:
Phytonutrient Dense, Caloric Shortage

- Neuroprotection
- Neurogenesis
- Synaptic Plasticity

Cognition/ Mood/ Behavior:

- Optimism
- Cognitive Resilience
- Enthusiasm
- Vigor and Energy



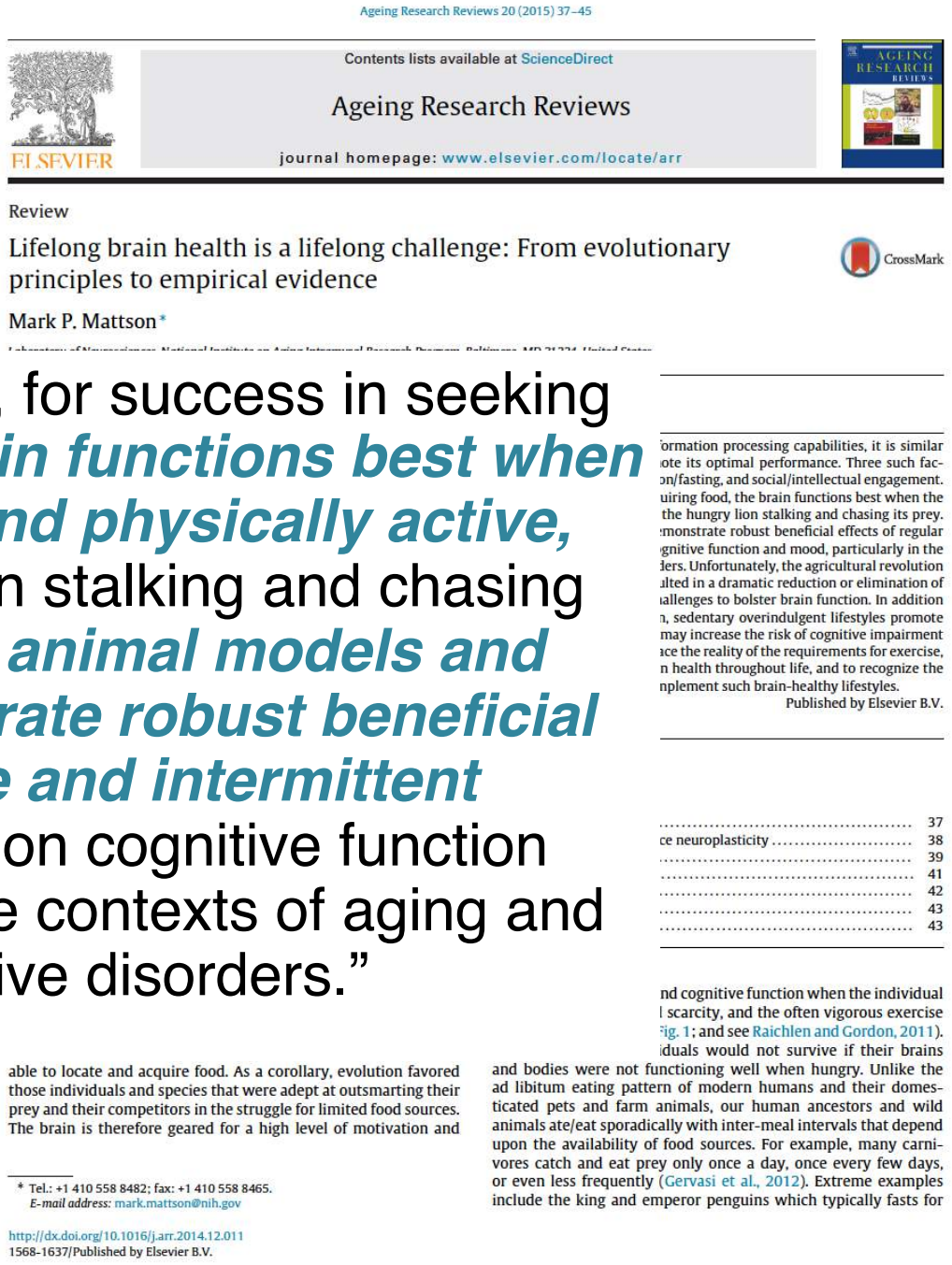
Modern Diet:
Phytonutrient Poor, Caloric Excess

- Cell Damage
- Cell Death
- Impaired Plasticity

Cognition/ Mood/ Behavior:

- Depression
- Cognitive Decline
- Hostility
- Fatigue and Malaise

Challenge



Ageing Research Reviews 20 (2015) 37–45

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/arr

Review

Lifelong brain health is a lifelong challenge: From evolutionary principles to empirical evidence

Mark P. Mattson*

ormation processing capabilities, it is similar
ote its optimal performance. Three such fac-
on/fasting, and social/intellectual engagement.
uiring food, the brain functions best when the
the hungry lion stalking and chasing its prey.
monstrate robust beneficial effects of regular
gnitive function and mood, particularly in the
lers. Unfortunately, the agricultural revolution
alted in a dramatic reduction or elimination of
allenges to bolster brain function. In addition
n, sedentary overindulgent lifestyles promote
may increase the risk of cognitive impairment
ace the reality of the requirements for exercise,
n health throughout life, and to recognize the
nplement such brain-healthy lifestyles.

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37
ce neuroplasticity 38
..... 39
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..... 43

able to locate and acquire food. As a corollary, evolution favored those individuals and species that were adept at outsmarting their prey and their competitors in the struggle for limited food sources. The brain is therefore geared for a high level of motivation and

nd cognitive function when the individual
l scarcity, and the often vigorous exercise
ig. 1; and see Raichlen and Gordon, 2011).
iduals would not survive if their brains and bodies were not functioning well when hungry. Unlike the ad libitum eating pattern of modern humans and their domesticated pets and farm animals, our human ancestors and wild animals ate/eat sporadically with inter-meal intervals that depend upon the availability of food sources. For example, many carnivores catch and eat prey only once a day, once every few days, or even less frequently (Gervasi et al., 2012). Extreme examples include the king and emperor penguins which typically fasts for

* Tel.: +1 410 558 8482; fax: +1 410 558 8465.
E-mail address: mark.mattson@nih.gov

http://dx.doi.org/10.1016/j.arr.2014.12.011
1568-1637/Published by Elsevier B.V.

"Because it evolved, in part, for success in seeking and acquiring food, ***the brain functions best when the individual is hungry and physically active,*** as typified by the hungry lion stalking and chasing its prey. Indeed, ***studies of animal models and human subjects demonstrate robust beneficial effects of regular exercise and intermittent energy restriction/fasting*** on cognitive function and mood, particularly in the contexts of aging and associated neurodegenerative disorders."

Ageing Res Rev. 2015 Mar;20C:37-45.

Less is more

"…we used nuclear magnetic resonance spectroscopy. to show that during aging ***caloric restriction (CR) preserves mitochondrial energy production, energy demand, and neuronal activity*** with a long-lived rodent model. These results provide a rationale for CR-induced sustenance of brain health with extended lifespan."

Journal of Cerebral Blood Flow & Metabolism (2014) 34, 1440–1443

www.jcbfm.com

BRIEF COMMUNICATION

Caloric restriction impedes age-related decline of mitochondrial function and neuronal activity

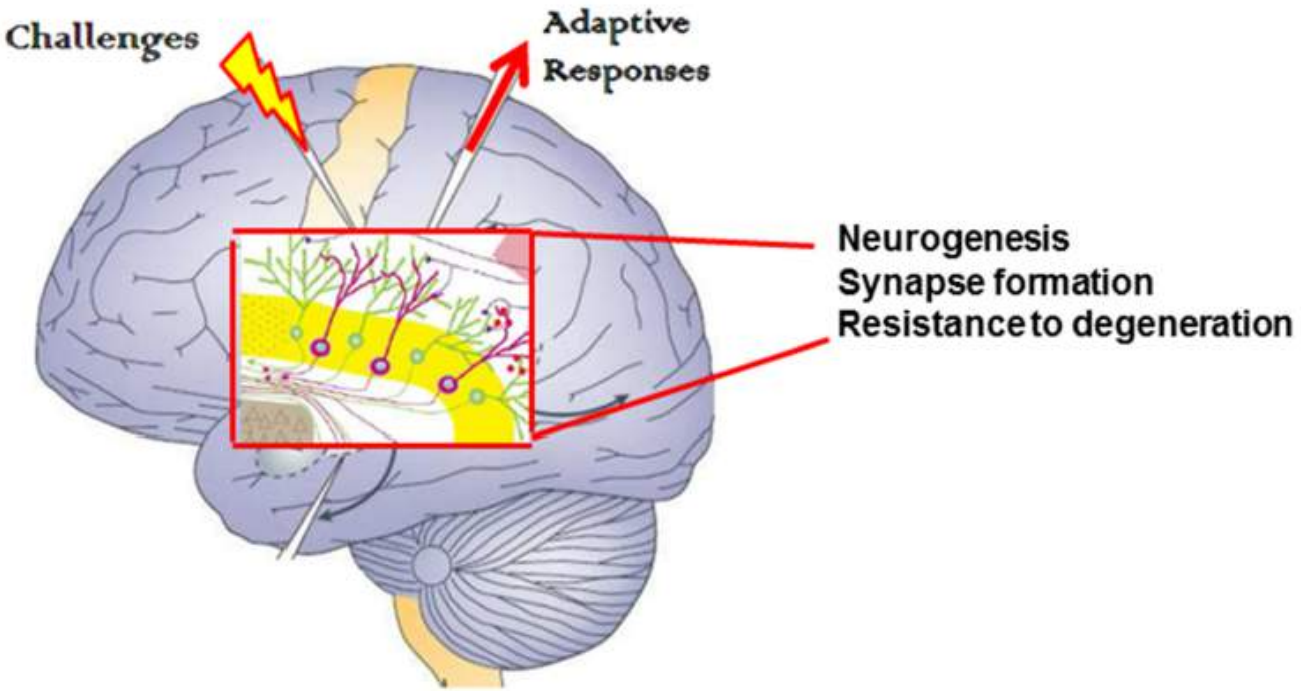
Ai-Ling Lin[1,2], Daniel Coman[3,4,5], Lihong Jiang[3,4,5], Douglas L Rothman[3,4,5,6] and Fahmeed Hyder[3,4,5,6]

Caloric restriction (CR) prolongs lifespan and retards many detrimental effects of aging, but its effect on brain mitochondrial function and neuronal activity—especially in healthy aging—remains unexplored. Here we measured rates of neuronal glucose oxidation and glutamate–glutamine neurotransmitter cycling in young control, old control (i.e., healthy aging), and old CR rats

.114; published online 2 July 2014

[1]Sanders-Brown Center on Aging, University of Kentucky, Lexington, Kentucky, USA; [2]Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, Kentucky, USA; [3]Magnetic Resonance Research Center, Yale University, New Haven, Connecticut, USA; [4]Quantitative Neuroscience with Magnetic Resonance Core Center, Yale University, New Haven, Connecticut, USA; [5]Department of Diagnostic Radiology, Yale University, New Haven, Connecticut, USA and [6]Department of Biomedical Engineering, Yale University, New Haven, Connecticut, USA. Correspondence: Dr A-L Lin, Sanders-Brown Center on Aging, University of Kentucky, 800S. Limestone, Lexington, KY 40536, USA or Dr F Hyder, N135 TAC (MRRC), Yale University, 300 Cedar Street, New Haven, CT 06519, USA.
E-mail: ailing.lin@uky.edu or fahmeed.hyder@yale.edu
This research was supported by NIH grants K01AG040164 (to ALL), P30 NS-052519 (to FH), R01 MH-067528 (to FH), R01 AG 034953 (to DLR), and American Federation for Aging Research grant #A12474 (to ALL).
Received 13 February 2014; revised 8 May 2014; accepted 5 June 2014; published online 2 July 2014

J Cereb Blood Flow Metab. 2014 Sep;34(9):



Energy Restriction
Fasting

↓

Mild Cellular Stress
(Energy, Calcium, ROS)
TF activation

↓

ADAPTIVE
RESPONSES

↓

Chaperones
UCPs
Mn-SOD
Trophic factors
APE1
PGC-1α

↓

Reduced Oxidative Stress
Improved Cellular Energy Metaboli
Reduced Inflammation
Reduced DNA Damage

↓

Resistance to Disease

Mattson MP. Challenging oneself intermittently to improve health. Dose Response. 2014 Oct 20;12(4):600-18.

Neurohormesis

ANTIOXIDANTS & REDOX SIGNALING
Volume 13, Number 11, 2010
© Mary Ann Liebert, Inc.
DOI: 10.1089/ars.2009.3074

COMPREHENSIVE INVITED REVIEW

Cellular Stress Responses, The Hormesis Paradigm, and Vitagenes: Novel Targets for Therapeutic Intervention in Neurodegenerative Disorders

Vittorio Calabrese,[1] Carolin Cornelius,[1] Albena T. Dinkova-Kostova,[2,3]

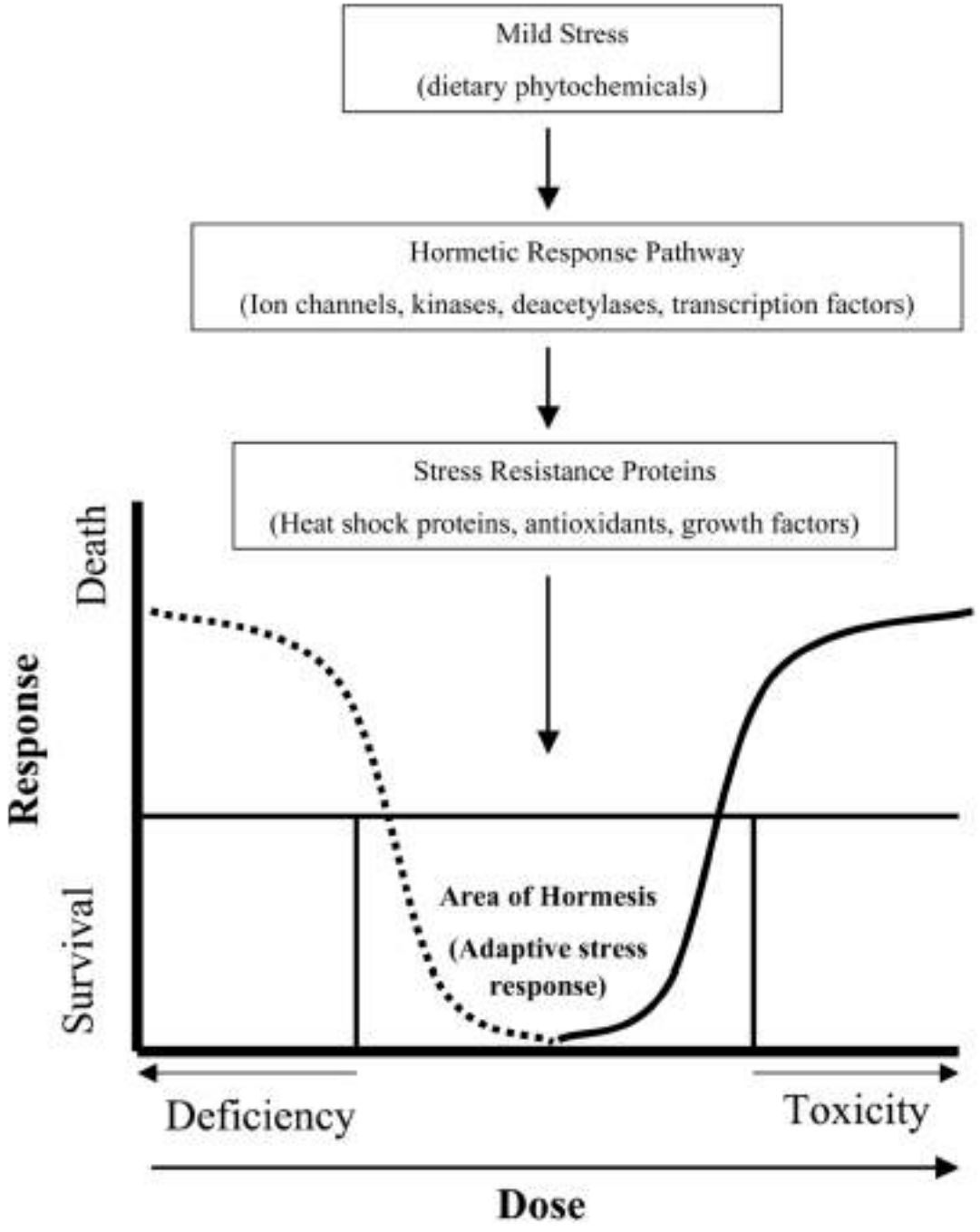
"From an evolutionary perspective, the noxious properties of such phytochemicals play an important role in dissuading insects and other pests from eating the plants. However, ***at the relatively small doses ingested by humans*** who consume the plants, ***the phytochemicals are not toxic and instead induce mild cellular stress responses.***"

rium, cells appear
eurodegenerative
pproach to thera-
This article intro-
that the hormetic
ramework for ex-
istic foundations,
for improving the
man population.
dogenous cellular
s responses in the
itric oxide, carbon
hip to membrane

Reviewing Editors: Narayen Bhat, Jin-Song Bian, Susan Browne, Enrique Cadenas, Paola Chiarugi, Jeffrey Keller, Daniel Linseman, Pamela Maher, Mark Smith, Russell Swerdlow, and Bobby Thomas

