Today's Presenter

Dr. Chris D. Meletis, ND

Dr. Chris Meletis is an educator, international author and lecturer. His personal mission is "Changing America's Health One Person at a Time." Dr. Meletis has authored 17 books and over 200 national scientific articles in journals including Natural Health, Alternative and Complementary Therapies, Townsend Letter for Doctors and Patients, Life Extension and Natural Pharmacy.

Dr. Meletis served as Dean of Naturopathic Medicine and Chief Medical Officer for 7 years for the National College of Naturopathic Medicine (now the National University of Natural Medicine). He was awarded the 2003 Physician of the Year by the American Association of Naturopathic Physicians. He has a deep passion for helping the underprivileged and spearheaded the creation of 16 free natural medicine healthcare clinics in the Portland metropolitan area of Oregon.

Family and Everyone Wellness

Dr. Chris D. Meletis
Naturopathic Physician

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Symptoms of Anxiety or Depressive Disorder and Use of Mental Health Care Among Adults During the COVID-19 Pandemic — United States, August 2020–February 2021

Weekly / April 2, 2021 / 70(13);490–494

On March 26, 2021, this report was posted online as an MMWR *Early Release.*

Anjel Vahratian, PhD[1]; Stephen J. Blumberg, PhD[1]; Emily P. Terlizzi, MPH[1]; Jeannine S. Schiller, MPH[1] (View author affiliations)

View suggested citation

Discussion

The percentage of adults who had symptoms of an anxiety or a depressive disorder during the past 7 days and those with unmet mental health needs during the past 4 weeks increased significantly from August 2020 to February 2021, with the largest increases among those aged 18–29 years and those with less than a high school education. During January 20, 2021–February 1, 2021, more than two in five adults aged ≥18 years experienced symptoms of an anxiety or a depressive disorder during the past 7 days. One in four adults who experienced these symptoms reported that they needed but did not receive counseling or therapy for their mental health.

These findings are consistent with results from surveys conducted early in the COVID-19 pandemic (March–June 2020) that showed an increased prevalence of mental health symptoms, especially among young adults (*5*–*7*). The more recent results indicate an increasing prevalence over time later in 2020, which remained increased in early 2021. The trends in symptoms of an anxiety or a depressive disorder from HPS have been shown to be consistent with trends in the weekly number of reported COVID-19 cases, and it has been theorized that increases in these mental health indicators correspond with pandemic trends (*8*).

VITALLEO HEALTH

Susceptibility 2018 and the Peer-Review Literature

AMERICAN SOCIETY FOR MICROBIOLOGY | Infection and Immunity®

What Is a Host? Attri

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Medical Center, Bronx, New York, USA

ABSTRACT In every epidemic some ind
whereas others recover from illness and
of disease. These differences highlight a
genesis: why are some individuals susce
who acquire the same microbe remain we
assumed the hand of providence. With t
the focus on disease causality became t
there can be different outcomes of infect
microbe. Here we examine the attribute
"damage-response framework" of microbi
that, although not independent, are suffic
microbiome, inoculum, sex, temperature,
nity, nutrition, and genetics. We use the f
MISTEACHING, underscoring the need for
ing disease causality to any single factor.
ations in the attributes that assemble into
combinations that can in turn translate in
counters. Combinatorial diversity among
natures" of susceptibility possible. How
and propensity to change, there may sti
regard to individual host-microbe intera
may be possible.

KEYWORDS host resistance, pathogenesis,

In a series of essays spanning almost 2
virulence and pathogenicity in the conte
damage-response framework (DRF). The f
Immunity in 1999 (1), and the concept wa
(2–5). The DRF is based on three assumptio
(i) there are two entities, a host and a micro
states of commensalism, colonization, and
damage that the host incurs, and this car
mensalism (e.g., due to presence of norm
homeostasis and results in disease; and
response, the microbe, or both (5). Althou
microbial pathogenesis course at the Albe
developed originally to explain the great d
to be highly flexible and able to account
microbe interaction, commensalism, colon

Februarv 2018 Volume 86 Issue 2 e00636-17

Clinical Infectious Diseases

MAJOR ARTICLE

Reduced Vitamin K Status a
Factor of Severe Coronaviru

Anton S. M. Dofferhoff,[1,a] Ianthe Piscaer,[2,a] Leon J. Schurgers,[3,a] Margot
Tilman M. Hackeng,[3] Henny van Daal,[5] Petra Lux,[3] Cecile Maassen,[3] Est
Loes E. M. Kistemaker,[9] Jona Walk,[1,b,©] and Rob Janssen[4,b]

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Health, Vienna, Austria, and [9]Aquilo BV, Groningen, The Netherlands

Background. Respiratory failure and thromboembolism
infected patients. Vitamin K activates both hepatic coagulat
quired for thrombosis prevention. In times of vitamin K insu
extrahepatic proteins. Vitamin K also activates matrix Gla p
fiber damage. We hypothesized that vitamin K may be implic
thromboembolic disease.

Methods. A total of 135 hospitalized COVID-19 patien
pendent MGP (desphospho-uncarboxylated [dp-uc] MGP)
extrahepatic and hepatic vitamin K status, respectively. Desr
Arterial calcification severity was assessed using computed to

Results. dp-ucMGP was elevated in COVID-19 patients
patients with poor outcomes ($P < .001$). PIVKA-II was nor
($P < .001$) and with coronary artery ($P = .002$) and thoracic a

Conclusions. dp-ucMGP was severely increased in C
which was related to poor outcome; hepatic procoagulant fa
extrahepatic vitamin K depletion leading to accelerated elast
activation of MGP and endothelial protein S, respectively.

Keywords. COVID-19; elastic fibers; factor II; matrix G

Coronavirus disease 2019 (COVID-19) is caused by seve
acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1
The majority of individuals who contract SARS-CoV-2 ha
mild symptoms; however, a significant proportion develop re
piratory failure due to pneumonia [1]. COVID-19 may al
have extrapulmonary manifestations, including coagulopat
and venous thromboembolism, which are associated with d
creased survival [2]. The mechanisms that activate coagulatio
in COVID-19 remain incompletely understood.

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online August 27, 2020.
[a]A. S. M. D., I. P., L. J. S., and M. P. J. V. contributed equally to this work.
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OPEN ACCESS

Vitamin D supplem
infections: systema
participant data

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Peter Bergman,[4] Gal Dubno
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Additional material is published online only. To view please visit the journal online.
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http://dx.doi.org/10.1136/bmj.i6583
Accepted: 01 December 2016

ABSTRACT

OBJECTIVES
To assess the overall effect of vit
supplementation on risk of acute
infection, and to identify factors

DESIGN
Systematic review and meta-ana
participant data (IPD) from rando
trials.

DATA SOURCES
Medline, Embase, the Cochrane
Controlled Trials, Web of Science,
the International Standard Rando
Number registry from inception to

ELIGIBILITY CRITERIA FOR STUD
Randomised, double blind, plac
supplementation with vitamin D
duration were eligible for inclusi
approved by a research ethics co
on incidence of acute respirator
collected prospectively and pres
outcome.

RESULTS
25 eligible randomised controlle
participants, aged 0 to 95 years)
were obtained for 10 933 (96.6%
D supplementation reduced the

WHAT IS ALREADY KNOWN ON THIS TOPIC
Randomised controlled trials of vitamin D supplementation fo
acute respiratory tract infection have yielded conflicting result
Individual participant data (IPD) meta-analysis has the potent
that may explain this heterogeneity, but this has not previous

WHAT THIS STUDY ADDS
Meta-analysis of IPD from 10 933 participants in 25 randomise
showed an overall protective effect of vitamin D supplementat
respiratory tract infection (number needed to treat (NNT)=33)
Benefit was greater in those receiving daily or weekly vitamin
bolus doses (NNT=20), and the protective effects against acut
infection in this group were strongest in those with profound v
baseline (NNT=4)
These findings support the introduction of public health meas
fortification to improve vitamin D status, particularly in setting
vitamin D deficiency is common

the bmj | BMJ 2017;356:i6583 | doi:10.1136/bmj.i6583

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Zinc Ionophore Activity of Quercetin a
From Hepa 1-6 Cells to a Liposome M

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Ciara K. O'Sullivan,[*,‡,∥] and Juan B. Fernández-Larrea[*,†]

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ABSTRACT: Labile zinc, a tiny fraction of total intracellular zinc that is
modulates the activity of numerous signaling and metabolic pathways. Die
(QCT) and epigallocatechin-gallate act as antioxidants and as signalin
enzymes that are targeted by polyphenols are dependent on zinc. We hav
cations and hypothesized that these flavonoids might be also acting as
plasma membrane. To prove this hypothesis, herein, we have demonstrat
rapidly increase labile zinc in mouse hepatocarcinoma Hepa 1-6 cells a
confirm that the polyphenols transport zinc cations across the plasma
transporters, QCT, epigallocatechin-gallate, or clioquinol (CQ), alone
dipalmitoylphosphocholine/cholesterol liposomes loaded with membrane
chelators with zinc triggered a rapid increase of FluoZin-3 fluorescence w
action of QCT, epigallocatechin-gallate, and CQ on lipid membrane syste
underlay the raising of labile zinc levels triggered in cells by polyphenol

KEYWORDS: *clioquinol, epigallocatechin-gallate, flavonoids, liposomes, qu*

1. INTRODUCTION

Quercetin (QCT), a water-insoluble flavonoid present in onions, nuts, and many other vegetables, and epigallocatechin-3-gallate (EGCG), a water-soluble flavonoid present in green tea, are among the most consumed and most studied polyphenols present in the human diet.[1] Flavonoids are considered bioactive micronutrients whose regular consumption, either as food components, or as dietary supplements and nutraceuticals,[2] entails benefits for human health, including prevention and amelioration of cancers,[3] diabetes, and cardiovascular[4] and neurodegenerative[5] diseases. Many of the health benefits of flavonoids have historically been ascribed to their antioxidant activity, which they exert directly by scavenging reactive oxygen species (ROS) and by chelating the redox-active transition metals iron and copper, which may act as ROS generators in biological systems.[6] Flavonoids also act as antioxidants indirectly by inhibiting redox-sensitive transcription factors and pro-oxidant enzymes as well as through induction of phase II and antioxidant enzymes.[7] However, it is currently believed that the levels of polyphenols achieved through ingestion are not enough to justify their wide array of biological actions. Beyond their antioxidant actions, flavonoids are also known to act as signaling molecules that, either directly or indirectly, interact with proteins and nucleic acids, thus modulating multiple cell signaling pathways, gene

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nutrients MDPI

Review

COVID-19: Role of Nutrition and Supplementation

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† These authors contributed equally to this work.