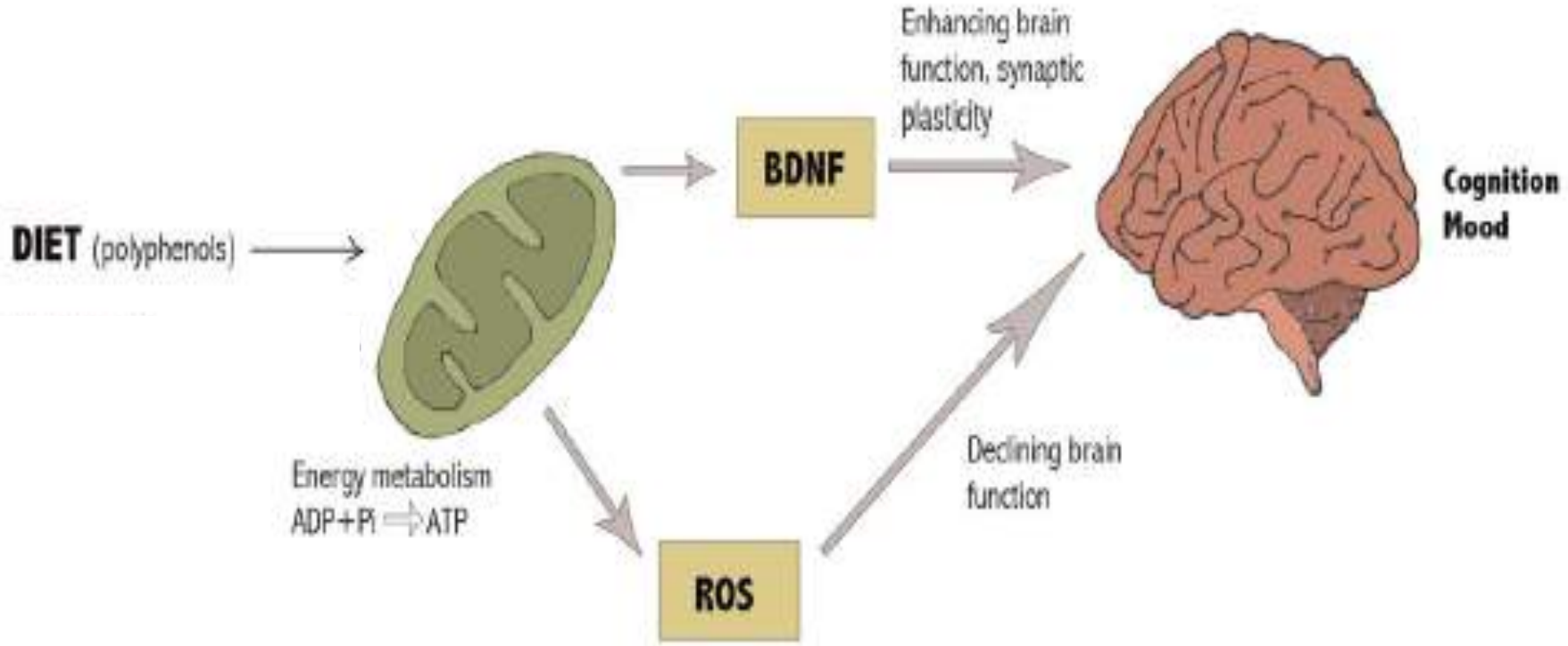
[1]Department of Chemistry, University of Catania, Catania, Italy.
[2]The Biomedical Research Institute, University of Dundee, Scotland, United Kingdom.
[3]Division of Clinical Pharmacology, Departments of Medicine and Pharmacology and Molecular Sciences, Johns Hopkins University School of Med
[4]Environme
[5]National I

Antioxid Redox Signal. 2010 Dec 1;13(11): 1763-811



Neuromolecular Med. 2008;10(4):

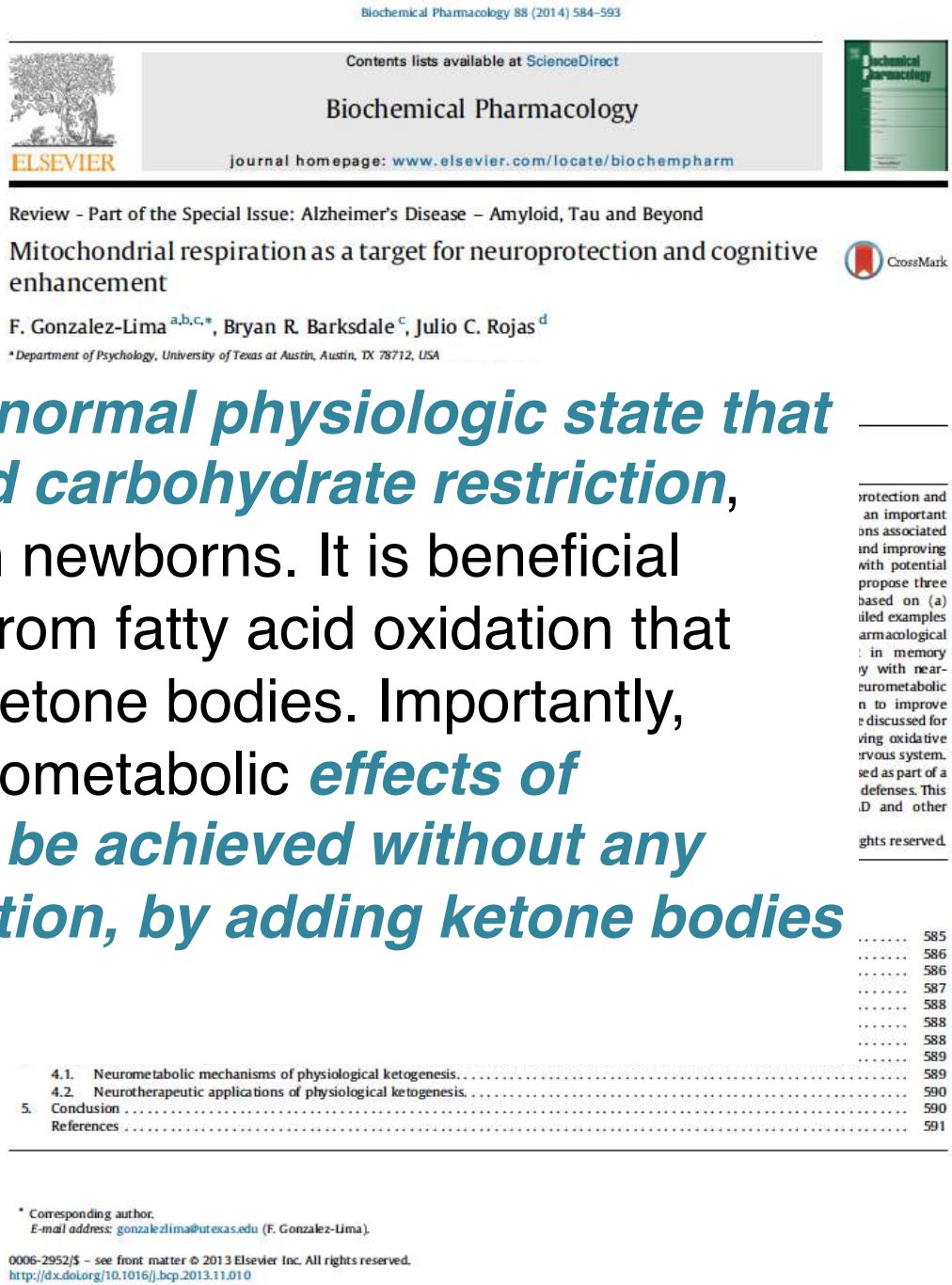
Diet and exercise can affect cellular metabolic activity, which can influence neuronal plasticity and cognitive processes



Gomez-Pinilla F, Nguyen TT. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. Nutr Neurosci. 2012 May;15(3):127-33.

Ketosis

"***The state of ketosis is a normal physiologic state that occurs during fasting and carbohydrate restriction***, and also normally occurs in newborns. It is beneficial because it derives energy from fatty acid oxidation that results in the formation of ketone bodies. Importantly, some of the beneficial neurometabolic ***effects of ketogenic diets may also be achieved without any significant dietary restriction, by adding ketone bodies to the diet.***"



Biochemical Pharmacology 88 (2014) 584–593

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review – Part of the Special Issue: Alzheimer's Disease – Amyloid, Tau and Beyond

Mitochondrial respiration as a target for neuroprotection and cognitive enhancement

F. Gonzalez-Lima [a,b,c,*], Bryan R. Barksdale [c], Julio C. Rojas [d]

[a] Department of Psychology, University of Texas at Austin, Austin, TX 78712, USA

* Corresponding author.
E-mail address: gonzalezlima@utexas.edu (F. Gonzalez-Lima).

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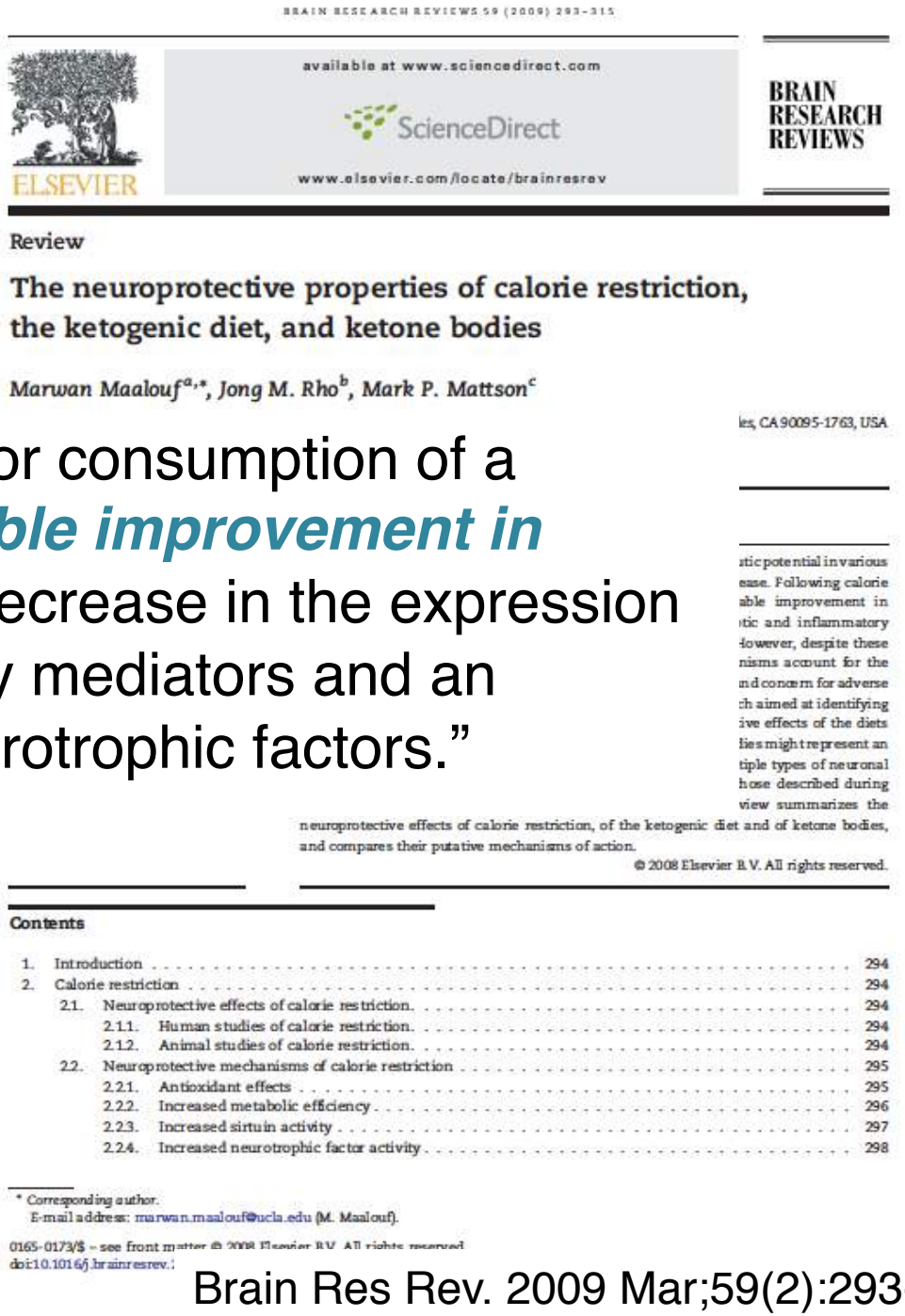
http://dx.doi.org/10.1016/j.bcp.2013.11.010

Biochem Pharmacol. 2014 Apr 15;88(4):584-

Fuel change



BRAIN RESEARCH REVIEWS 59 (2009) 293–315

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

ELSEVIER

BRAIN RESEARCH REVIEWS

Review

The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies

Marwan Maalouf[a,*], *Jong M. Rho*[b], *Mark P. Mattson*[c]

les, CA 90095-1763, USA

tic potential in various
ease. Following calorie
able improvement in
tic and inflammatory
lowever, despite these
nisms account for the
nd concern for adverse
ch aimed at identifying
ive effects of the diets
lies might represent an
tiple types of neuronal
hose described during
view summarizes the
neuroprotective effects of calorie restriction, of the ketogenic diet and of ketone bodies, and compares their putative mechanisms of action.

Contents

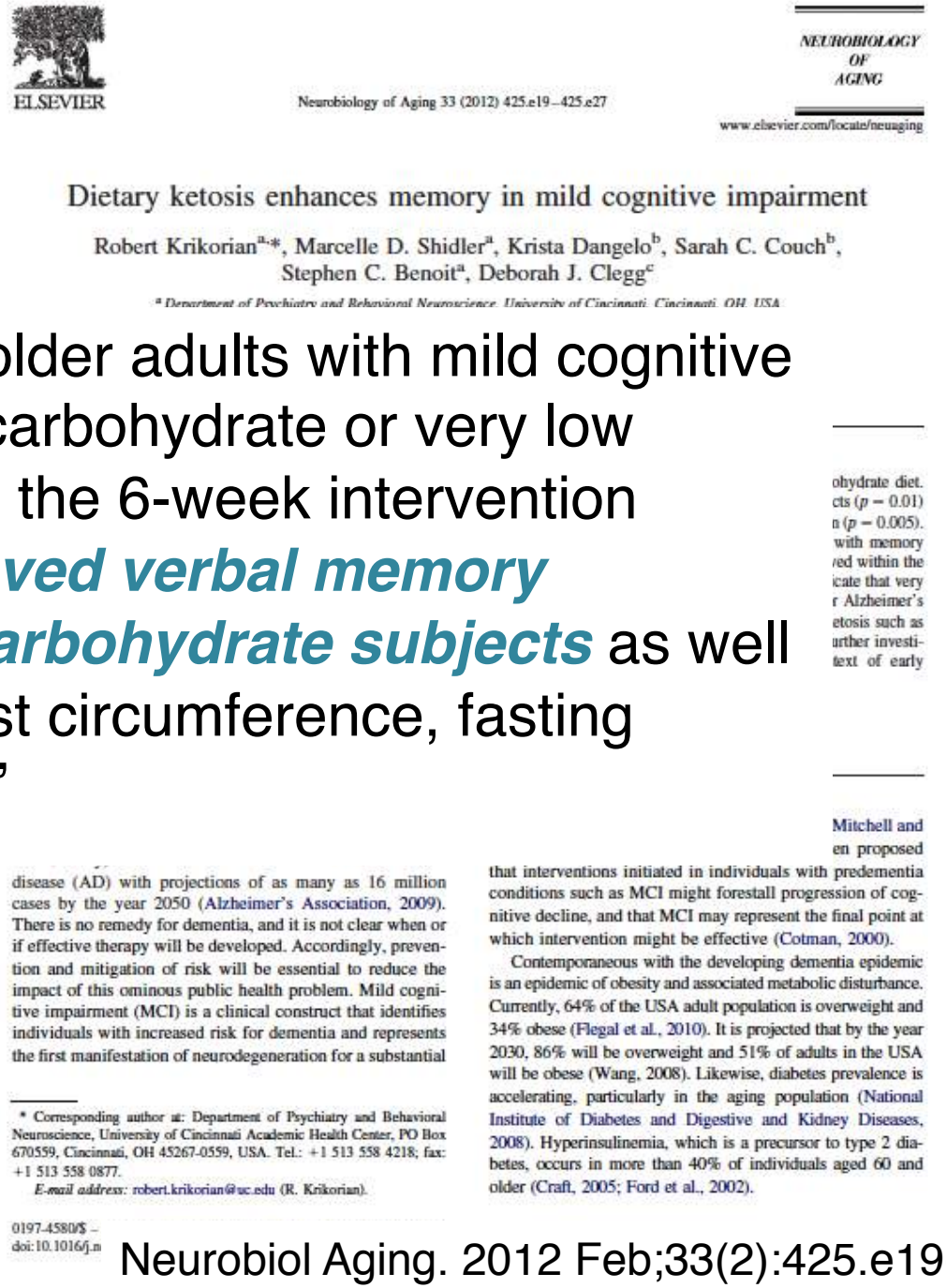
* Corresponding author.
E-mail address: marwan.maalouf@ucla.edu (M. Maalouf).

0165-0173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.

Brain Res Rev. 2009 Mar;59(2):293-3

"Following calorie restriction or consumption of a ketogenic diet, ***there is notable improvement in mitochondrial function***, a decrease in the expression of apoptotic and inflammatory mediators and an increase in the activity of neurotrophic factors."

Grain brain



ELSEVIER

Neurobiology of Aging 33 (2012) 425.e19–425.e27

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Dietary ketosis enhances memory in mild cognitive impairment

Robert Krikorian[a,*], Marcelle D. Shidler[a], Krista Dangelo[b], Sarah C. Couch[b], Stephen C. Benoit[a], Deborah J. Clegg[c]

[a] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA

ohydrate diet.
cts ($p = 0.01$)
n ($p = 0.005$).
with memory
ved within the
icate that very
r Alzheimer's
etosis such as
urther investi-
text of early

disease (AD) with projections of as many as 16 million cases by the year 2050 (Alzheimer's Association, 2009). There is no remedy for dementia, and it is not clear when or if effective therapy will be developed. Accordingly, prevention and mitigation of risk will be essential to reduce the impact of this ominous public health problem. Mild cognitive impairment (MCI) is a clinical construct that identifies individuals with increased risk for dementia and represents the first manifestation of neurodegeneration for a substantial

Mitchell and
en proposed
that interventions initiated in individuals with predementia conditions such as MCI might forestall progression of cognitive decline, and that MCI may represent the final point at which intervention might be effective (Cotman, 2000).

Contemporaneous with the developing dementia epidemic is an epidemic of obesity and associated metabolic disturbance. Currently, 64% of the USA adult population is overweight and 34% obese (Flegal et al., 2010). It is projected that by the year 2030, 86% will be overweight and 51% of adults in the USA will be obese (Wang, 2008). Likewise, diabetes prevalence is accelerating, particularly in the aging population (National Institute of Diabetes and Digestive and Kidney Diseases, 2008). Hyperinsulinemia, which is a precursor to type 2 diabetes, occurs in more than 40% of individuals aged 60 and older (Craft, 2005; Ford et al., 2002).

* Corresponding author at: Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati Academic Health Center, PO Box 670559, Cincinnati, OH 45267-0559, USA. Tel.: +1 513 558 4218; fax: +1 513 558 0877.
E-mail address: robert.krikorian@uc.edu (R. Krikorian).

0197-4580/$ –
doi:10.1016/j.n

Neurobiol Aging. 2012 Feb;33(2):425.e19-2

"We randomly assigned 23 older adults with mild cognitive impairment to either a high carbohydrate or very low carbohydrate diet. Following the 6-week intervention period, ***we observed improved verbal memory performance for the low carbohydrate subjects*** as well as reductions in weight, waist circumference, fasting glucose, and fasting insulin."

Coconut Oil

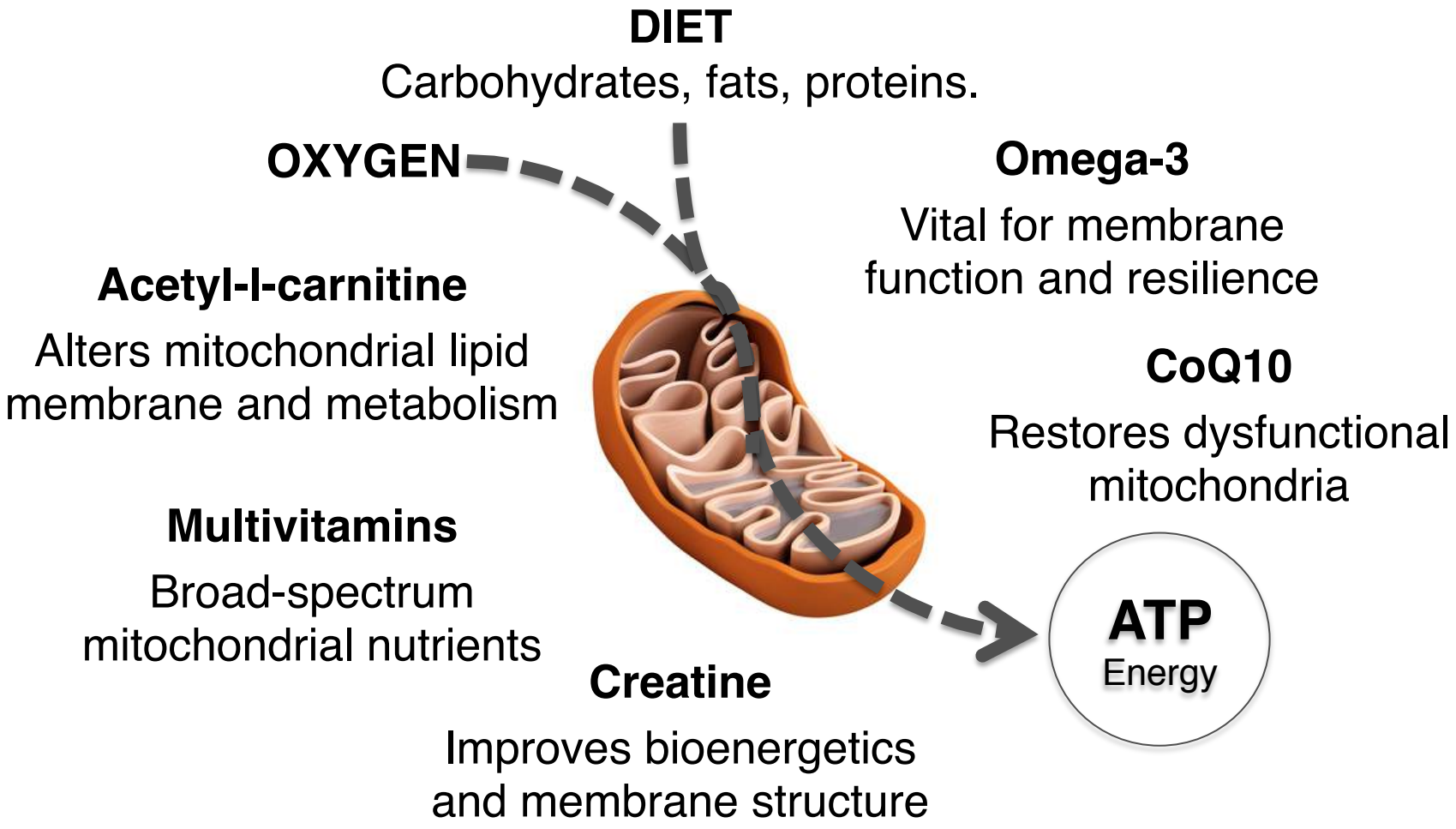
During the 4-week study people with moderate to severe Alzheimer's disease added 20 grams (about 1.5 tablespoons) of virgin coconut oil to their regular diet while maintaining their regular medication.

Coconut oil had significant beneficial effects on cognitive performance within 2-weeks, with a bigger effect after the 4-weeks *and the effects were even sustained for at least 2-weeks* after they stopped taking the oil.

The majority of the study participants caregivers also observed improvements in alertness, expression of language, overall activity and mood.

Gandotra S, et al. Efficacy of Adjunctive Extra Virgin Coconut Oil Use in Moderate to Severe Alzheimer's Disease. Int J Sch Cog Psychol 2014, 1:2

Qi-Nutrition



Qi-Nutrition

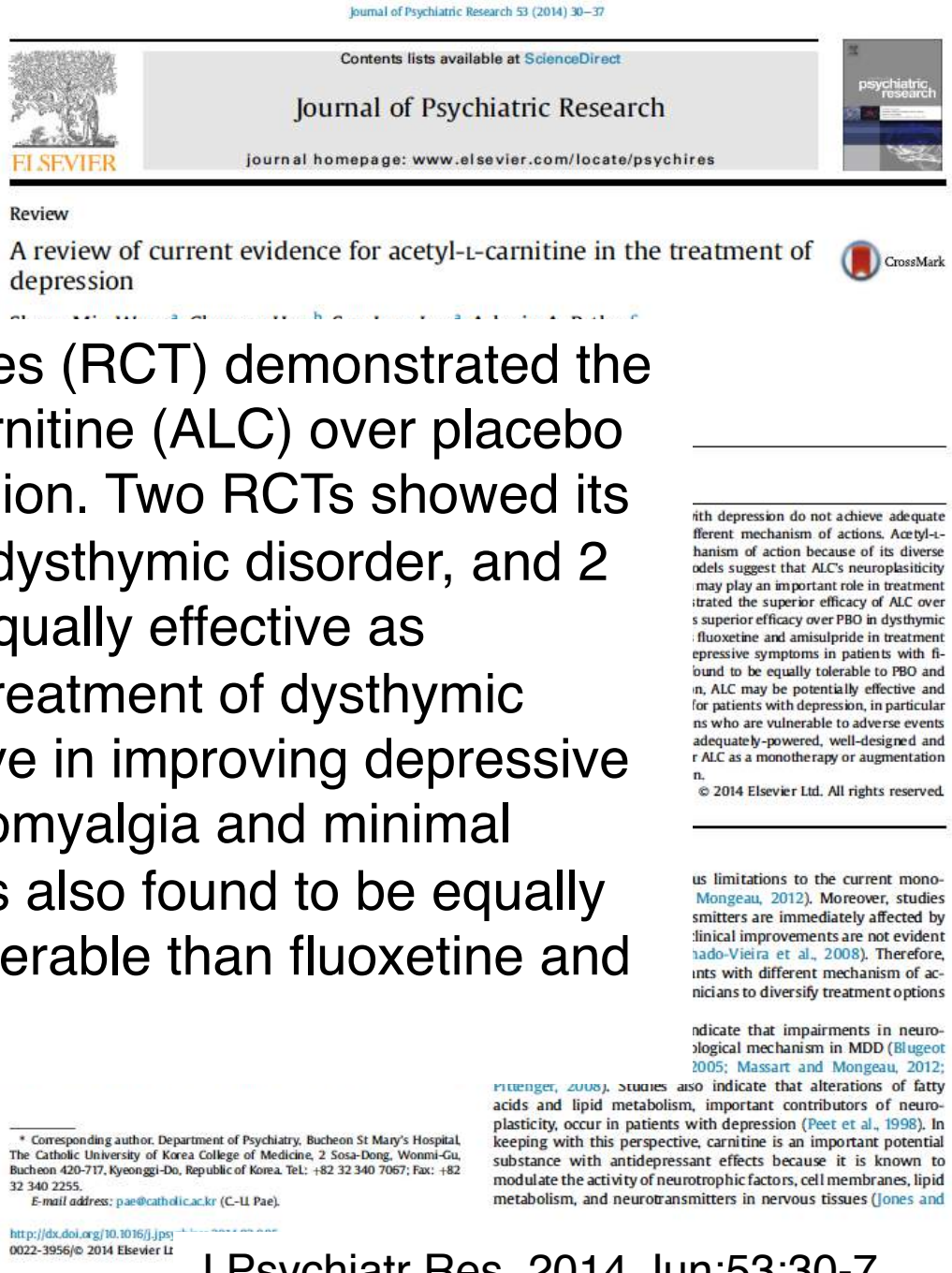
DIET
Carbohydrates, fats, proteins.

OXYGEN

Acetyl-l-carnitine
Alters mitochondrial lipid membrane and metabolism

ATP
Energy

Acetyl-l-carnitine



Journal of Psychiatric Research 53 (2014) 30–37

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Review

A review of current evidence for acetyl-L-carnitine in the treatment of depression

ith depression do not achieve adequate
fferent mechanism of actions. Acetyl-L-
hanism of action because of its diverse
odels suggest that ALC's neuroplasiticity
may play an important role in treatment
itrated the superior efficacy of ALC over
s superior efficacy over PBO in dysthymic
fluoxetine and amisulpride in treatment
epressive symptoms in patients with fi-
ound to be equally tolerable to PBO and
n, ALC may be potentially effective and
for patients with depression, in particular
ns who are vulnerable to adverse events
adequately-powered, well-designed and
r ALC as a monotherapy or augmentation
n.

us limitations to the current mono-
Mongeau, 2012). Moreover, studies
smitters are immediately affected by
clinical improvements are not evident
ado-Vieira et al., 2008). Therefore,
nts with different mechanism of ac-
nicians to diversify treatment options

ndicate that impairments in neuro-
ological mechanism in MDD (Blugeot
2005; Massart and Mongeau, 2012;
Pittenger, 2008). Studies also indicate that alterations of fatty acids and lipid metabolism, important contributors of neuroplasticity, occur in patients with depression (Peet et al., 1998). In keeping with this perspective, carnitine is an important potential substance with antidepressant effects because it is known to modulate the activity of neurotrophic factors, cell membranes, lipid metabolism, and neurotransmitters in nervous tissues (Jones and

* Corresponding author. Department of Psychiatry, Bucheon St Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon 420-717, Kyeonggi-Do, Republic of Korea. Tel.: +82 32 340 7067; Fax: +82 32 340 2255.
E-mail address: pae@catholic.ac.kr (C.-U. Pae).

http://dx.doi.org/10.1016/j.jpsy
0022-3956/

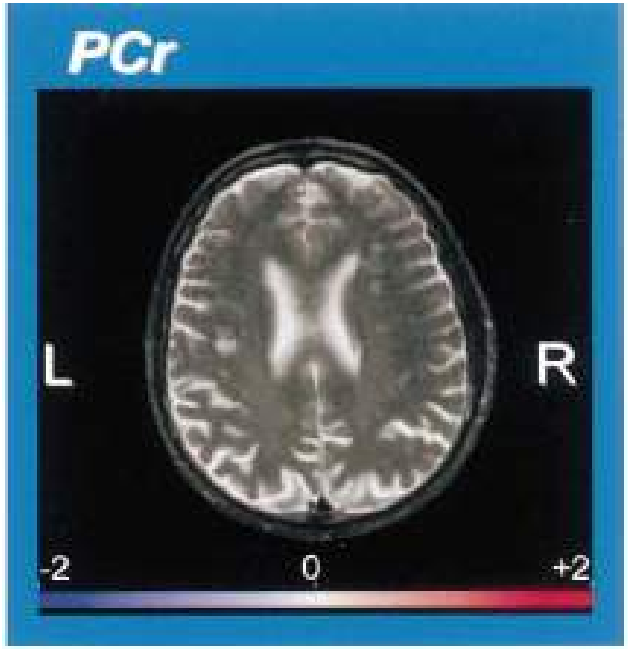
Four randomized clinical studies (RCT) demonstrated the superior efficacy of acetyl-l-carnitine (ALC) over placebo (PBO) in patients with depression. Two RCTs showed its superior efficacy over PBO in dysthymic disorder, and 2 other RCTs showed that it is equally effective as fluoxetine and amisulpride in treatment of dysthymic disorder. ALC was also effective in improving depressive symptoms in patients with fibromyalgia and minimal hepatic encephalopathy. It was also found to be equally tolerable to PBO and better tolerable than fluoxetine and amisulpride.

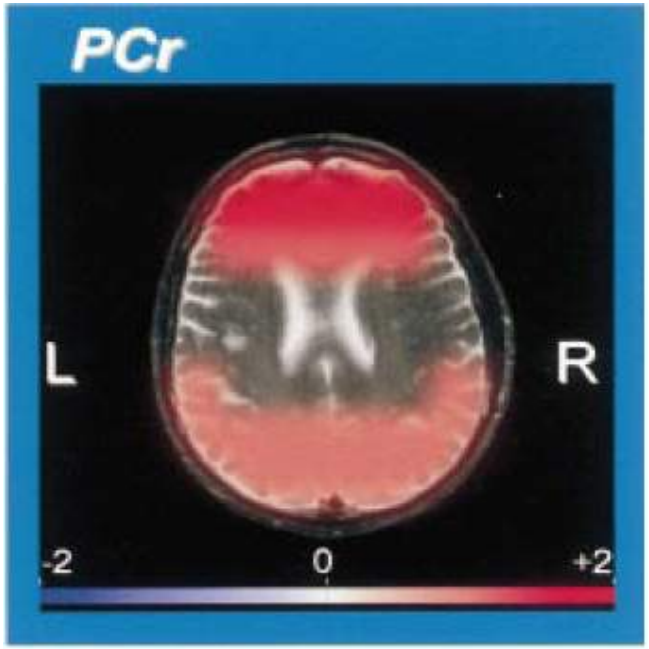
J Psychiatr Res. 2014 Jun;53:30-7

Re-energize

1. Low brain energy (phosphocreatine [PCr]) levels in a depressed person

2. Brain energy levels increased after with acetyl-l-carnitine and depressive symptoms diminished





Pettegrew JW, et al. 31P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results

Qi-Nutrition

DIET

Carbohydrates, fats, proteins.