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Abstract: At the end of 2019, a new coronavirus (COVID-19) appeared on the world scene, which mainly affects the respiratory system, causing pneumonia and multi-organ failure, and, although it starts with common symptoms such as shortness of breath and fever, in about 2–3% of cases it leads to death. Unfortunately, to date, no specific treatments have been found for the cure of this virus and, therefore, it is advisable to implement all possible strategies in order to prevent infection. In this context, it is important to better define the role of all behaviors, in particular nutrition, in order to establish whether these can both prevent infection and improve the outcome of the disease in patients with COVID-19. In the literature, it is widely shown that states of malnutrition, overweight, and obesity negatively affect the immune system, leading to viral infections, and several studies have shown that nutritional interventions can act as immunostimulators, helping to prevent viral infections. Even if several measures, such as the assumption of a specific diet regimen, the use of dietary supplements, and other similar interventions, are promising for the prevention, management, and recovery of COVID-19 patients, it is important to highlight that strong data from randomized clinical trials are needed to support any such assumption. Considering this particular scenario, we present a literature review addressing several important aspects related to diet and SARS-CoV-2 infection, in order to highlight the importance of diet and supplementation in prevention and management of, as well as recovery from COVID-19.

Keywords: nutrition; COVID-19; dietary supplement; COVID-19 and diet

1. Introduction

Since its appearance at the end of 2019, coronavirus disease 2019 (COVID-19) has immediately shown a high rate of transmission, forcing the World Health Organization (WHO) to declare in March 2020 that this unknown coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), can be characterized as a pandemic [1,2]. In the past twenty years, coronavirus (CoV) infections have raised many concerns for public health. In fact, in 2002, there was the first epidemic due to a coronavirus, originating in China, which was related to a severe acute respiratory syndrome, called SARS-CoV [3]. Subsequently, in 2012, a new viral outbreak with characteristics similar to SARS-CoV was

Nutrients **2021**, *13*, 976. https://doi.org/10.3390/nu13030976 https://www.mdpi.com/journal/nutrients

It is ALL ABOUT Susceptibility 2018 - Revisited

ABSTRACT In every epidemic some individuals become sick and some may die, whereas others recover from illness and still others show no signs or symptoms of disease. These differences highlight a fundamental question of microbial pathogenesis: why are some individuals susceptible to infectious diseases while others who acquire the same microbe remain well? For most of human history, the answer assumed the hand of providence. With the advent of the germ theory of disease, the focus on disease causality became the microbe, but this did not explain how there can be different outcomes of infection in different individuals with the same microbe. Here we examine the attributes of susceptibility in the context of the "damage-response framework" of microbial pathogenesis. We identify 11 attributes that, although not independent, are sufficiently distinct to be considered separately: microbiome, inoculum, sex, temperature, environment, age, chance, history, immunity, nutrition, and genetics. We use the first letter of each to create the mnemonic MISTEACHING, underscoring the need for caution in accepting dogma and attributing disease causality to any single factor. For both populations and individuals, variations in the attributes that assemble into MISTEACHING can create an enormity of combinations that can in turn translate into different outcomes of host-microbe encounters. Combinatorial diversity among the 11 attributes makes identifying "signatures" of susceptibility possible. However, with their inevitable uncertainties and propensity to change, there may still be a low likelihood for prediction with regard to individual host-microbe interactions, although probabilistic prediction may be possible.

Fueling the Mitochondria and Nutritional Status

- It is essential that we fuel the mitochondria for thyroid responsiveness while also supporting the nutrient needs of the HPT axis.
- Critical illnesses lead to one or more nutrient deficits that can lead to both mitochondrial and thyroid dysfunction.
- Performing an OAP Panel with Environmental Pollutant Panel can offer meaningful insights as to where a patient may have arrived at insufficient nutrient status to sustain either the thyroid or mitochondria (likely both).

Organic Acids Profile

Provider: Sample Report
Patient:
Accession #: 2021000068

Sex:
Age: 49
Sample Type:

Collected: 2021-03-17
Received: 2021-03-17
Completed: 2021-03-22

Analyte	Result (µg/mg creatinine)	Reference Range	Population Percentile
Glycolysis			
1. Pyruvate	1.65	< 2.10	83%
2. Lactate	2.93	< 23.10	7%
Citric Acid Cycle			
3. Citrate	150.57	34.30 - 751.30	19%
4. Cis-Aconitate	18.58	< 65.00	9%
5. Isocitrate (L)	25.69	28.00 - 70.00	5%
6. Alpha-Ketoglutarate	11.19	< 26.00	62%
7. Succinate	1.84	< 22.50	12%
8. Fumarate	0.59	< 1.90	67%
9. Malate	0.77	< 4.00	13%
Fatty Acid Oxidation			
10. Adipate (H)	>ULOQ	< 4.40	N/A
11. Suberate (H)	3.87	< 2.80	92%
12. Ethylmalonate	1.52	< 5.50	9%
13. Methylsuccinate	0.69	< 3.10	7%
Markers for Protein Metabolism			
14. Alpha-Ketoisovalerate	0.30	< 0.40	87%
15. Alpha-Ketoisocaproate (H)	0.76	< 0.50	93%
16. Alpha-Keto-Beta-Methylvalerate (H)	2.24	< 2.10	91%
17. Beta-Hydroxyisovalerate	4.22	< 11.20	30%
18. Methylmalonate	0.91	< 1.60	50%
19. Hydroxymethylglutarate	4.03	< 5.90	82%

Reference range updated 6/17/2019. Reference range is not gender adjusted. Reference range is age adjusted for children. Method: LC/MS/MS. LLOQ: Lower limit of quantitation ULOQ: Upper limit of quantitation. Lactate is reported as D- and L-Lactate combined on OAP. This test is not intended to diagnose, treat, cure, or prevent any disease or replace the medical advice and/or treatment obtained from a qualified healthcare practitioner. US BioTek Laboratories has developed and determined the performance characteristic of this test under the Clinical Laboratory Improvement Amendments (CLIA). This test has not been evaluated by the U.S. Food and Drug Administration. This test does not assess for neonatal inborn errors of metabolism and is based on stable renal function and normal renal clearance.

CLIA : 50D0965661 CAP accredited 1 of 3
http://www.usbiotek.com Director: Jillian Harrington, PhD, HCLD (ABB)

16020 Linden Ave North, Shoreline, WA 98133, USA

Not Fade Away: Mechanisms of Neuronal ATP Homeostasis

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The generation of a biochemical map detailing the metabolic pathways responsible for the homeostatic maintenance of cellular ATP represents one of the great scientific achievements of the 20th century. The "metabolic map," which appears far more complex than a diagram of the New York City subway system, details the cellular uptake, conversion, storage, breakdown, and use of carbon sources that provide the raw material for ATP production, the evolutionarily conserved power source for all of cell biology. These discoveries touch upon nearly every aspect of modern medicine, including aging, cancer, cardiac disease, epilepsy, and the myriad effects of diet on human health and wellbeing.

The brain is a primary beneficiary of the complexities of metabolic homeostasis. It is well established that the brain consumes a disproportionate amount of ATP compared to other organs, estimated to be as much as 20% of total ATP consumption (Yellen, 2018). This makes sense. The electrochemical reactions that drive neuronal signaling are energetically expensive. Neurons maintain a hyperpolarized resting membrane potential, ship proteins throughout an expansive cellular architecture, maintain an enormous membrane surface area (plasma membrane and smooth endoplasmic reticulum [ER]), and continually release and recycle synaptic vesicles at each of the trillions of synapses throughout the brain. Recently, there has been an attempt to pinpoint the subcellular processes within a neuron that are the primary sink for ATP, with evidence focusing on synaptic vesicle recycling (Rangaraju et al., 2014; Pathak et al., 2015). Regardless, with more than 80 billion neurons and trillions of synapses, the human brain is an energy hog.

Despite the importance of metabolic signaling for the maintenance of normal brain function, our understanding of how the biochemical metabolic map is instantiated within individual neurons and coupled to their changing energetic demands remains poorly understood. For example, we appreciate that supplying the brain with fuel is a dilemma. It appears that the brain does not rely upon β-oxidation, eliminating the breakdown of fatty acids as a major fuel source (Schönfeld and Reiser, 2017). Furthermore, unlike muscle, the brain does not maintain appreciable stores of fuel in the form of glycogen. Although astrocytes maintain a glycogen reserve, neurons appear to rely primarily on fuel delivered in the form of blood glucose (Yellen, 2018). Indeed, this is the source of the signal used in functional magnetic resonance imaging (blood-oxygen-level-dependent [BOLD] signals) (Yellen, 2018). An increase in neuronal activity is associated with increased blood flow, providing both oxygen and glucose and eliminating CO_2, the byproduct of oxidative phosphorylation.