OXYGEN

Acetyl-l-carnitine

Alters mitochondrial lipid membrane and metabolism

Multivitamins

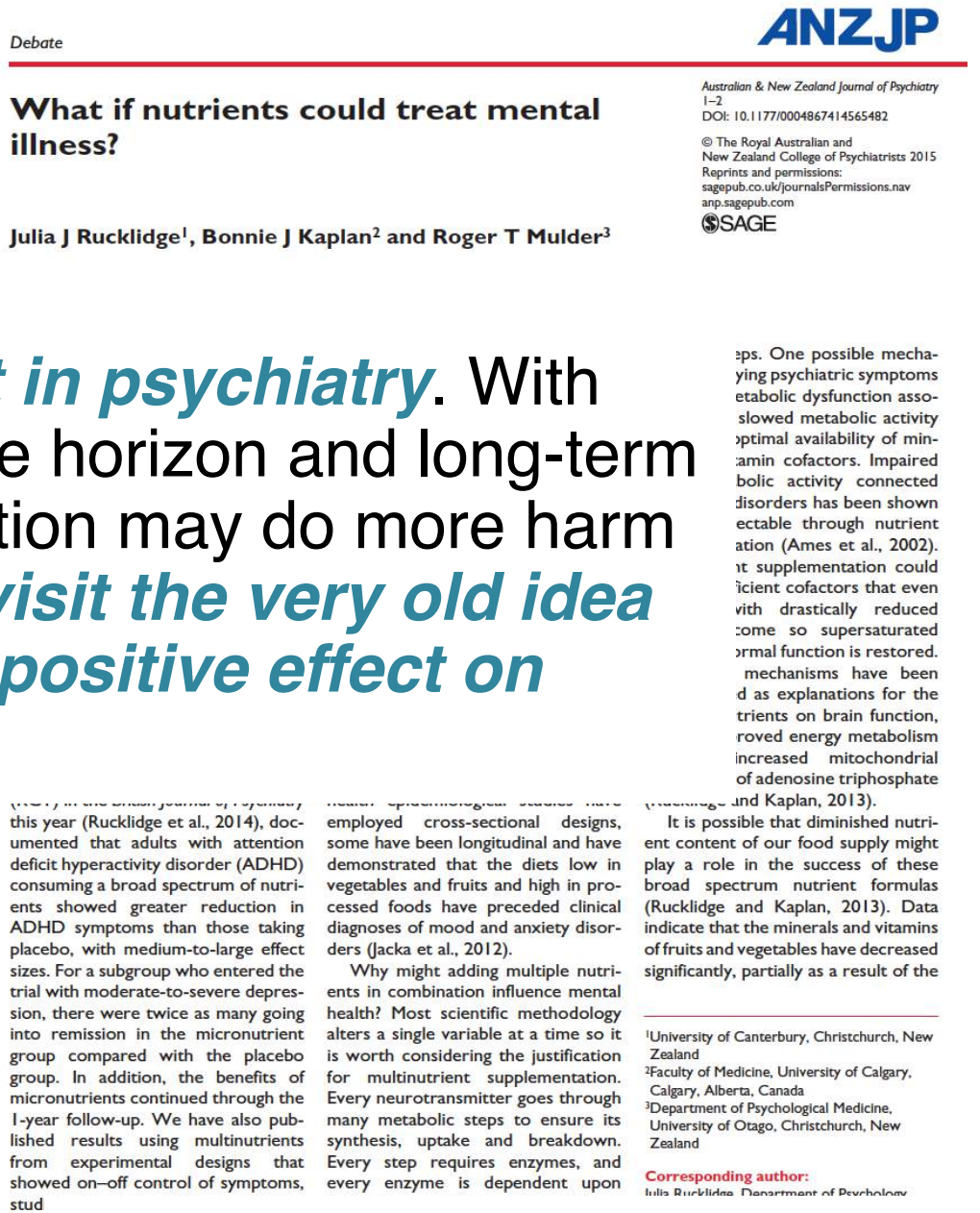
Broad-spectrum mitochondrial nutrients

ATP

Energy

Multivitamins

"***We are at a tipping point in psychiatry***. With few psychiatric drugs on the horizon and long-term studies suggesting medication may do more harm than good, ***it is time to revisit the very old idea that nutrition can have a positive effect on mental health.***"



Debate

ANZJP

Australian & New Zealand Journal of Psychiatry
1–2
DOI: 10.1177/0004867414565482

What if nutrients could treat mental illness?

Julia J Rucklidge[1], Bonnie J Kaplan[2] and Roger T Mulder[3]

eps. One possible mecha-
ying psychiatric symptoms
etabolic dysfunction asso-
slowed metabolic activity
ptimal availability of min-
amin cofactors. Impaired
bolic activity connected
disorders has been shown
ectable through nutrient
ation (Ames et al., 2002).
t supplementation could
ficient cofactors that even
vith drastically reduced
come so supersaturated
rmal function is restored.
mechanisms have been
d as explanations for the
trients on brain function,
roved energy metabolism
increased mitochondrial
of adenosine triphosphate
nd Kaplan, 2013).

this year (Rucklidge et al., 2014), documented that adults with attention deficit hyperactivity disorder (ADHD) consuming a broad spectrum of nutrients showed greater reduction in ADHD symptoms than those taking placebo, with medium-to-large effect sizes. For a subgroup who entered the trial with moderate-to-severe depression, there were twice as many going into remission in the micronutrient group compared with the placebo group. In addition, the benefits of micronutrients continued through the 1-year follow-up. We have also published results using multinutrients from experimental designs that showed on–off control of symptoms,

employed cross-sectional designs, some have been longitudinal and have demonstrated that the diets low in vegetables and fruits and high in processed foods have preceded clinical diagnoses of mood and anxiety disorders (Jacka et al., 2012).

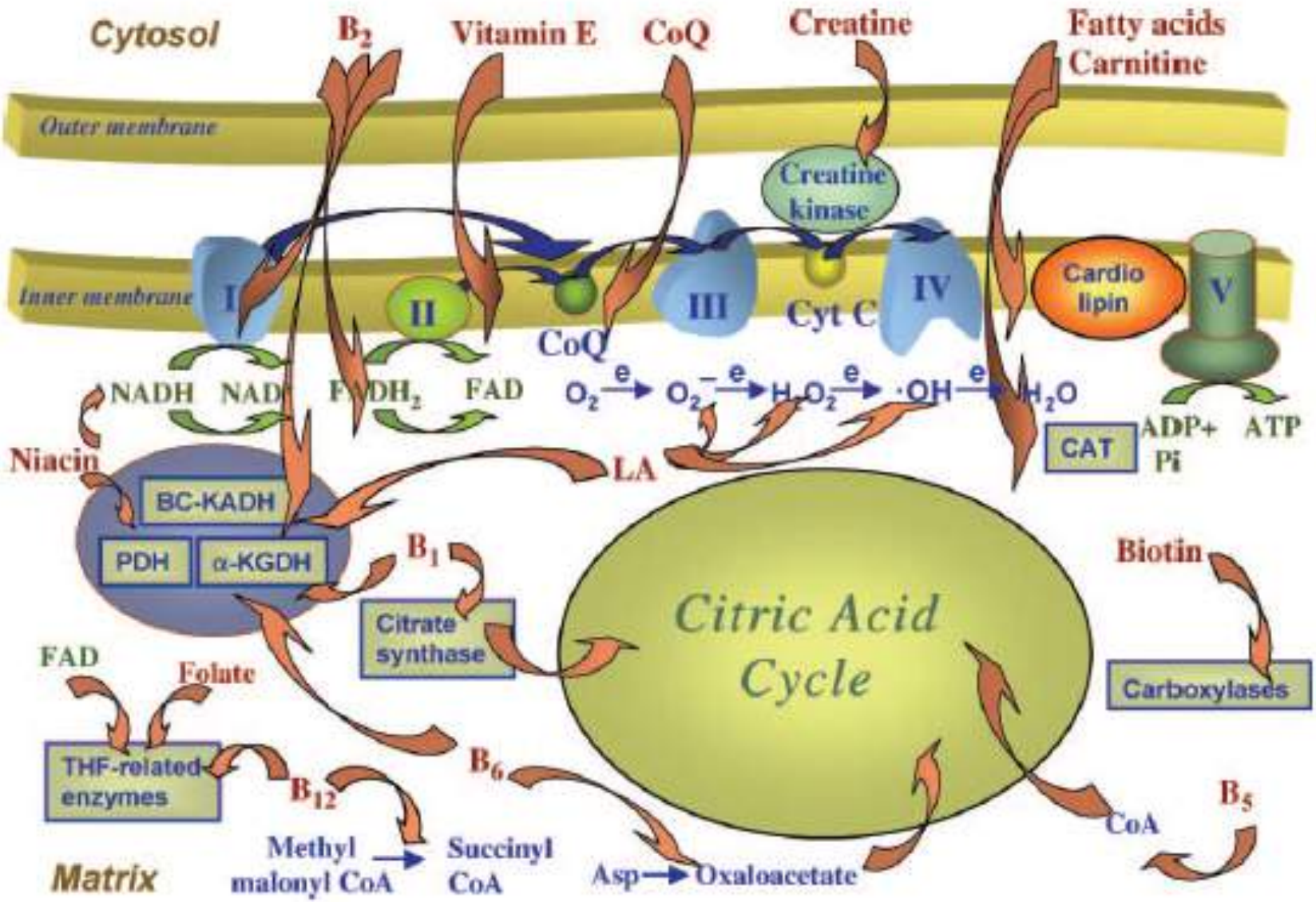
Why might adding multiple nutrients in combination influence mental health? Most scientific methodology alters a single variable at a time so it is worth considering the justification for multinutrient supplementation. Every neurotransmitter goes through many metabolic steps to ensure its synthesis, uptake and breakdown. Every step requires enzymes, and every enzyme is dependent upon

It is possible that diminished nutrient content of our food supply might play a role in the success of these broad spectrum nutrient formulas (Rucklidge and Kaplan, 2013). Data indicate that the minerals and vitamins of fruits and vegetables have decreased significantly, partially as a result of the

[1]University of Canterbury, Christchurch, New Zealand
[2]Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada
[3]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

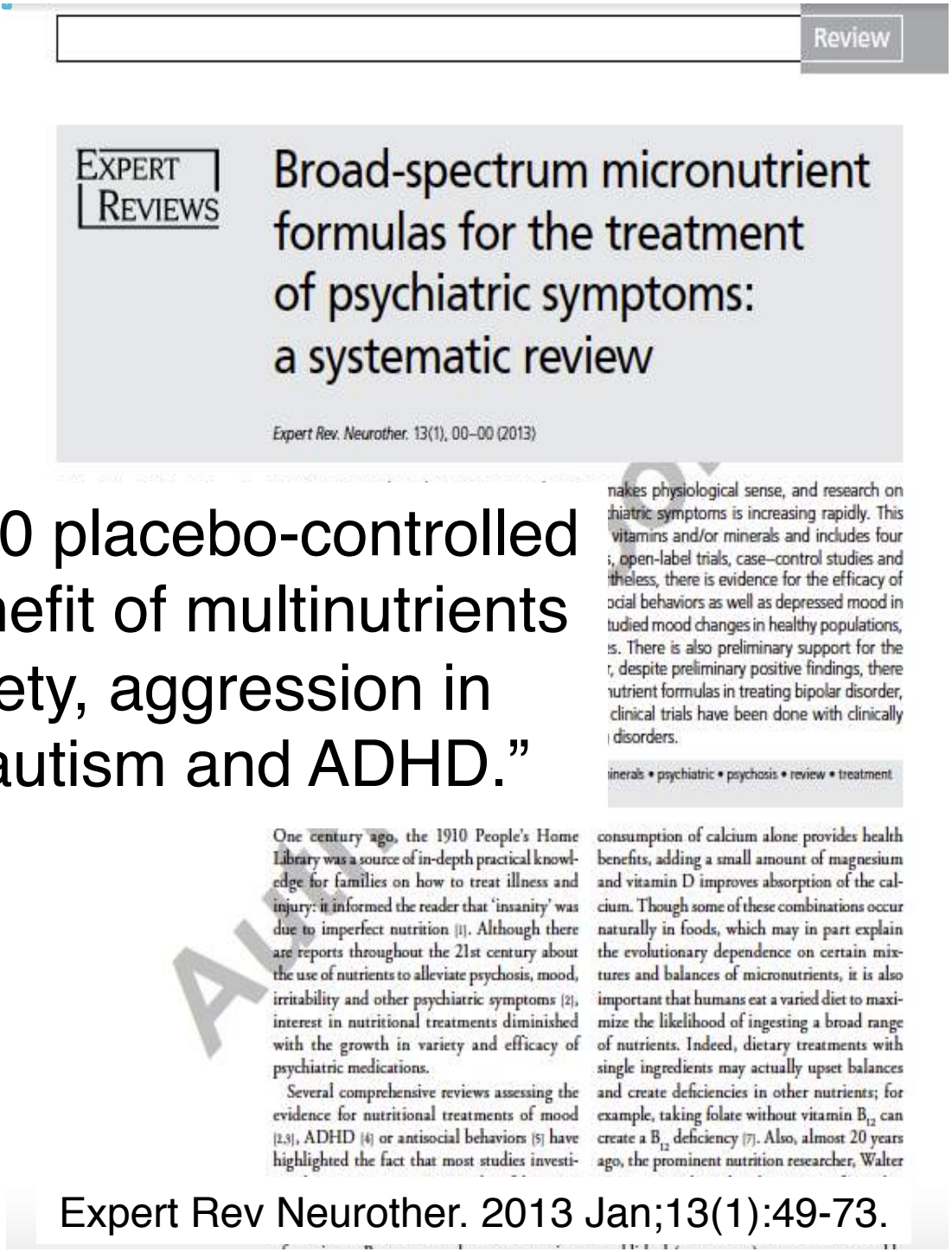
Corresponding author:

Aust N Z J Psychiatry. 2015 Jan 13. [Epub ahead of print]



Liu J, Ames BN. Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease. Nutr Neurosci. 2005 Apr;8(2):67-89.

Tipping point



Review

EXPERT REVIEWS

Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review

Expert Rev. Neurother. 13(1), 00–00 (2013)

nakes physiological sense, and research on
hiatric symptoms is increasing rapidly. This
vitamins and/or minerals and includes four
, open-label trials, case–control studies and
itheless, there is evidence for the efficacy of
ocial behaviors as well as depressed mood in
tudied mood changes in healthy populations,
s. There is also preliminary support for the
, despite preliminary positive findings, there
utrient formulas in treating bipolar disorder,
clinical trials have been done with clinically
disorders.

inerals • psychiatric • psychosis • review • treatment

One century ago, the 1910 People's Home Library was a source of in-depth practical knowledge for families on how to treat illness and injury: it informed the reader that 'insanity' was due to imperfect nutrition [1]. Although there are reports throughout the 21st century about the use of nutrients to alleviate psychosis, mood, irritability and other psychiatric symptoms [2], interest in nutritional treatments diminished with the growth in variety and efficacy of psychiatric medications.

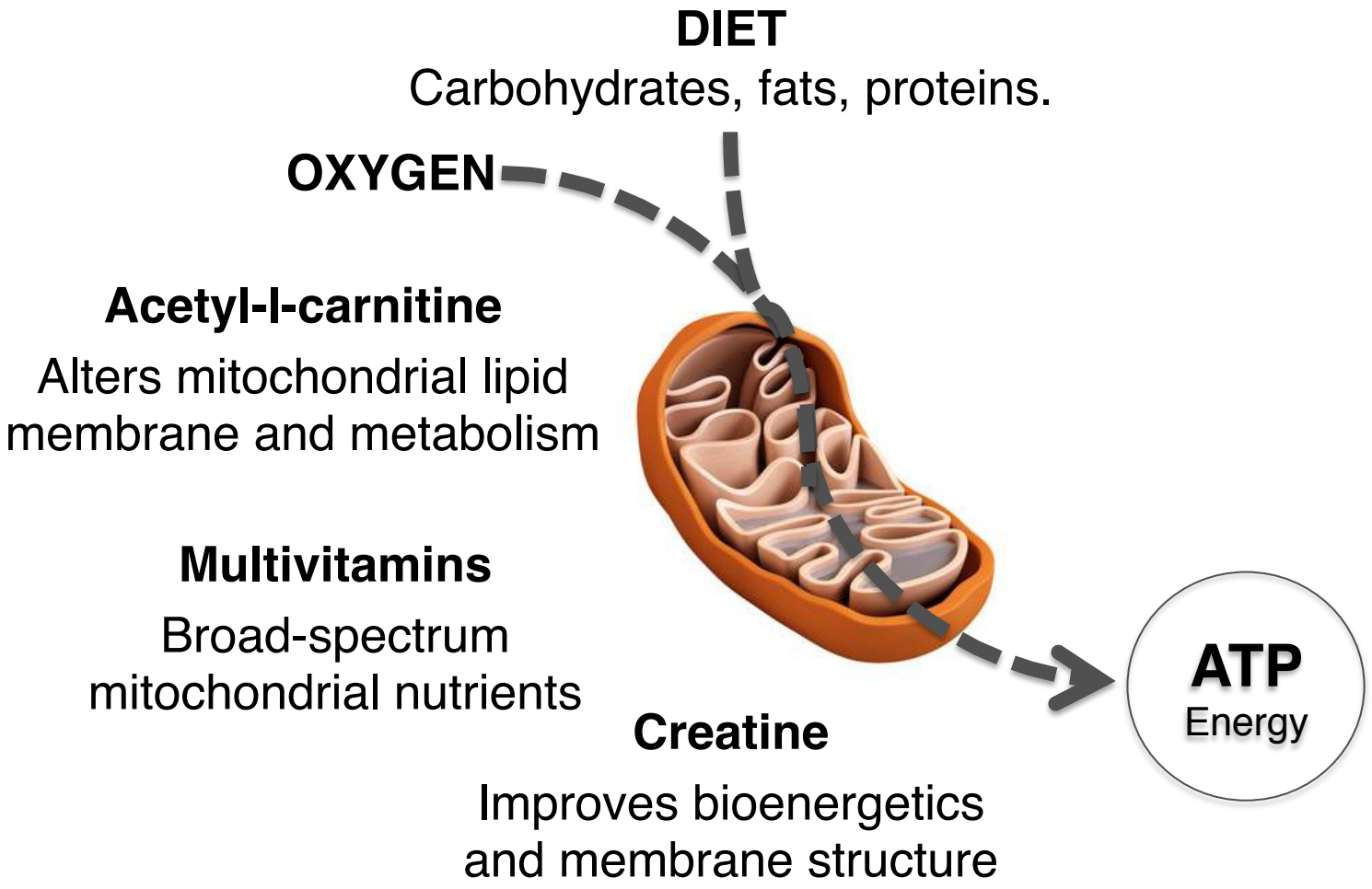
Several comprehensive reviews assessing the evidence for nutritional treatments of mood [2,3], ADHD [4] or antisocial behaviors [5] have highlighted the fact that most studies investi-

consumption of calcium alone provides health benefits, adding a small amount of magnesium and vitamin D improves absorption of the calcium. Though some of these combinations occur naturally in foods, which may in part explain the evolutionary dependence on certain mixtures and balances of micronutrients, it is also important that humans eat a varied diet to maximize the likelihood of ingesting a broad range of nutrients. Indeed, dietary treatments with single ingredients may actually upset balances and create deficiencies in other nutrients; for example, taking folate without vitamin B_{12} can create a B_{12} deficiency [7]. Also, almost 20 years ago, the prominent nutrition researcher, Walter

Expert Rev Neurother. 2013 Jan;13(1):49-73.