Essential to Fuel the Billions of Neurons

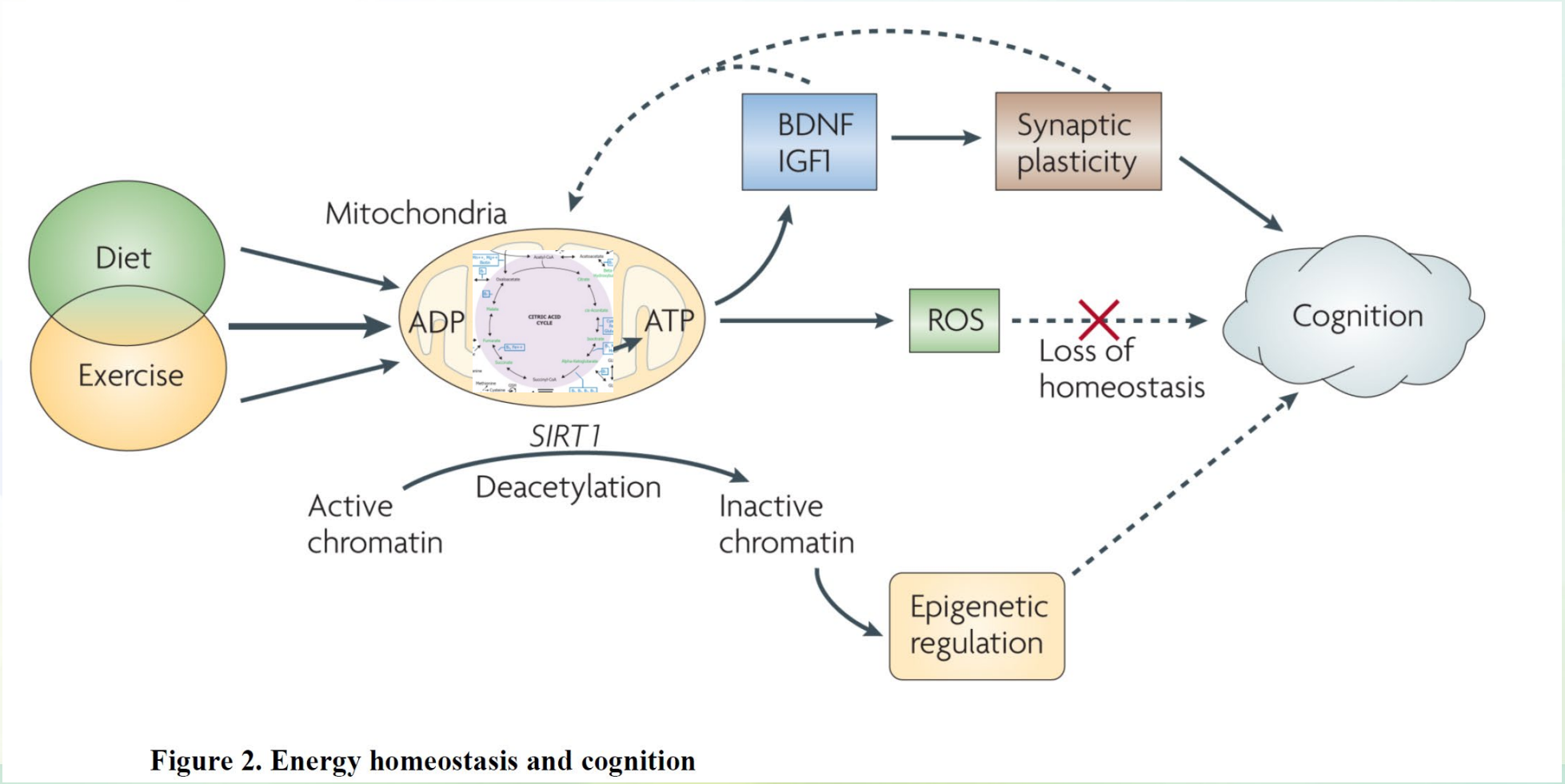
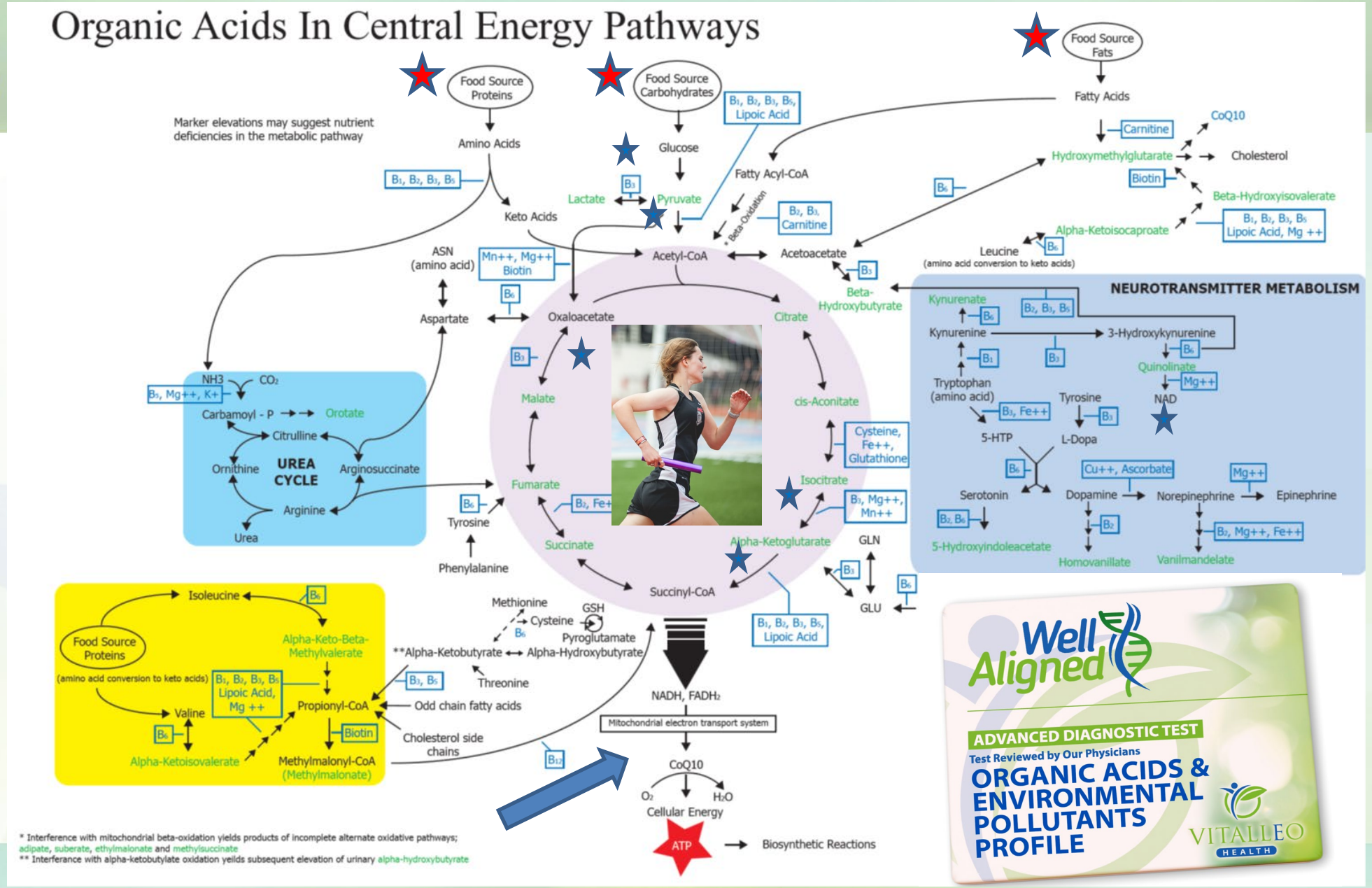
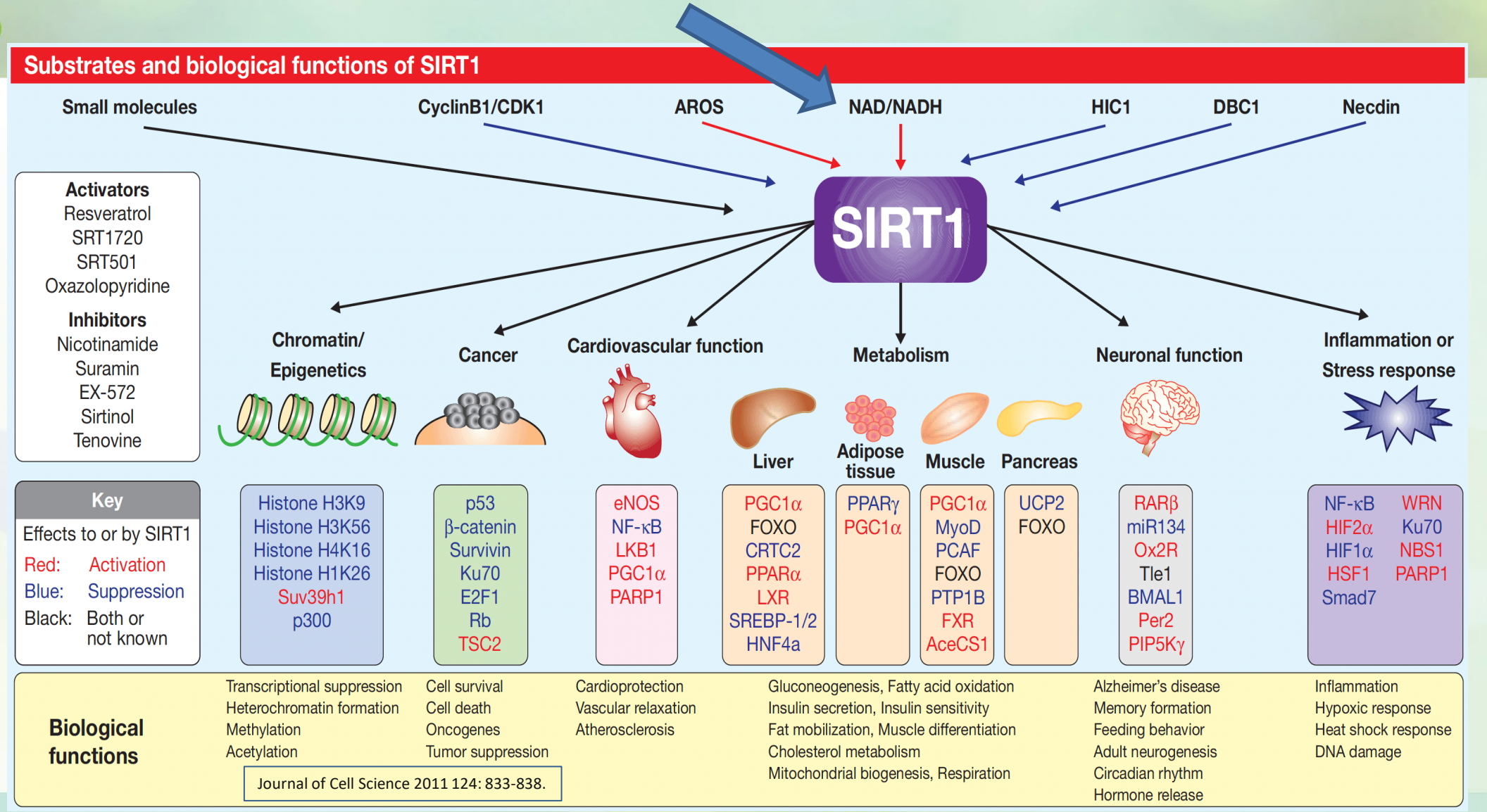


Figure 2. Energy homeostasis and cognition



Which Test is This? Does Well Aligned Offer it?

Substrates and biological functions of SIRT1



Journal of Cell Science 2011 124: 833-838.

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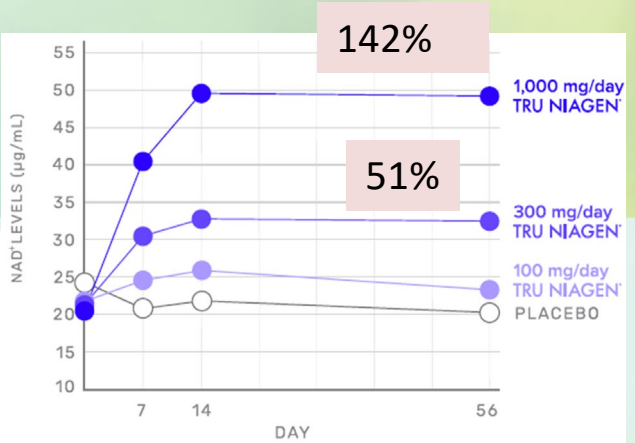


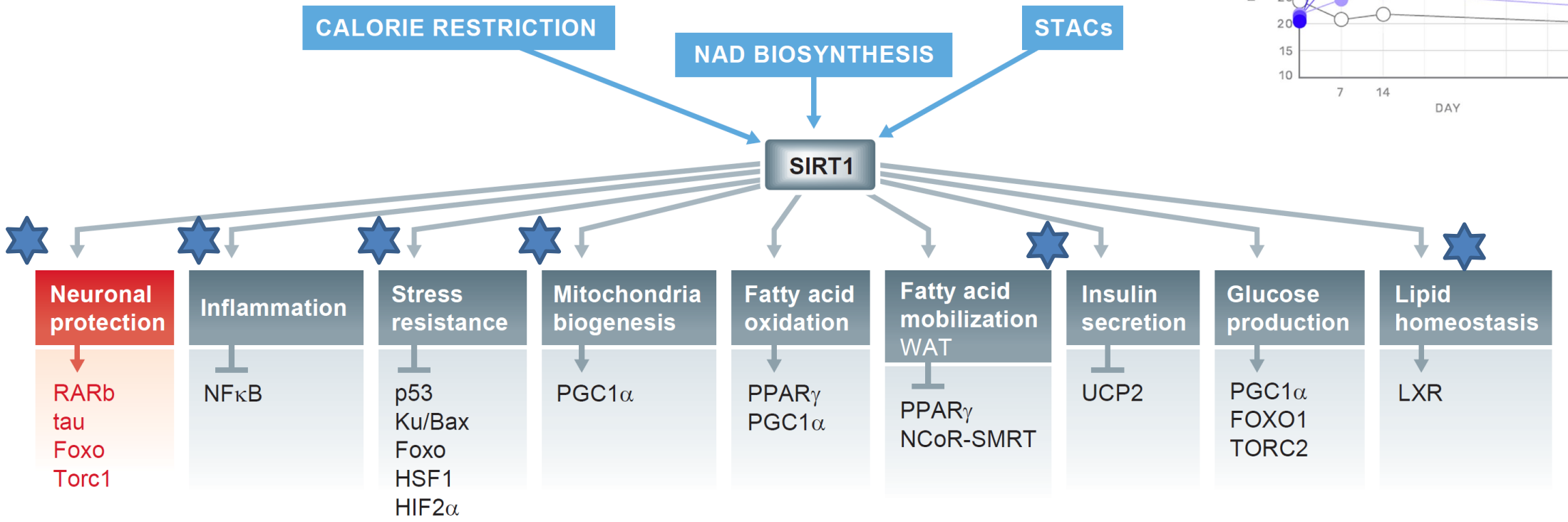


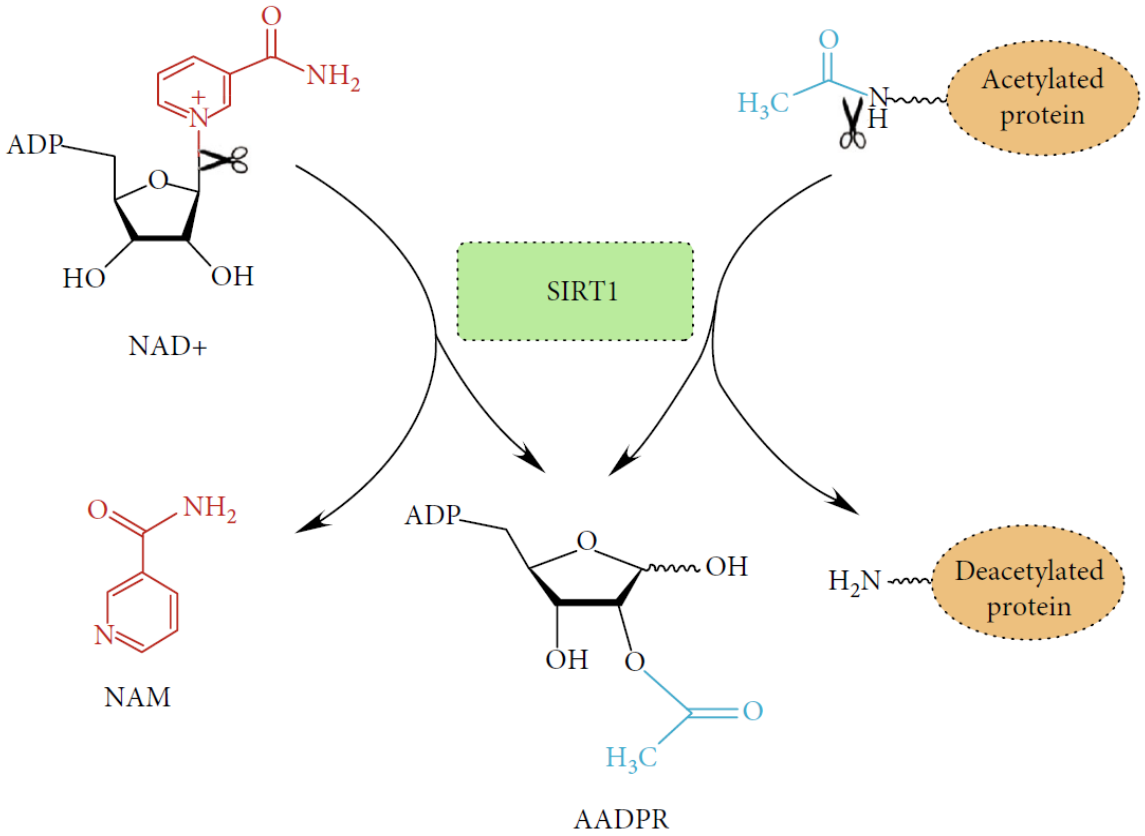
Figure 1. The targets and interacting partners of SIRT1. SIRT1 has many targets that play roles in different molecular pathways including neuronal protection, inflammation, stress resistance, mitochondrial biogenesis, fatty acid oxidation and mobilization, insulin secretion, glucose production and lipid homeostasis. SIRT1 is activated by CR, NAD biosynthesis and small molecule sirtuin activators (STACs).