"There are now over 20 placebo-controlled RCTs showing the benefit of multinutrients in treating stress, anxiety, aggression in prisoners, low mood, autism and ADHD."

Qi-Nutrition



Creatine

"Impairments in creatine metabolism have also been implicated in the pathogenesis of psychiatric disorders, leaving clinicians, researchers and patients alike wondering if dietary creatine has therapeutic value for treating mental illness."

Neuroscience and Biobehavioral Reviews 36 (2012) 1442–1462

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value?

Patricia J. Allen *

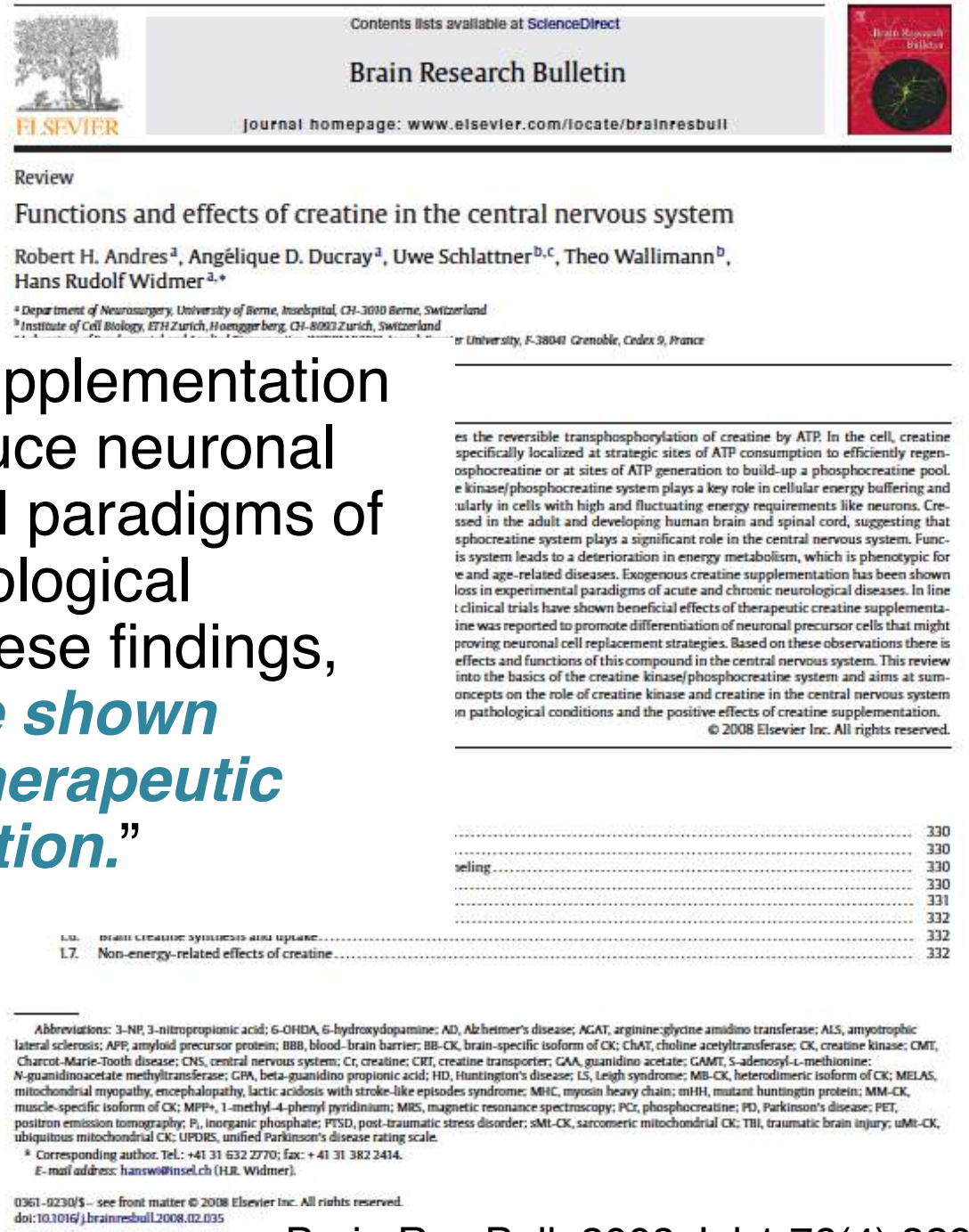
Department of Psychology, Tufts University, Psychology Building, 490 Boston Ave., Medford, MA 02155, USA

rsonnel use dietary creatine as an ergogenic aid to boost physical
ırsts of high-intensity muscle activity. Lesser known is the essen-
energy homeostasis, plays in brain function and development.
omise as a safe, effective, and tolerable adjunct to medication for
linked with dysfunctional energy metabolism, such as Hunting-
npairments in creatine metabolism have also been implicated in
s, leaving clinicians, researchers and patients alike wondering if
r treating mental illness. The present review summarizes the neu-
ine circuit and its relation to psychological stress, schizophrenia,
ent knowledge of the role of creatine in cognitive and emotional
ırch on this endogenous metabolite has the potential to advance
s of psychopathology and improve current therapeutic strategies.

* Tel.: +1 617 627 3523; fax: +1 617 627 3181.

Neurosci Biobehav Rev. 2012 May;36(5):1442-62.

Diverse effects



Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

Functions and effects of creatine in the central nervous system

Robert H. Andres[a], Angélique D. Ducray[a], Uwe Schlattner[b,c], Theo Wallimann[b], Hans Rudolf Widmer[a,*]

[a] Department of Neurosurgery, University of Berne, Inselspital, CH-3010 Berne, Switzerland
[b] Institute of Cell Biology, ETH Zurich, Hoenggerberg, CH-8093 Zurich, Switzerland
[c] University, F-38041 Grenoble, Cedex 9, France

es the reversible transphosphorylation of creatine by ATP. In the cell, creatine specifically localized at strategic sites of ATP consumption to efficiently regen- osphocreatine or at sites of ATP generation to build-up a phosphocreatine pool. e kinase/phosphocreatine system plays a key role in cellular energy buffering and ularly in cells with high and fluctuating energy requirements like neurons. Cre- ssed in the adult and developing human brain and spinal cord, suggesting that sphocreatine system plays a significant role in the central nervous system. Func- is system leads to a deterioration in energy metabolism, which is phenotypic for e and age-related diseases. Exogenous creatine supplementation has been shown loss in experimental paradigms of acute and chronic neurological diseases. In line t clinical trials have shown beneficial effects of therapeutic creatine supplementa- ine was reported to promote differentiation of neuronal precursor cells that might proving neuronal cell replacement strategies. Based on these observations there is effects and functions of this compound in the central nervous system. This review into the basics of the creatine kinase/phosphocreatine system and aims at sum- oncepts on the role of creatine kinase and creatine in the central nervous system n pathological conditions and the positive effects of creatine supplementation.

Abbreviations: 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; AGAT, arginine:glycine amidino transferase; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BBB, blood–brain barrier; BB-CK, brain-specific isoform of CK; ChAT, choline acetyltransferase; CK, creatine kinase; CMT, Charcot-Marie-Tooth disease; CNS, central nervous system; Cr, creatine; CRT, creatine transporter; GAA, guanidino acetate; GAMT, S-adenosyl-L-methionine: *N*-guanidinoacetate methyltransferase; GPA, beta-guanidino propionic acid; HD, Huntington's disease; LS, Leigh syndrome; MB-CK, heterodimeric isoform of CK; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes syndrome; MHC, myosin heavy chain; mHH, mutant huntingtin protein; MM-CK, muscle-specific isoform of CK; MPP+, 1-methyl-4-phenyl pyridinium; MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; PD, Parkinson's disease; PET, positron emission tomography; P_i, inorganic phosphate; PTSD, post-traumatic stress disorder; sMt-CK, sarcomeric mitochondrial CK; TBI, traumatic brain injury; uMt-CK, ubiquitous mitochondrial CK; UPDRS, unified Parkinson's disease rating scale.

* Corresponding author. Tel.: +41 31 632 2770; fax: +41 31 382 2414.
E-mail address: hanswi@insel.ch (H.R. Widmer).

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doi:10.1016/j.brainresbull.2008.02.035

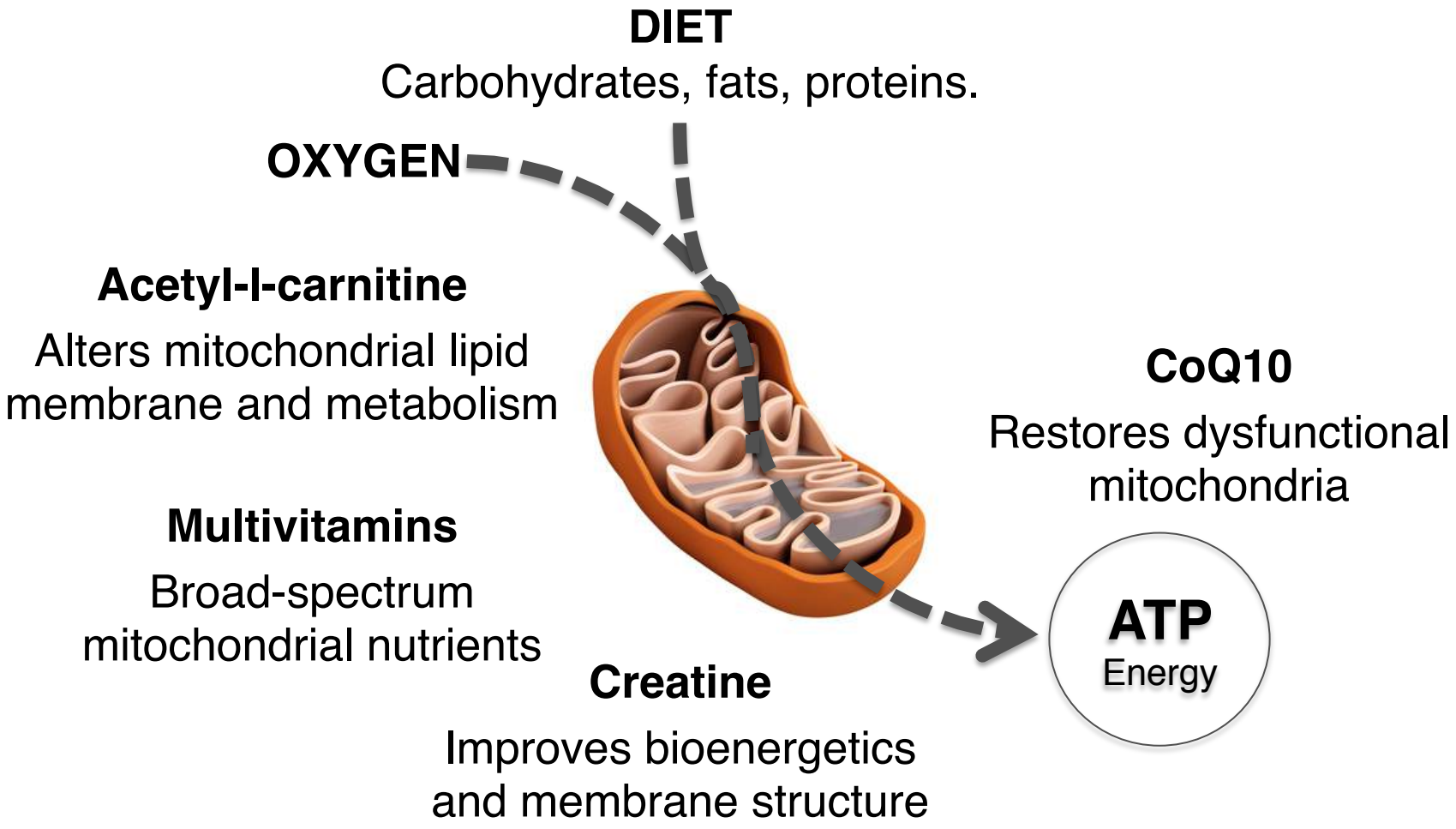
"Exogenous creatine supplementation has been shown to reduce neuronal cell loss in experimental paradigms of acute and chronic neurological diseases. In line with these findings, first ***clinical trials have shown beneficial effects of therapeutic creatine supplementation.***"

Brain Res Bull. 2008 Jul 1;76(4):329-

Reference	Study group	Intervention	Results
43	Women with major depressive disorder	5 grams of creatine per day for 8 weeks	Significantly improved depressive symptoms
44	Female adolescents with SSRI-resistant major depressive disorder	4 grams of creatine for 8 weeks	Reduced depressive symptoms and increased brain phosphocreatine
45	Unipolar and bipolar patients with treatment-resistant depression	3-5 g creatine per day for 4 weeks	Patients with unipolar (but not bipolar) depression improved
46	Case report of a patient with fibromyalgia and depression	3-5 g creatine per day for 8 weeks	Improved depressive symptoms
47	Patients with treatment-resistant posttraumatic stress disorder	Dose and duration unknown	Improved symptoms; greatest benefit in in patients diagnosed with comorbid depression

Brown, BI. JOM, 2012; 27(4): 177-186.

Qi-Nutrition



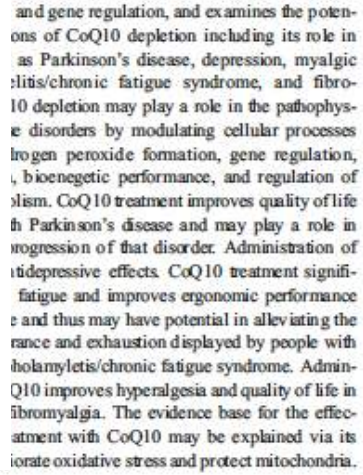
CoQ10

Mol Neurobiol (2013) 48:883–903
DOI 10.1007/s12035-013-8477-8

Coenzyme Q10 Depletion in Medical and Neuropsychiatric Disorders: Potential Repercussions and Therapeutic Implications

Gerwyn Morris · George Anderson · Michael Berk · Michael Maes

"A relationship exists between lowered CoQ10 levels and elevated immune-inflammatory and oxidative and nitrosative stress pathways and mitochondrial dysfunction and the generation of specific symptoms/behaviors, including fatigue, hyperalgesia, and depression, and the onset of neurodegenerative processes."



and gene regulation, and examines the poten-
ons of CoQ10 depletion including its role in
as Parkinson's disease, depression, myalgic
elitis/chronic fatigue syndrome, and fibro-
10 depletion may play a role in the pathophys-
e disorders by modulating cellular processes
lrogen peroxide formation, gene regulation,
, bioenegetic performance, and regulation of
olism. CoQ10 treatment improves quality of life
h Parkinson's disease and may play a role in
rogression of that disorder. Administration of
tidepressive effects. CoQ10 treatment signifi-
fatigue and improves ergonomic performance
e and thus may have potential in alleviating the
rance and exhaustion displayed by people with
holamyletis/chronic fatigue syndrome. Admin-
Q10 improves hyperalgesia and quality of life in
ibromyalgia. The evidence base for the effec-
atment with CoQ10 may be explained via its
iorate oxidative stress and protect mitochondria.

M. Berk
Department of Psychiatry, University of Melbourne, Parkville, VIC 3052, Australia

M. Berk
Orygen Youth Health Research Centre, 35 Poplar Road, Parkville, VIC 3052, Australia

M. Berk
Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, VIC 3052, Australia

M. Maes
Department of Psychiatry, Chulalongkorn University, Rama Road, Bangkok, Thailand

Keywords Coenzyme Q10 · Oxidative and nitrosative stress · Inflammation · Cytokines · Mitochondria

Abbreviations

CoQ10	Coenzyme Q10
ATP	Adenosine triphosphate
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
O&NS	Oxidative and nitrosative stress
NF-κB	Nuclear factor-κB
MDA	Malondialdehyde
SOD	Superoxide dismutase

Mol Neurobiol. 2013 Dec;48(3):883-90

Recovery catalyst

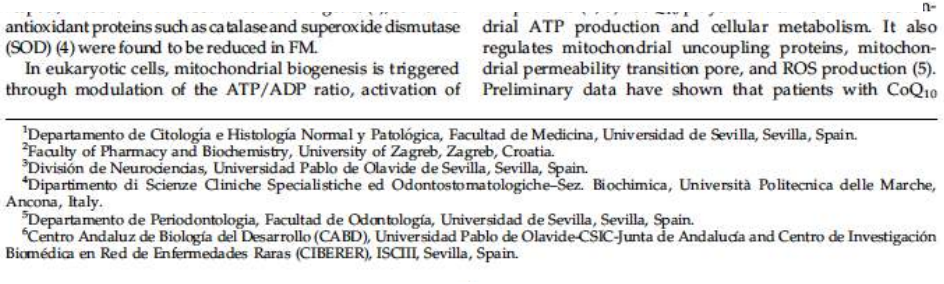
ANTIOXIDANTS & REDOX SIGNALING
Volume 00, Number 00, 2013

DOI: 10.1089/ars.2013.5260

NEWS & VIEWS

Can Coenzyme Q_{10} Improve Clinical and Molecular Parameters in Fibromyalgia?

An important clinical improvement was evident after CoQ10 versus placebo treatment showing a reduction of FIQ, and a most prominent reduction in pain, fatigue, and morning tiredness subscales from FIQ. Furthermore, we observed an important reduction in the pain visual scale and a reduction in tender points ***, including recovery of inflammation, antioxidant enzymes, mitochondrial biogenesis, and AMPK gene expression levels***, associated with phosphorylation of the AMPK activity.



antioxidant proteins such as catalase and superoxide dismutase (SOD) (4) were found to be reduced in FM.

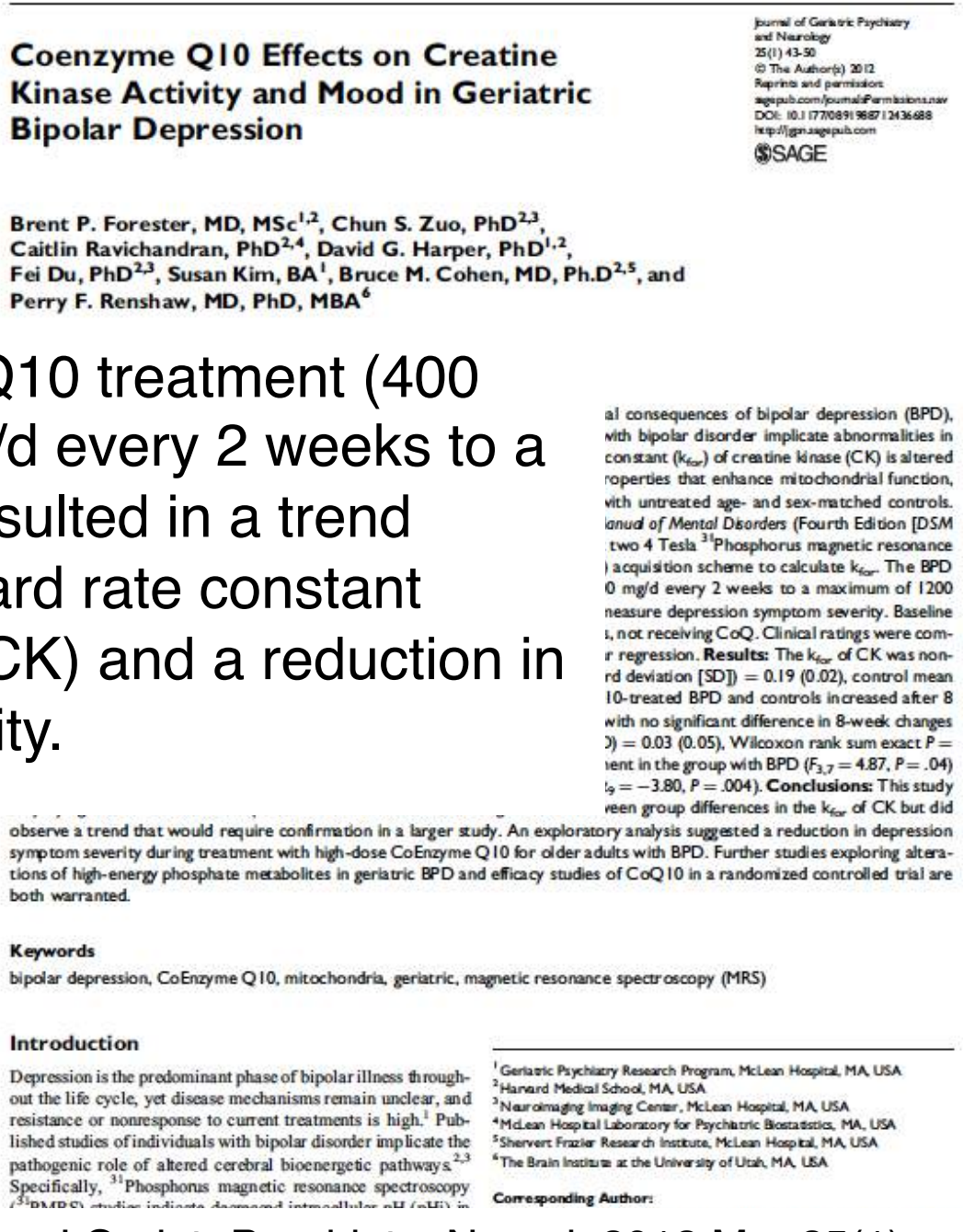
In eukaryotic cells, mitochondrial biogenesis is triggered through modulation of the ATP/ADP ratio, activation of drial ATP production and cellular metabolism. It also regulates mitochondrial uncoupling proteins, mitochondrial permeability transition pore, and ROS production (5). Preliminary data have shown that patients with CoQ_{10}

[1]Departamento de Citología e Histología Normal y Patológica, Facultad de Medicina, Universidad de Sevilla, Sevilla, Spain.
[2]Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia.
[3]División de Neurociencias, Universidad Pablo de Olavide de Sevilla, Sevilla, Spain.
[4]Dipartimento di Scienze Cliniche Specialistiche ed Odontostomatologiche–Sez. Biochimica, Università Politecnica delle Marche, Ancona, Italy.
[5]Departamento de Periodontología, Facultad de Odontología, Universidad de Sevilla, Sevilla, Spain.
[6]Centro Andaluz de Biología del Desarrollo (CABD), Universidad Pablo de Olavide-CSIC-Junta de Andalucía and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), ISCIII, Sevilla, Spain.

Antioxid Redox Signal. 2013 Oct 20;19(12):

Biplolar

- In an open label study, CoQ10 treatment (400 mg/d titrated up by 400 mg/d every 2 weeks to a maximum of 1200 mg/d) resulted in a trend towards improved the forward rate constant (k(for)) of creatine kinase (CK) and a reduction in depression symptom severity.



Coenzyme Q10 Effects on Creatine Kinase Activity and Mood in Geriatric Bipolar Depression

Journal of Geriatric Psychiatry and Neurology
25(1) 43-50
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DOI: 10.1177/0891988711436688
http://jgpn.sagepub.com
SAGE

Brent P. Forester, MD, MSc[1,2], Chun S. Zuo, PhD[2,3], Caitlin Ravichandran, PhD[2,4], David G. Harper, PhD[1,2], Fei Du, PhD[2,3], Susan Kim, BA[1], Bruce M. Cohen, MD, Ph.D[2,5], and Perry F. Renshaw, MD, PhD, MBA[6]

al consequences of bipolar depression (BPD), with bipolar disorder implicate abnormalities in constant (k_{for}) of creatine kinase (CK) is altered roperties that enhance mitochondrial function, with untreated age- and sex-matched controls. *anual of Mental Disorders* (Fourth Edition [*DSM* two 4 Tesla ^{31}Phosphorus magnetic resonance) acquisition scheme to calculate k_{for}. The BPD 0 mg/d every 2 weeks to a maximum of 1200 neasure depression symptom severity. Baseline s, not receiving CoQ. Clinical ratings were com- r regression. **Results:** The k_{for} of CK was non- rd deviation [SD]) = 0.19 (0.02), control mean 10-treated BPD and controls increased after 8 with no significant difference in 8-week changes 0) = 0.03 (0.05), Wilcoxon rank sum exact $P =$ ent in the group with BPD ($F_{3,7} = 4.87$, $P = .04$) $t_9 = -3.80$, $P = .004$). **Conclusions:** This study veen group differences in the k_{for} of CK but did observe a trend that would require confirmation in a larger study. An exploratory analysis suggested a reduction in depression symptom severity during treatment with high-dose CoEnzyme Q10 for older adults with BPD. Further studies exploring alterations of high-energy phosphate metabolites in geriatric BPD and efficacy studies of CoQ10 in a randomized controlled trial are both warranted.

Keywords
bipolar depression, CoEnzyme Q10, mitochondria, geriatric, magnetic resonance spectroscopy (MRS)

Introduction

Depression is the predominant phase of bipolar illness throughout the life cycle, yet disease mechanisms remain unclear, and resistance or nonresponse to current treatments is high.[1] Published studies of individuals with bipolar disorder implicate the pathogenic role of altered cerebral bioenergetic pathways.[2,3] Specifically, ^{31}Phosphorus magnetic resonance spectroscopy (^{31}PMRS) studies indicate decreased intracellular pH (pHi) in

[1]Geriatric Psychiatry Research Program, McLean Hospital, MA, USA
[2]Harvard Medical School, MA, USA
[3]Neuroimaging Imaging Center, McLean Hospital, MA, USA
[4]McLean Hospital Laboratory for Psychiatric Biostatistics, MA, USA
[5]Sherwert Frazier Research Institute, McLean Hospital, MA, USA
[6]The Brain Institute at the University of Utah, MA, USA

Corresponding Author:

J Geriatr Psychiatry Neurol. 2012 Mar;25(1): 43-50

Depression

"CoQ10 and serotonin levels in platelets from FM patients were restored in the COQ10-treated group com- pared to placebo group. Interestingly, a notable improvement in depressive symptoms evaluated with the BDI scale was also observed in the CoQ10- treated group compared to the placebo group."

Coenzyme Q_{10} Regulates Serotonin Levels and Depressive Symptoms in Fibromyalgia Patients
Results of a Small Clinical Trial

To the Editors:

randomized in a double-blind fashion, according to a 1:1 ratio, to CoQ_{10} or placebo. Ten subjects received CoQ_{10} (Pharma Nord, Vejle, Denmark) in soft gel capsules for 40 days (300 mg/d CoQ_{10} divided into 3 daily doses), whereas another group of 10 subjects received a matching placebo.

Early-morning samples of blood were collected under fasting conditions and platelets were isolated. CoQ_{10} levels were determined by HPLC and serotonin levels by

CA). CoQ_{10}
althy platelets
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levels in platelets from FM patients and depressive symptoms improvement.

The study protocol was reviewed and approved by the Ethical Committee of the University of Sevilla. All the participants of the study gave their written informed consent before initiating the study. This study was carried out in compliance with the Declaration of Helsinki, and all the International Conferences on Harmonisation and Good Clinical Practice Guidelines. Twenty patients diagnosed with FM were distributed in a clinical trial as described in Cordero et al.[2] The patients were diagnosed with FM by exclusion of other diseases and syndromes, and in accordance with the American College of Rheumatology criteria. Subjects were

However, there is no information about the effect of CoQ_{10} treatment in serotonin levels. In our study, CoQ_{10} and serotonin levels in platelets from FM patients were restored in the COQ_{10}-treated group compared to placebo group (Fig. 1A and B). Interestingly, a notable improvement in depressive symptoms evaluated with the BDI scale was also observed in the CoQ_{10}-treated group compared to the placebo group [placebo group, 24.1 (3.5); CoQ_{10} group, 6.2 (1.9)] ($P < 0.001$).

To verify the role of CoQ_{10} in the serotonin alterations observed in FM patients, we induced CoQ_{10} deficiency in platelets from healthy controls by inhibiting the endogenous biosynthesis of CoQ_{10} with PABA treatment, a competitive inhibitor of polyprenyl-4-hydroxybenzoate transferase (Coq2p). Platelets were cultured for 24 hours in the presence of 1-mM PABA, or alternatively PABA + 10 μM CoQ_{10}, and PABA + 10 mM N-acetylcysteine (N-Acet) (Sigma Chemical Co). Serotonin levels in platelets were significantly reduced by PABA treatment (Fig. 1D). Reduced serotonin levels in platelets were restored in the presence of 2 antioxidants, CoQ_{10}, or N-Acet, being more significant in platelets treated with CoQ_{10}. Taken together, these results suggest that CoQ_{10} deficiency affects serotonin content in platelets and, presumably, in other cells such as neurons of the central nervous system. CoQ_{10} is an important component of the mitochondrial respiratory chain enabling the generation of adenosine triphosphate by oxidative phosphorylation. Because adenosine triphosphate levels have been observed to be reduced in platelets from FM patients and FM has been related with alterations of the hypothalamic-pituitary-adrenal (HPA) axis, and hormone and neurotransmitter secretion,[7] a possible explanation for our results is that CoQ_{10} may play an essential role in the regulation of bioenergetics status in platelets and in other cells such as neurons of the central nervous system and thus, it may affect serotonin content, transmission, and function. These results may also contribute to explain the antidepressant effect of CoQ_{10} treatment. Our findings also support the hypothesis that CoQ_{10} supplementation can be used as an alternative therapy for controlling depression.

Further analyses involving more patients in doubled-blind placebo-controlled clinical trials are required to confirm these observations. Indeed, our research group is currently working in this direction, based on the conclusions of the exploratory work discussed in this article.

F1

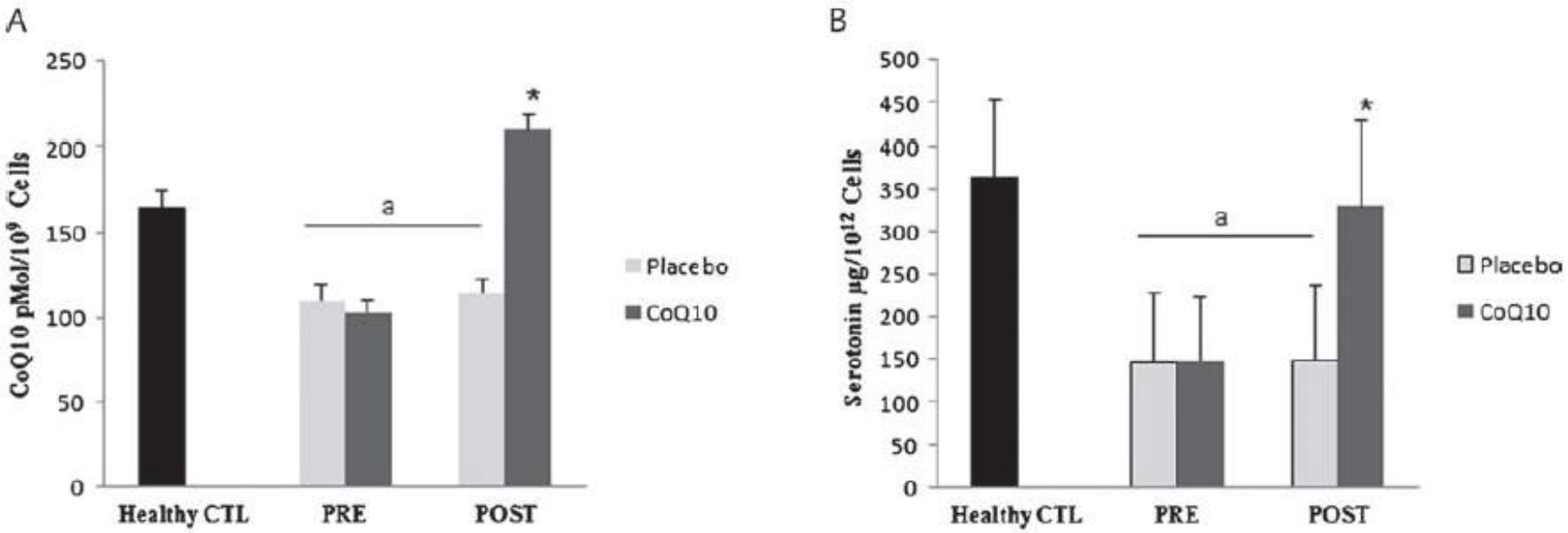
AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

Elísabet Alcocer-Gómez, DSc
Jose Antonio Sánchez-Alcázar, MD, PhD
Centro Andaluz de Biología del Desarrollo
Universidad Pablo de Olavide-CSIC-Junta de Andalucía and Centro de Investigación Biomédica en Red de Enfermedades Raras
ISCIII, Sevilla, Spain
Mario D. Cordero, BSc
Research Laboratory
Dental School, University of Sevilla
Sevilla, Spain
mdcormor@us.es