Well Aligned

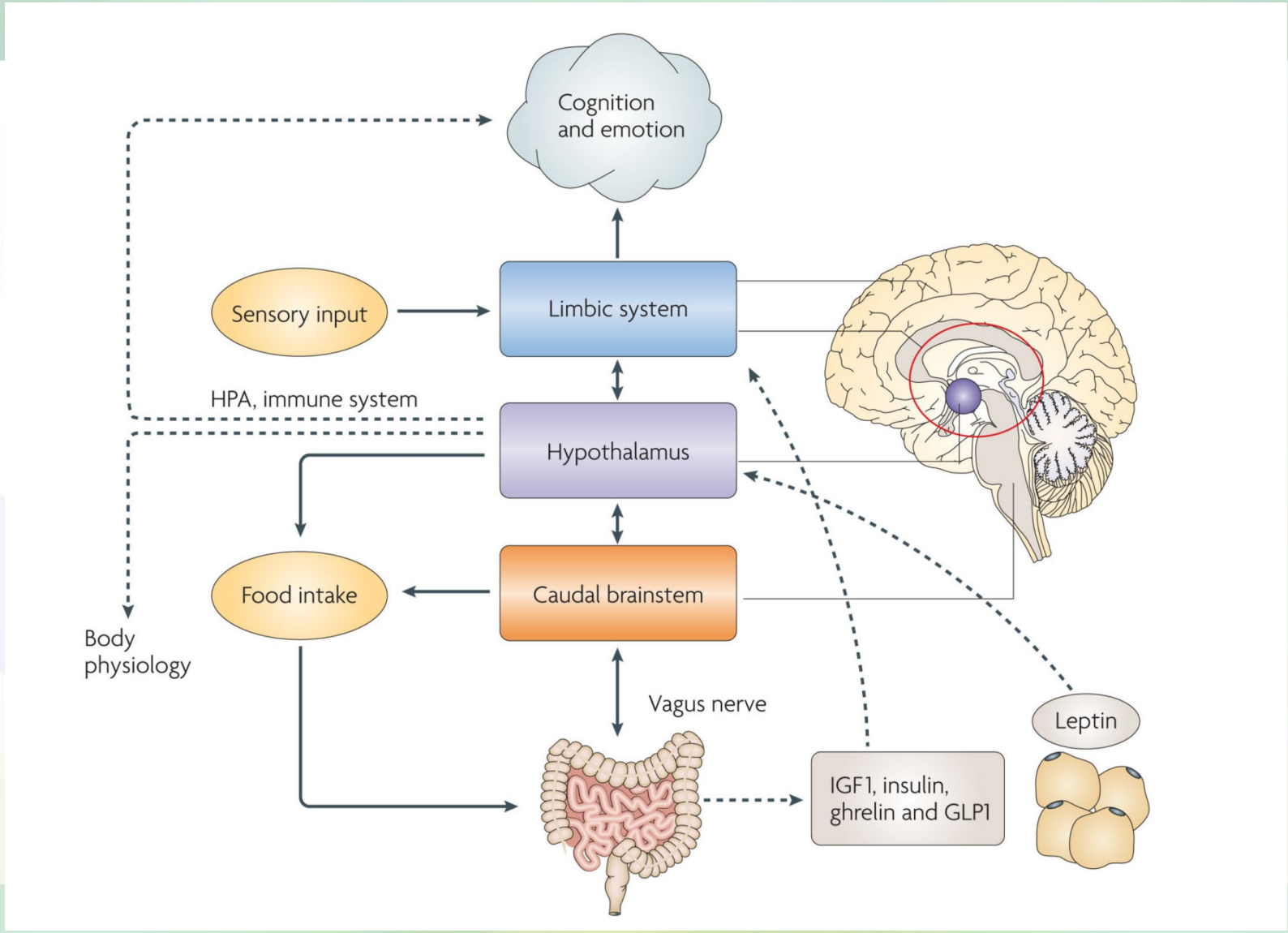
Catalytic Mechanism of SIRT1

3. Catalytic Mechanism of SIRT1

As the histone deacetylases, mammalian sirtuins share a conserved catalytic domain. For human SIRT1, the catalytic core consists of two domains. The larger NAD^+-binding domain composes of a Rossmann fold, and the smaller domain consists of a helical (269–324 residues) and a zinc-binding module (362–419 residues) [32]. On the basis of the three-dimensional crystal structures of a sirtuin protein, the catalytic pocket between large and small domains is frequently divided into three active sites: the site A is involved in binding of the adenine-ribose part of NAD, the site B is involved in binding of the nicotinamide-ribose portion, and the site C is the deep location of the NAD-binding pocket [33]. The molecular mechanism of the deacetylation reaction is complicated. Several studies have reported the possible mechanism of the reaction. Briefly, the catalytic reaction begins with forming the ternary complex, which is mediated by NAD+, and an acetylated substrate both binds to the sirtuin enzyme [34]. In this deacetylation process, the glycosidic bond of NAD+-linking nicotinamide and ADP-ribose moiety is cleaved, and the free nicotinamide is released. Then,



Oxidative Medicine Cell Longevity 2020; (6782872):1-19.



Nat Rev Neursci 2008; 9(7):568-78.

EMBO reports

Depression: a new enzyme AT play

Helena Caria Martins & Gerhard Schratt

Neuronal activity is the main contributor to the high-energy demand of the human brain. ATP is needed for the maintenance of ionic gradients, neurotransmitter transport, and release, as well as the signaling pathways that follow activation of postsynaptic receptors. The inability to maintain a high supply of ATP through tight regulatory mechanisms can, therefore, have severe consequences for brain function. In this issue of *EMBO Reports*, Cui *et al* [1] show that pharmacological inhibition or genetic inactivation of CD39, an ectonucleotide tri(di)phosphohydrolase responsible for converting ATP into AMP, has antidepressant-like effects by maintaining high extracellular ATP levels in the presence of stress.