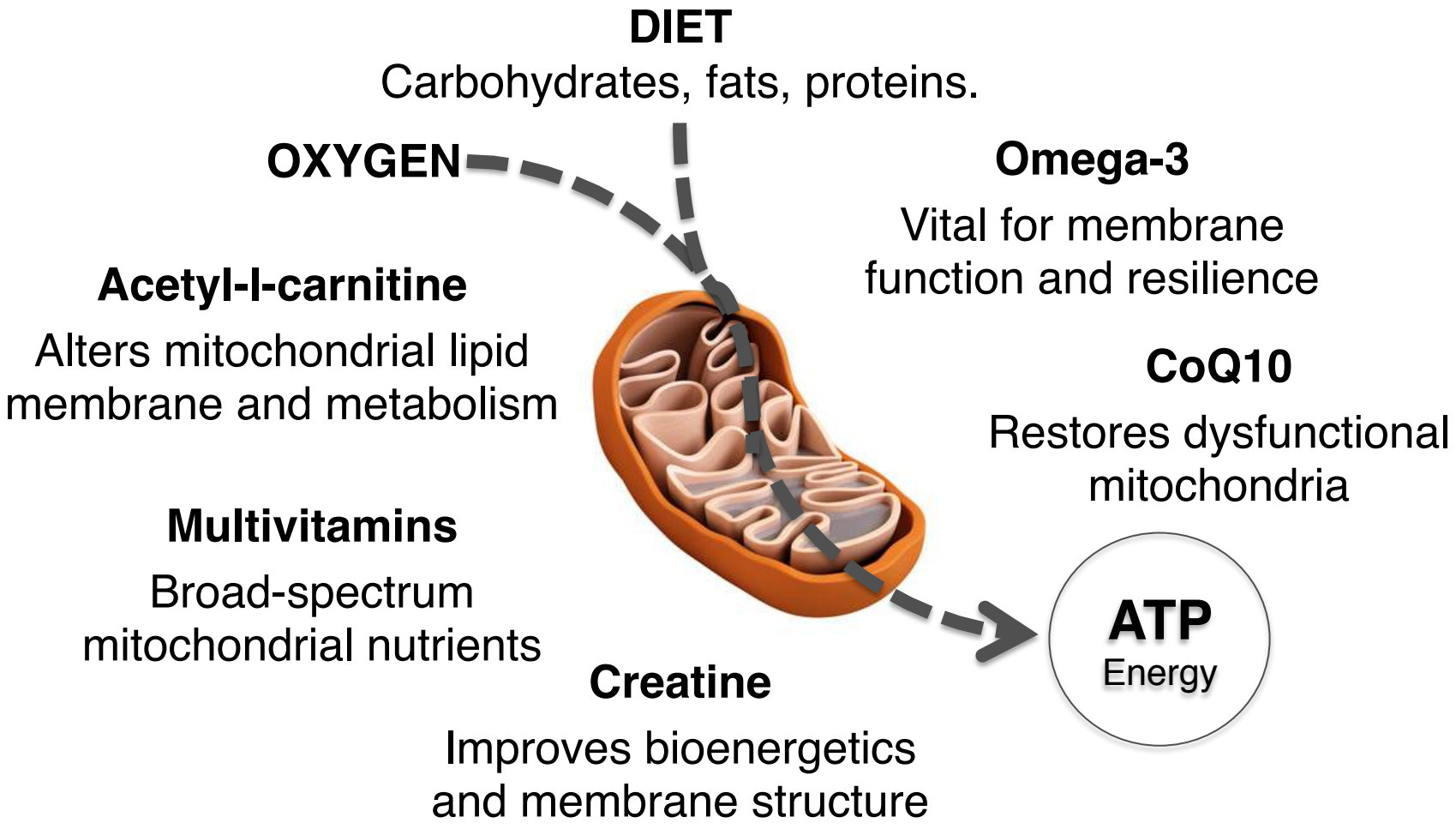
J Clin Psychopharmacol. 2014 Apr;34(2):277-8

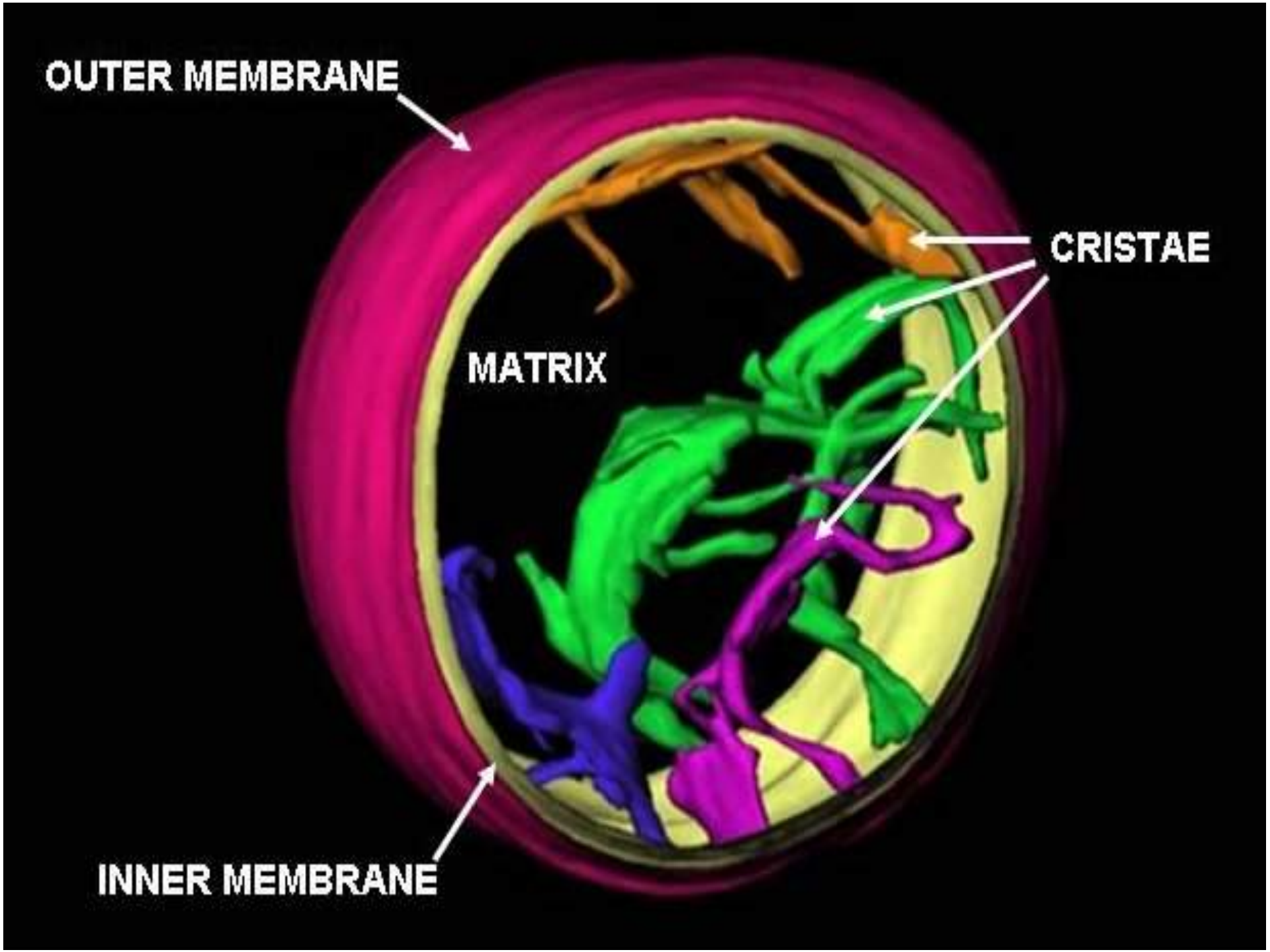
CoQ10 & serotonin



Alcocer-Gómez E, et al. Coenzyme q10 regulates serotonin levels and depressive symptoms in fibromyalgia patients: results of a small clinical trial. J Clin Psychopharmacol. 2014 Apr;34(2):277-8.

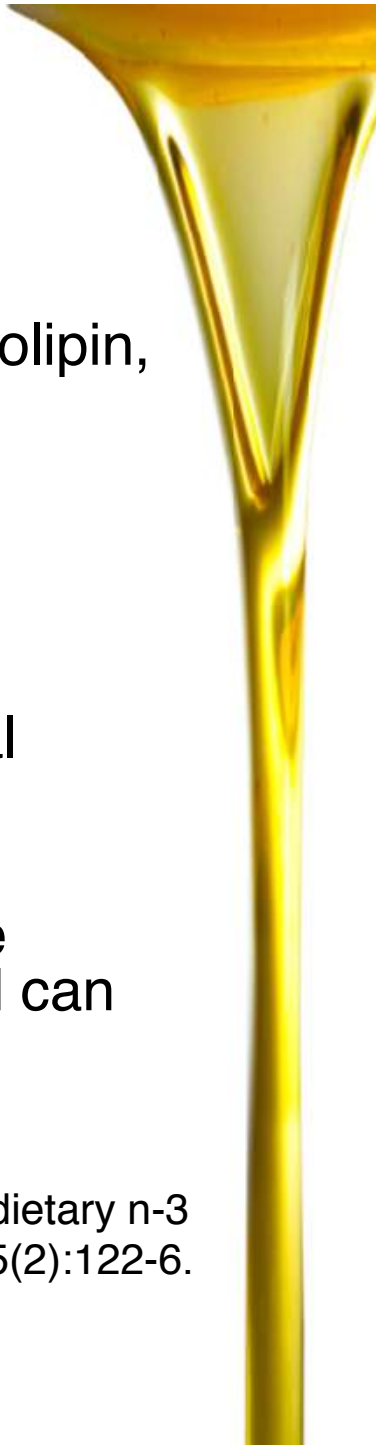
Qi-Nutrition




OUTER MEMBRANE
CRISTAE
MATRIX
INNER MEMBRANE

Cardiolipin

- ✓ Mitochondrial membranes contain high levels of cardiolipin, a tetra-acyl phospholipid
- ✓ Cardiolipin comprises 10–20% of the mass of total mitochondrial phospholipid
- ✓ Depletion of cardiolipin results in severe mitochondrial dysfunction
- ✓ Supplementation with n-3 PUFA increases membrane phospholipid DHA and depletes arachidonic acid, and can increase cardiolipin



Stanley WC, et al. Update on lipids and mitochondrial function: impact of dietary n-3 polyunsaturated fatty acids. Curr Opin Clin Nutr Metab Care. 2012 Mar;15(2):122-6.

Remodeling

Omega-3 supplementation [2 g eicosapentaenoic acid (EPA) and 1 g docosahexanoic acid (DHA) per day] for 12 weeks of leads to a remodeling of the mitochondrial membrane with significant incorporation of omega-3 fatty acids into various phospholipid species and displaces omega-6. Mitochondrial ADP sensitivity and maximal mitochondrial ROS emission were also increased.

J Physiol 592.6 (2014) pp 1341–1352

Omega-3 supplementation alters mitochondrial membrane composition and respiration kinetics in human skeletal muscle

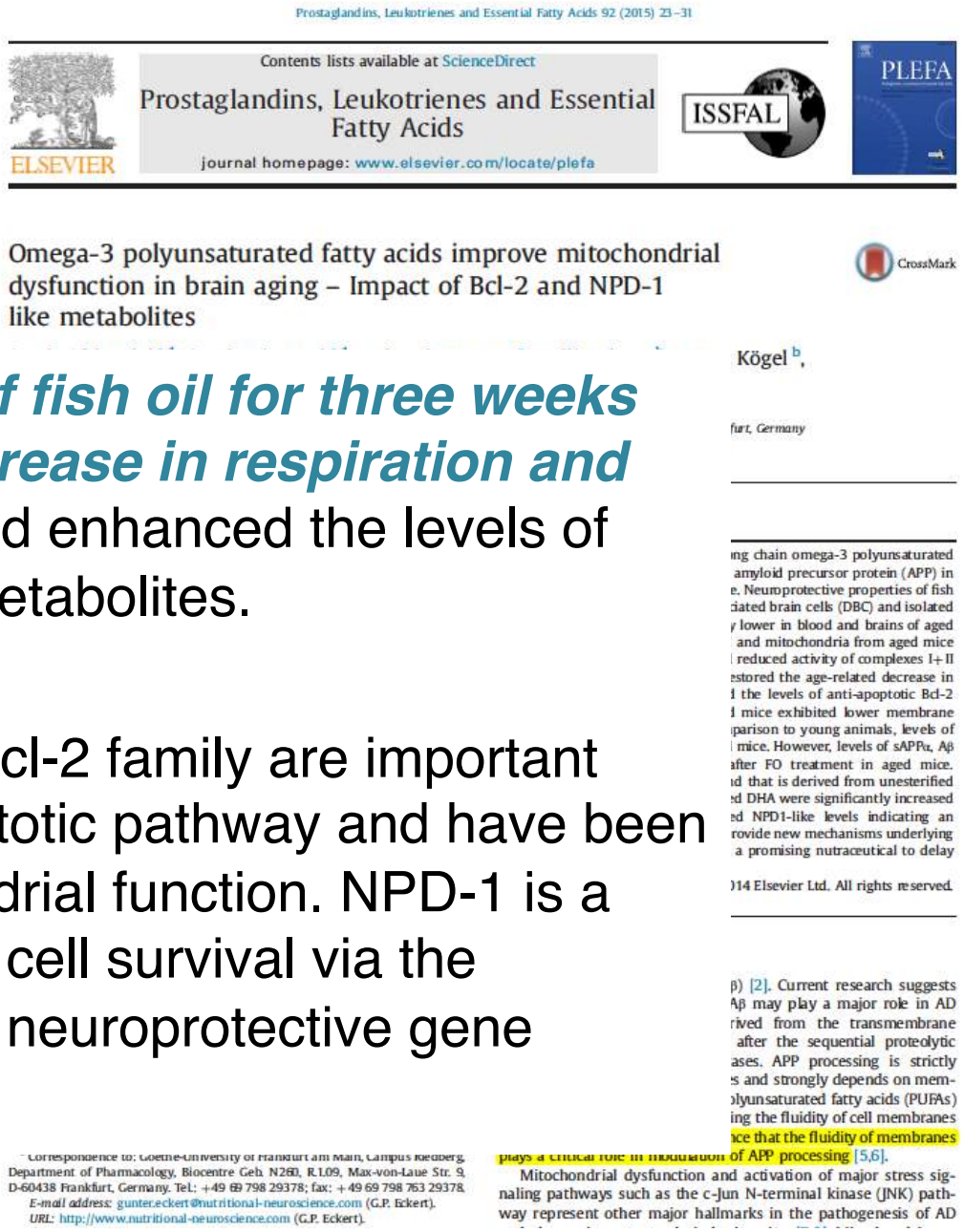
E. A. F. Herbst[1], S. Paglialunga[1], C. Gerling[1], J. Whitfield[1], K. Mukai[1], A. Chabowski[3], G. J. F. Heigenhauser[2], L. L. Spriet[1] and G. P. Holloway[1]

[1]*Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario N1G 2W1, Canada*
[2]*Department of Medicine, McMaster University, Hamilton, Ontario L8N 3Z5, Canada*
[3]*Department of Physiology, Medical University of Bialystok, 15–222 Bialystok, Poland*

Key points

J Physiol. 2014 Mar 15;592(Pt 6):1341-

MemBrain



Prostaglandins, Leukotrienes and Essential Fatty Acids 92 (2015) 23–31

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

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PLEFA

Omega-3 polyunsaturated fatty acids improve mitochondrial dysfunction in brain aging – Impact of Bcl-2 and NPD-1 like metabolites

CrossMark

Kögel [b],

furt, Germany

ng chain omega-3 polyunsaturated
amyloid precursor protein (APP) in
e. Neuroprotective properties of fish
ciated brain cells (DBC) and isolated
lower in blood and brains of aged
and mitochondria from aged mice
reduced activity of complexes I+ II
estored the age-related decrease in
the levels of anti-apoptotic Bcl-2
mice exhibited lower membrane
parison to young animals, levels of
mice. However, levels of sAPPα, Aβ
after FO treatment in aged mice.
d that is derived from unesterified
d DHA were significantly increased
d NPD1-like levels indicating an
rovide new mechanisms underlying
a promising nutraceutical to delay

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β) [2]. Current research suggests
Aβ may play a major role in AD
rived from the transmembrane
after the sequential proteolytic
ases. APP processing is strictly
s and strongly depends on mem-
olyunsaturated fatty acids (PUFAs)
ing the fluidity of cell membranes
ce that the fluidity of membranes
plays a critical role in modulation of APP processing [5,6].
Mitochondrial dysfunction and activation of major stress signaling pathways such as the c-Jun N-terminal kinase (JNK) pathway represent other major hallmarks in the pathogenesis of AD