EMBO Reports (2020) 21: e49921

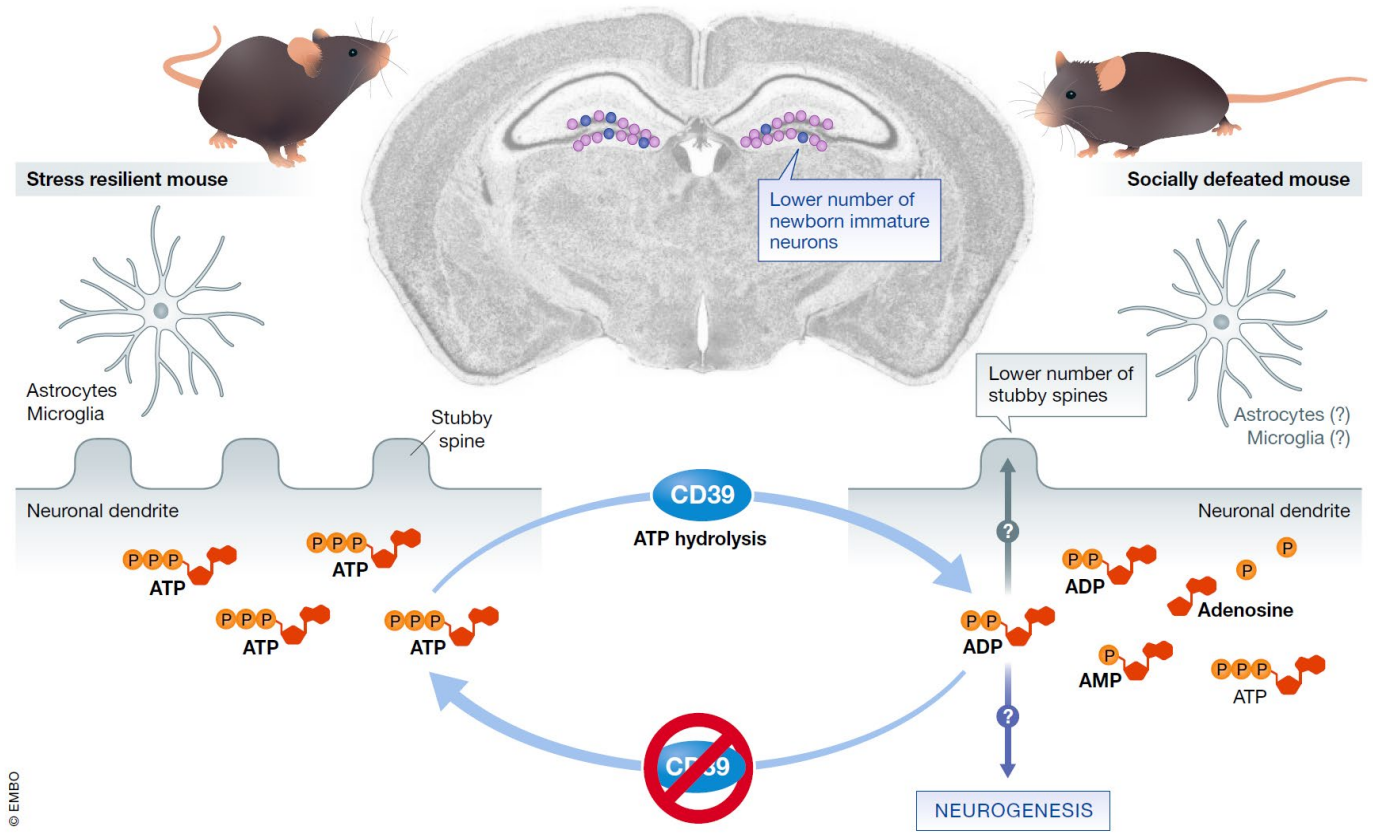
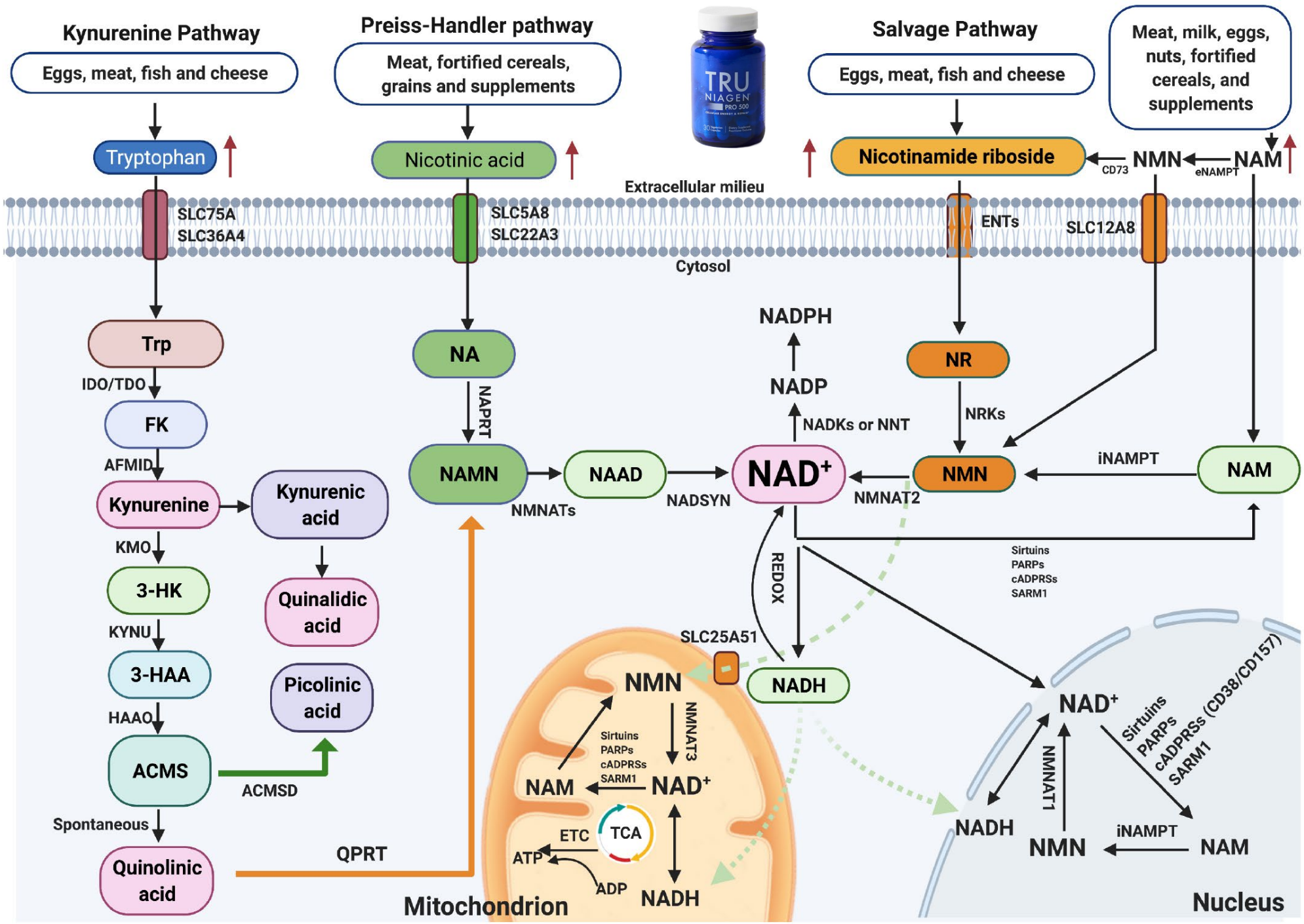
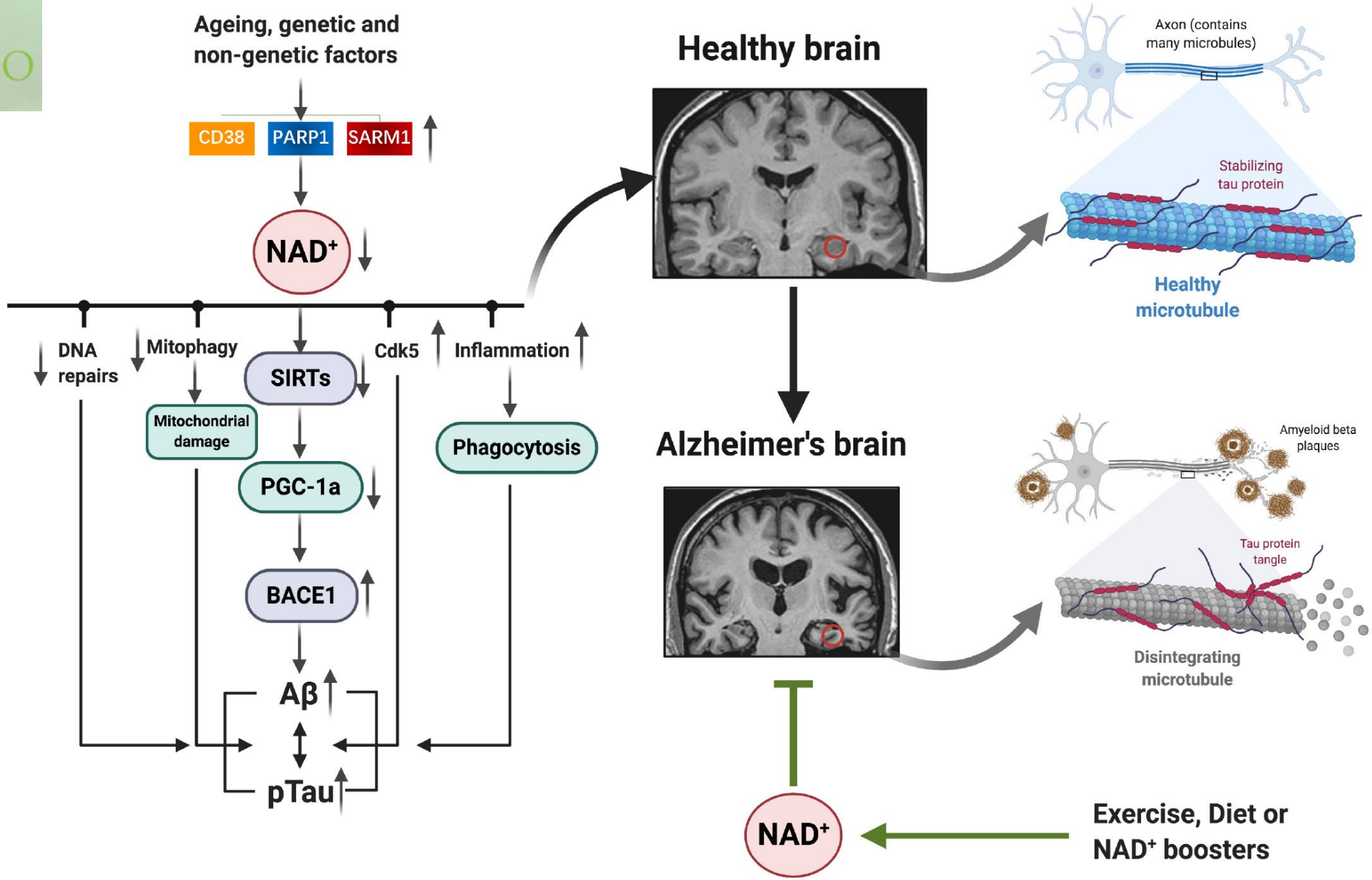


Figure 1. Model of CD39 function in stress coping.

Cui *et al* showed that after chronic social defeat stress, susceptible mice (right) show increased hydrolysis of extracellular ATP by the enzyme CD39 compared with control mice (left). Infusion of a functional analog of CD39 into the hippocampus produced depressive-like behaviors, such as social avoidance, anhedonia, and despair. On the other hand, both inhibition and genetic silencing of CD39 abolished the excessive ATPase activity and restored ATP levels in susceptible mice. Socially defeated mice also showed less newborn immature neurons (light blue, upper panel) and stubby spines (dark blue, lower panel). Suppressing CD39 activity attenuated both of the cellular and behavioral phenotypes.


Kynurenine Pathway
Eggs, meat, fish and cheese
Tryptophan
Trp
IDO/TDO
FK
AFMID
Kynurenine
Kynurenic acid
Quinalidic acid
KMO
3-HK
KYNU
3-HAA
Picolinic acid
HAAO
ACMS
ACMSD
Spontaneous
Quinolinic acid
QPRT
Preiss-Handler pathway
Meat, fortified cereals, grains and supplements
Nicotinic acid
NA
NAPRT
NAMN
NMNATs
NAAD
NADSYN
Salvage Pathway
Eggs, meat, fish and cheese
Meat, milk, eggs, nuts, fortified cereals, and supplements
Nicotinamide riboside
CD73
NMN
eNAMPT
NAM
Extracellular milieu
SLC75A
SLC36A4
SLC5A8
SLC22A3
ENTs
SLC12A8
Cytosol
NADPH
NADP
NADKs or NNT
NR
NRKs
NAD+
NMN
NMNAT2
iNAMPT
NAM
REDOX
Sirtuins
PARPs
cADPRSs
SARM1
SLC25A51
NADH
NMN
NMNAT3
Sirtuins
PARPs
cADPRSs
SARM1
NAM
NAD+
ETC
TCA
ATP
ADP
NADH
Mitochondrion
NAD+
Sirtuins
PARPs
cADPRSs (CD38/CD157)
SARM1
NMNAT1
NADH
NMN
iNAMPT
NAM
Nucleus



Front Cell Dev Biol 2021; 9:668491

Foundational Cellular Wellness Factors

- With decreased energy production, cellular function can become impacted leading to common signs and symptoms of aging; skin changes, slower healing rates, overall resilience, organ function, etc.
- ATP also plays an important role in the synthesis of nucleic acids.
- ATP is most typically in mitochondria by ox-phos under the catalytic influence of ATP synthase.
- Total quantity of stored ATP in the human body is about 0.1 mole.
- Energy used by human cells requires the hydrolysis of 200 to 300 moles of ATP daily.
- **Each ATP molecule is recycled 2000 to 3000 times during a single day.**

https://pubchem.ncbi.nlm.nih.gov/compound/Adenosine-5-triphosphate

The Role NAD+ within our Patients

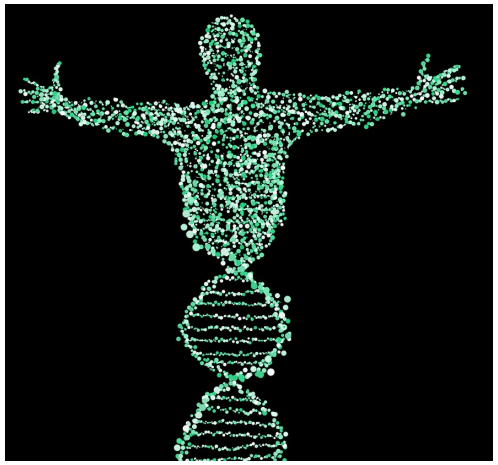
- NAD+ is an essential resource for cellular energy production.
- **NAD+ levels decline between the ages of 40 and 60.**
- Low NAD+ levels contribute to diminished energy needed to maintain health as we age.

Maintains Healthy Mitochondria

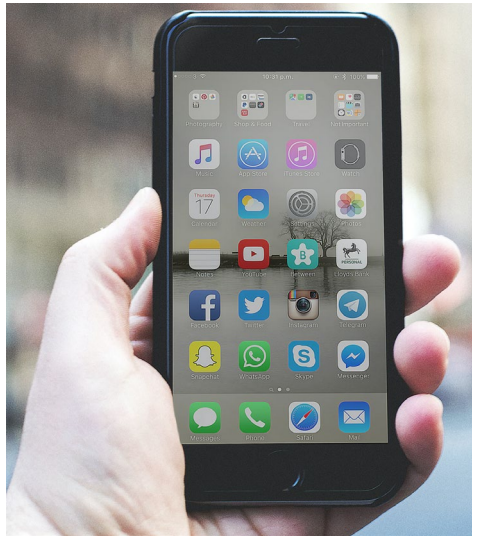
Energizes Your Cells

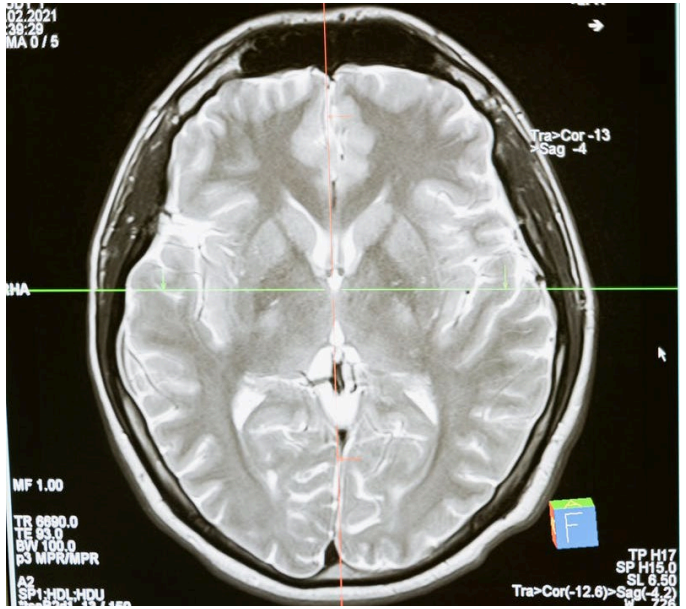
Promotes Cellular Repair

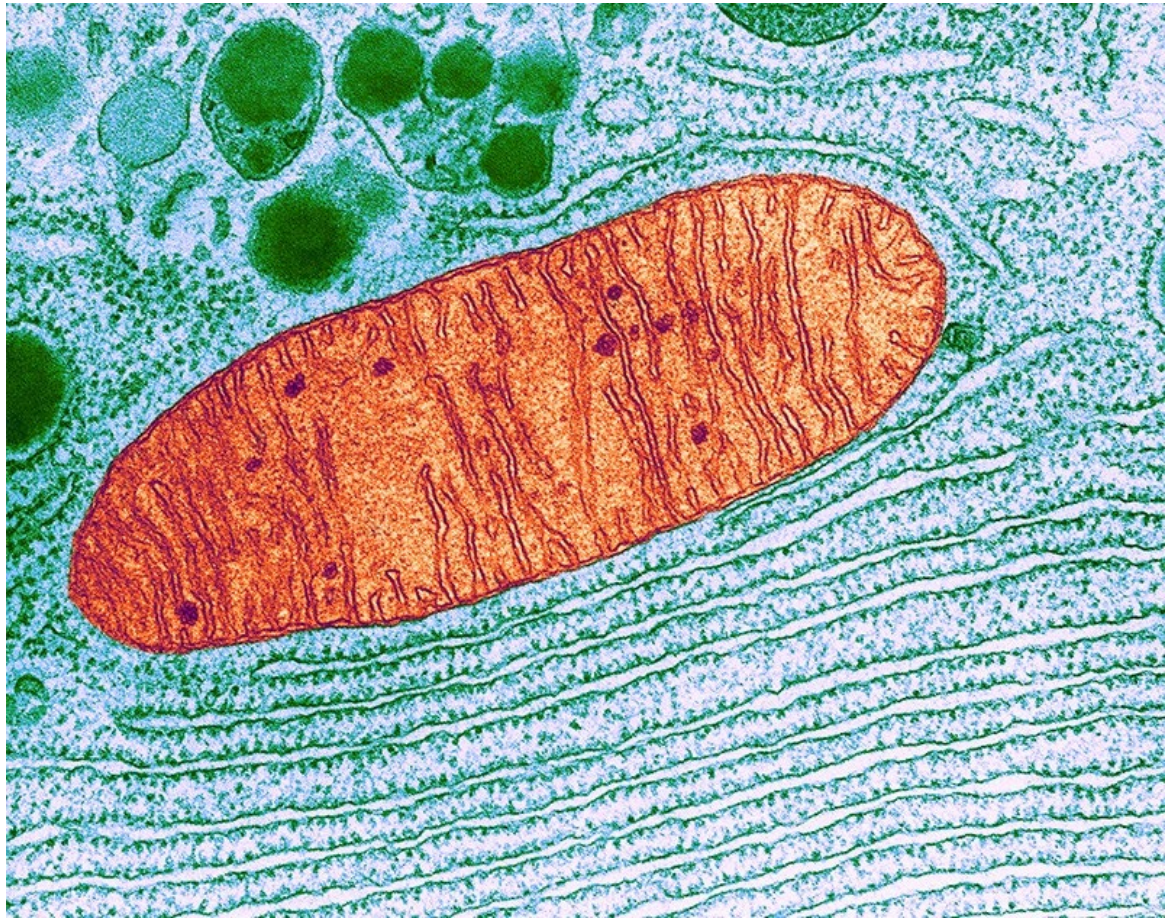
How “Charged Up” are your Patient’s Brain Cells?



If APPs = DNA (software);
Then Battery Charge = ATP



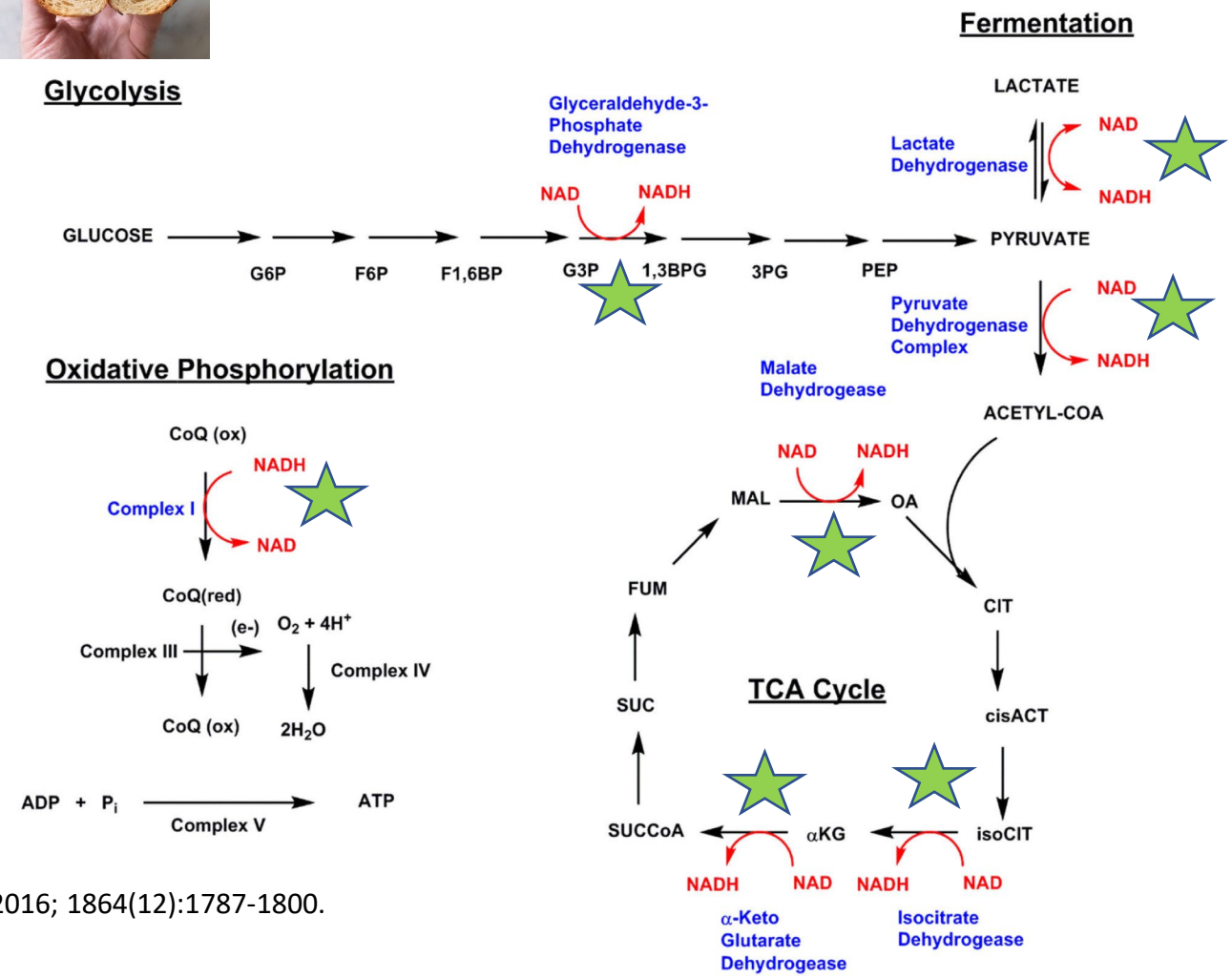




In a cell, a mitochondrion (red) appears near the endoplasmic reticulum, a protein and fat-making organelle (shown in the lower part of the image).Credit: K.R. Porter/SPL (www.Nature.com)