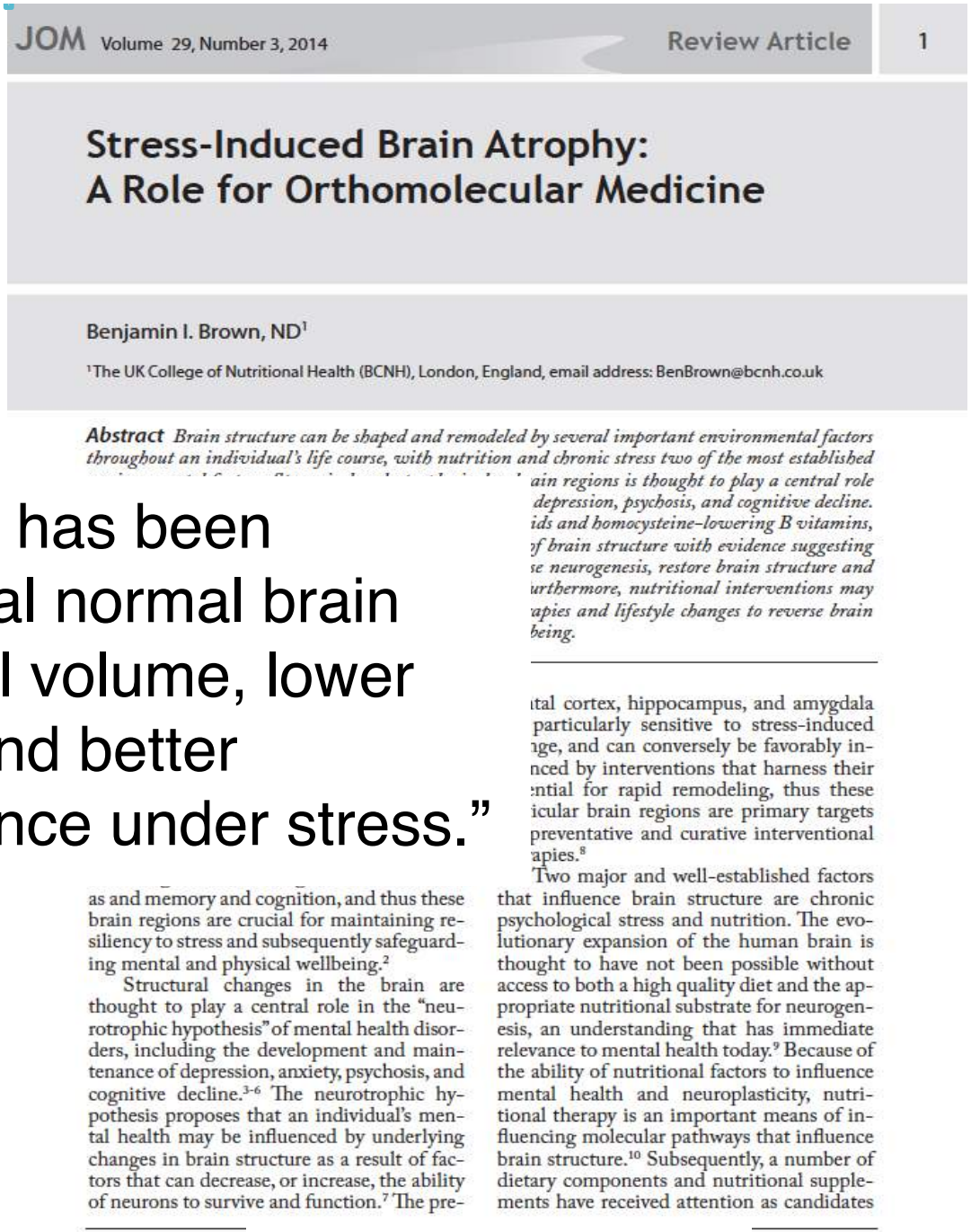
Correspondence to: Goethe-University of Frankfurt am Main, Campus Riedberg, Department of Pharmacology, Biocentre Geb. N260, R.1.09, Max-von-Laue Str. 9, D-60438 Frankfurt, Germany. Tel.: +49 69 798 29378; fax: +49 69 798 763 29378.
E-mail address: gunter.eckert@nutritional-neuroscience.com (G.P. Eckert).
URL: http://www.nutritional-neuroscience.com (G.P. Eckert).

Sub-chronic ***administration of fish oil for three weeks restored the age-related decrease in respiration and improved ATP production*** and enhanced the levels of Bcl-2 protein and NPD-1like metabolites.

Mitochondrial proteins of the Bcl-2 family are important regulators of the intrinsic apoptotic pathway and have been directly implicated in mitochondrial function. NPD-1 is a DHA metabolite that promotes cell survival via the induction of anti-apoptotic and neuroprotective gene expression.

Prostaglandins Leukot Essent Fatty Acids. 2015 Jan;92:23-31.

Omega-3 index



JOM Volume 29, Number 3, 2014 Review Article 1

Stress-Induced Brain Atrophy: A Role for Orthomolecular Medicine

Benjamin I. Brown, ND[1]

[1]The UK College of Nutritional Health (BCNH), London, England, email address: BenBrown@bcnh.co.uk

Abstract *Brain structure can be shaped and remodeled by several important environmental factors throughout an individual's life course, with nutrition and chronic stress two of the most established*

ain regions is thought to play a central role depression, psychosis, and cognitive decline. ids and homocysteine–lowering B vitamins, of brain structure with evidence suggesting se neurogenesis, restore brain structure and urthermore, nutritional interventions may apies and lifestyle changes to reverse brain being.

ital cortex, hippocampus, and amygdala particularly sensitive to stress-induced age, and can conversely be favorably inanced by interventions that harness their ential for rapid remodeling, thus these icular brain regions are primary targets preventative and curative interventional apies.[8]

as and memory and cognition, and thus these brain regions are crucial for maintaining resiliency to stress and subsequently safeguarding mental and physical wellbeing.[2]

Structural changes in the brain are thought to play a central role in the "neurotrophic hypothesis" of mental health disorders, including the development and maintenance of depression, anxiety, psychosis, and cognitive decline.[3-6] The neurotrophic hypothesis proposes that an individual's mental health may be influenced by underlying changes in brain structure as a result of factors that can decrease, or increase, the ability of neurons to survive and function.[7] The pre-

Two major and well-established factors that influence brain structure are chronic psychological stress and nutrition. The evolutionary expansion of the human brain is thought to have not been possible without access to both a high quality diet and the appropriate nutritional substrate for neurogenesis, an understanding that has immediate relevance to mental health today.[9] Because of the ability of nutritional factors to influence mental health and neuroplasticity, nutritional therapy is an important means of influencing molecular pathways that influence brain structure.[10] Subsequently, a number of dietary components and nutritional supplements have received attention as candidates

JOM, 2014; 29(3): 115-122

"A higher omega-3 index has been correlated with larger total normal brain volume and hippocampal volume, lower depressive symptoms, and better neurocognitive performance under stress."

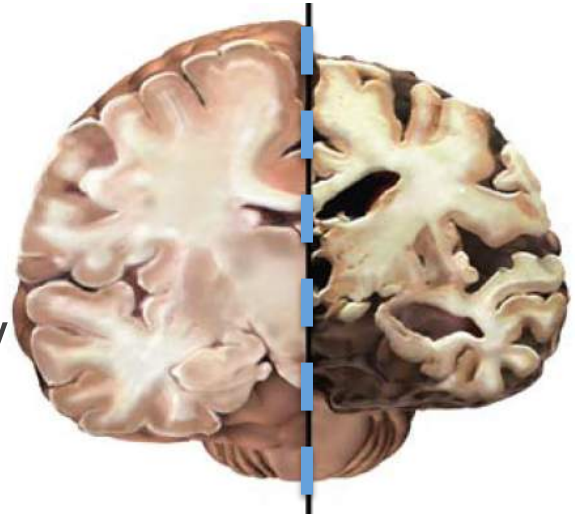
Brain Food: Diet and Mental Health

Natural Diet:
Phytonutrient Dense, Caloric Shortage

- Neuroprotection
- Neurogenesis
- Synaptic Plasticity

Cognition/ Mood/ Behavior:

- Optimism
- Cognitive Resilience
- Enthusiasm
- Vigor and Energy



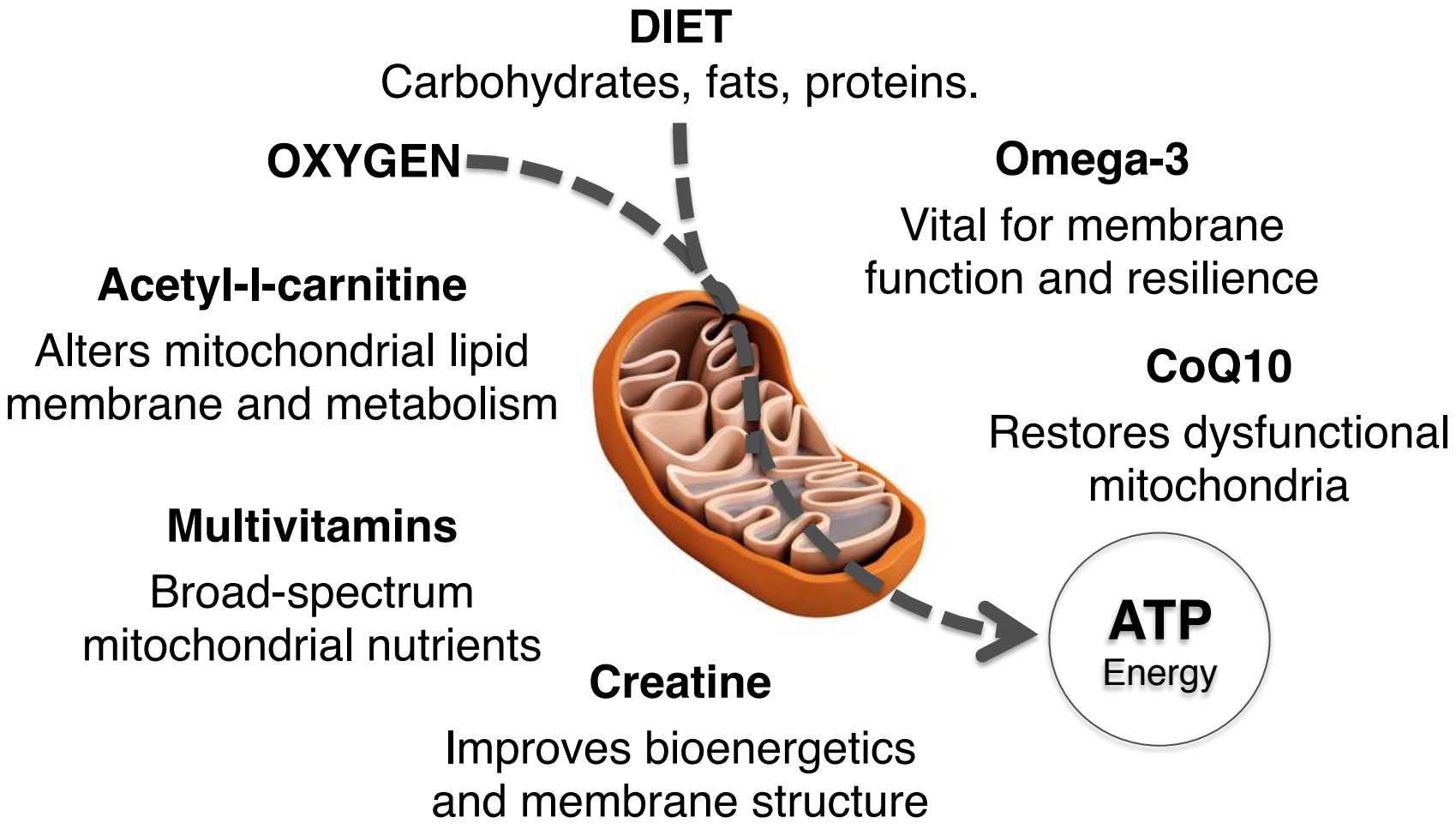
Modern Diet:
Phytonutrient Poor, Caloric Excess

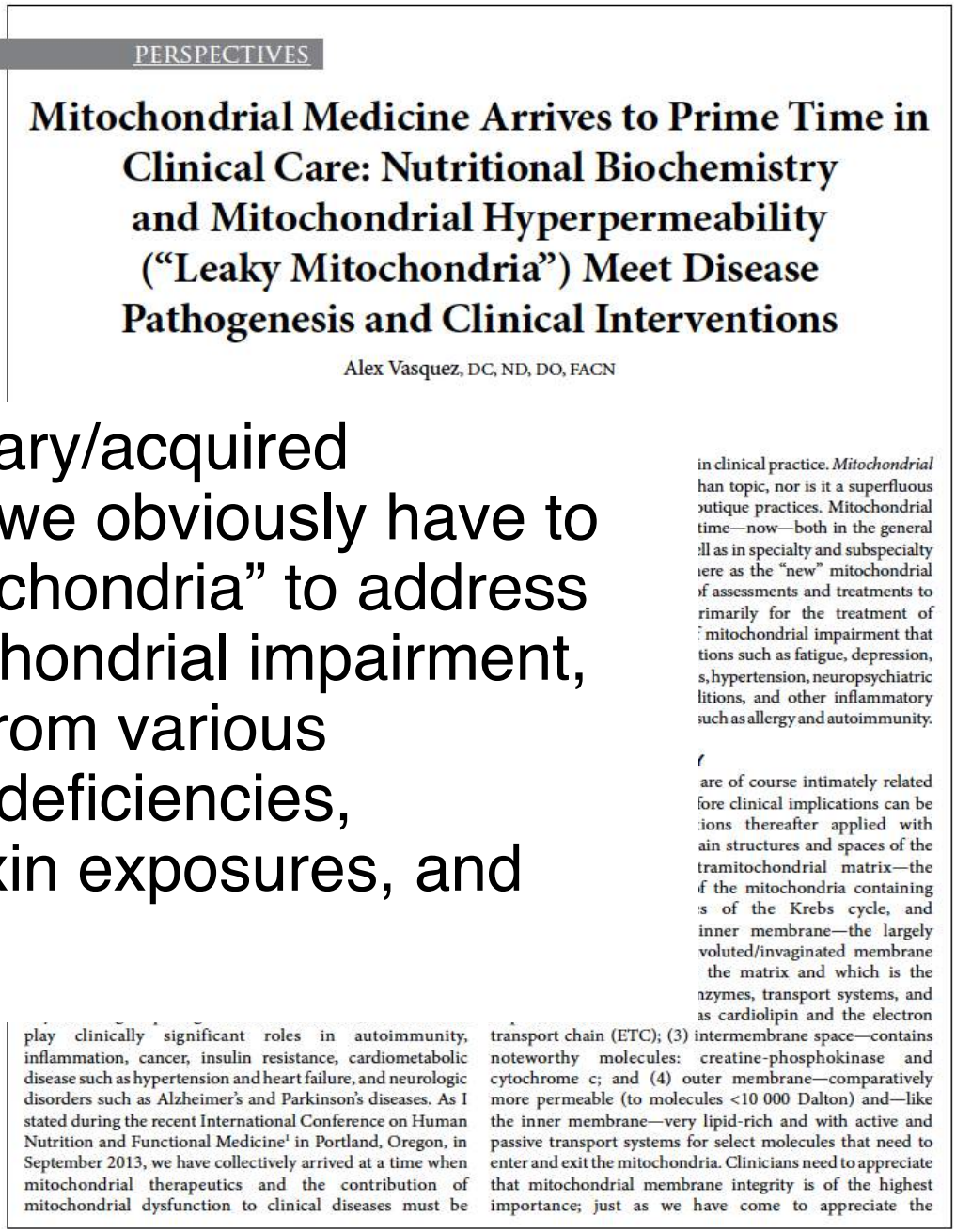
- Cell Damage
- Cell Death
- Impaired Plasticity

Cognition/ Mood/ Behavior:

- Depression
- Cognitive Decline
- Hostility
- Fatigue and Malaise

Qi-Nutrition





PERSPECTIVES

Mitochondrial Medicine Arrives to Prime Time in Clinical Care: Nutritional Biochemistry and Mitochondrial Hyperpermeability ("Leaky Mitochondria") Meet Disease Pathogenesis and Clinical Interventions

Alex Vasquez, DC, ND, DO, FACN

in clinical practice. *Mitochondrial*
han topic, nor is it a superfluous
outique practices. Mitochondrial
time—now—both in the general
ll as in specialty and subspecialty
ere as the "new" mitochondrial
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rimarily for the treatment of
mitochondrial impairment that
tions such as fatigue, depression,
s, hypertension, neuropsychiatric
litions, and other inflammatory
such as allergy and autoimmunity.

are of course intimately related
fore clinical implications can be
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ain structures and spaces of the
tramitochondrial matrix—the
f the mitochondria containing
s of the Krebs cycle, and
inner membrane—the largely
voluted/invaginated membrane
the matrix and which is the
nzymes, transport systems, and
as cardiolipin and the electron

play clinically significant roles in autoimmunity, inflammation, cancer, insulin resistance, cardiometabolic disease such as hypertension and heart failure, and neurologic disorders such as Alzheimer's and Parkinson's diseases. As I stated during the recent International Conference on Human Nutrition and Functional Medicine[1] in Portland, Oregon, in September 2013, we have collectively arrived at a time when mitochondrial therapeutics and the contribution of mitochondrial dysfunction to clinical diseases must be

transport chain (ETC); (3) intermembrane space—contains noteworthy molecules: creatine-phosphokinase and cytochrome c; and (4) outer membrane—comparatively more permeable (to molecules <10 000 Dalton) and—like the inner membrane—very lipid-rich and with active and passive transport systems for select molecules that need to enter and exit the mitochondria. Clinicians need to appreciate that mitochondrial membrane integrity is of the highest importance; just as we have come to appreciate the

"…when treating secondary/acquired mitochondrial disorders, we obviously have to "think outside of the mitochondria" to address the cause(s) of the mitochondrial impairment, most commonly arising from various combinations of nutrient deficiencies, carbohydrate excess, toxin exposures, and microbial colonizations."

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