NAD$^+$ – A Critical Energy Cofactor for Brain and Body

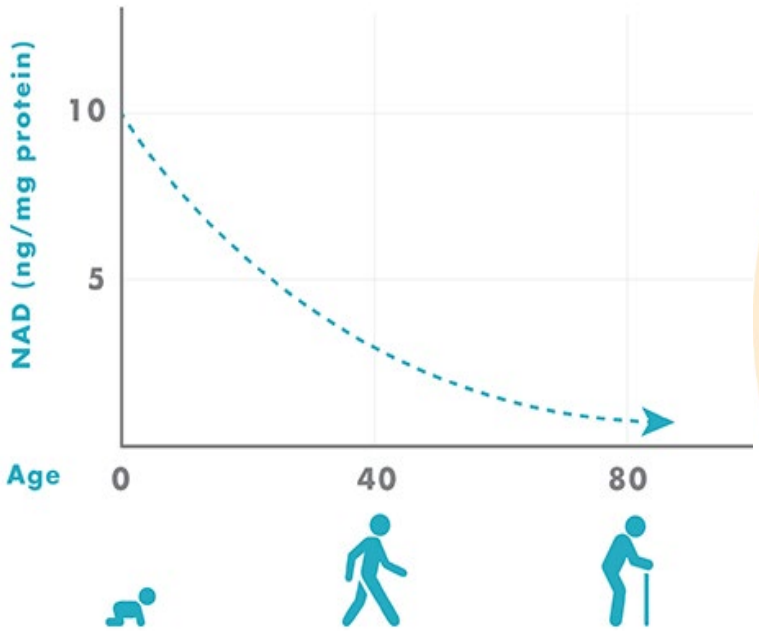
- NAD$^+$ Levels Decrease with Aging
- A Glimpse into one of Several Roles
- NAD$^+$ Confers in Energy Metabolism



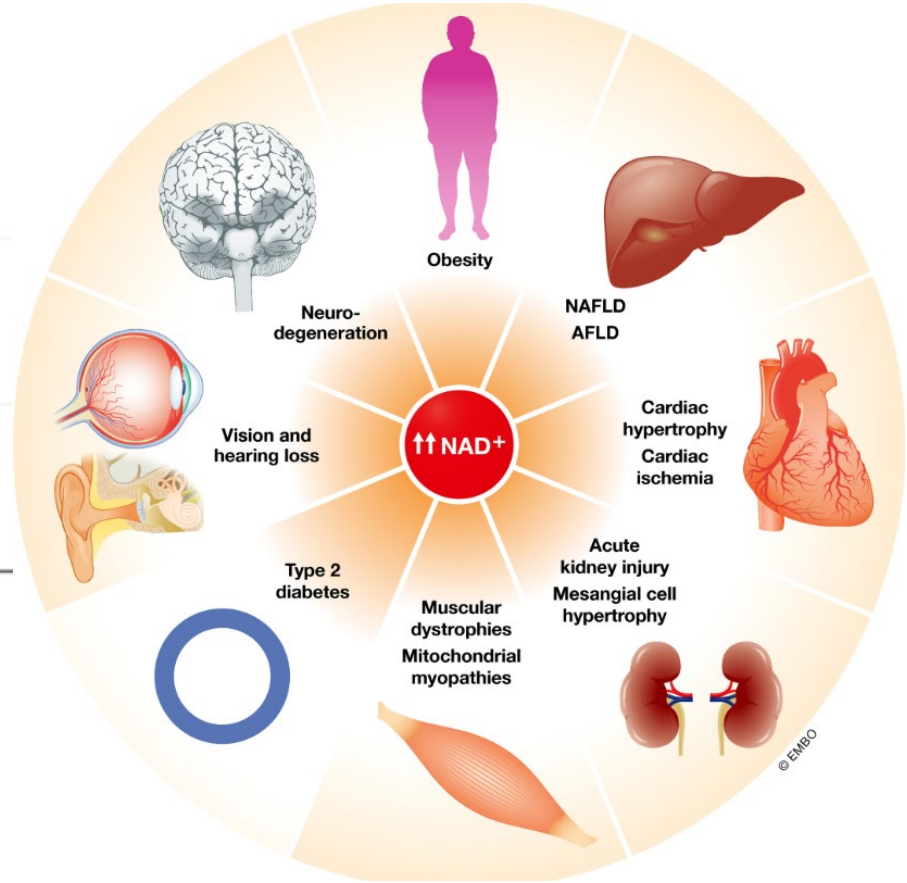
BioChim Biophys Acta. 2016; 1864(12):1787-1800.

Declining NAD+ linked to Aging and Dysfunction

- NAD+ declines with age and exposure to metabolic stressors.
- Declines in NAD+ linked to:
  - Neuro and muscular degeneration
  - Poor cardiometabolic health
  - Decreased capacity for cellular repair and resiliency.

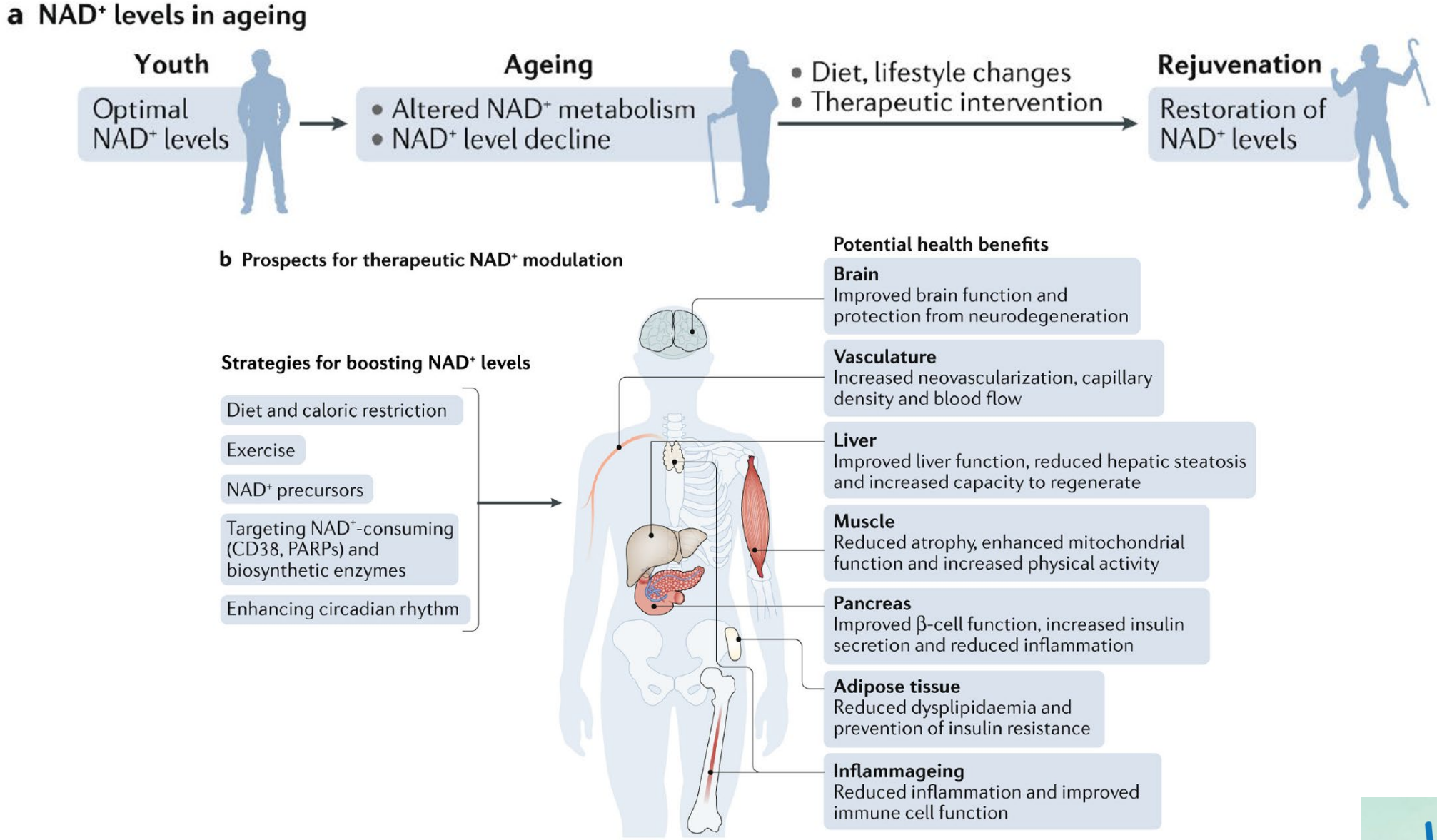


Based on Massudi, et al., 2012
NAD measurements in human skin



Katsyuba and Auwerx 2017

Katsyuba and Auwerx. *Modulating NAD(+) metabolism, from bench to bedside.* 2017
Massudi et al., *Age-associated changes in oxidative stress and NAD+ metabolism in human tissue.* 2012



Nat Rev Mol Cell Biol 2021; 22(2):119-141.

Neurotransmission- Fueled

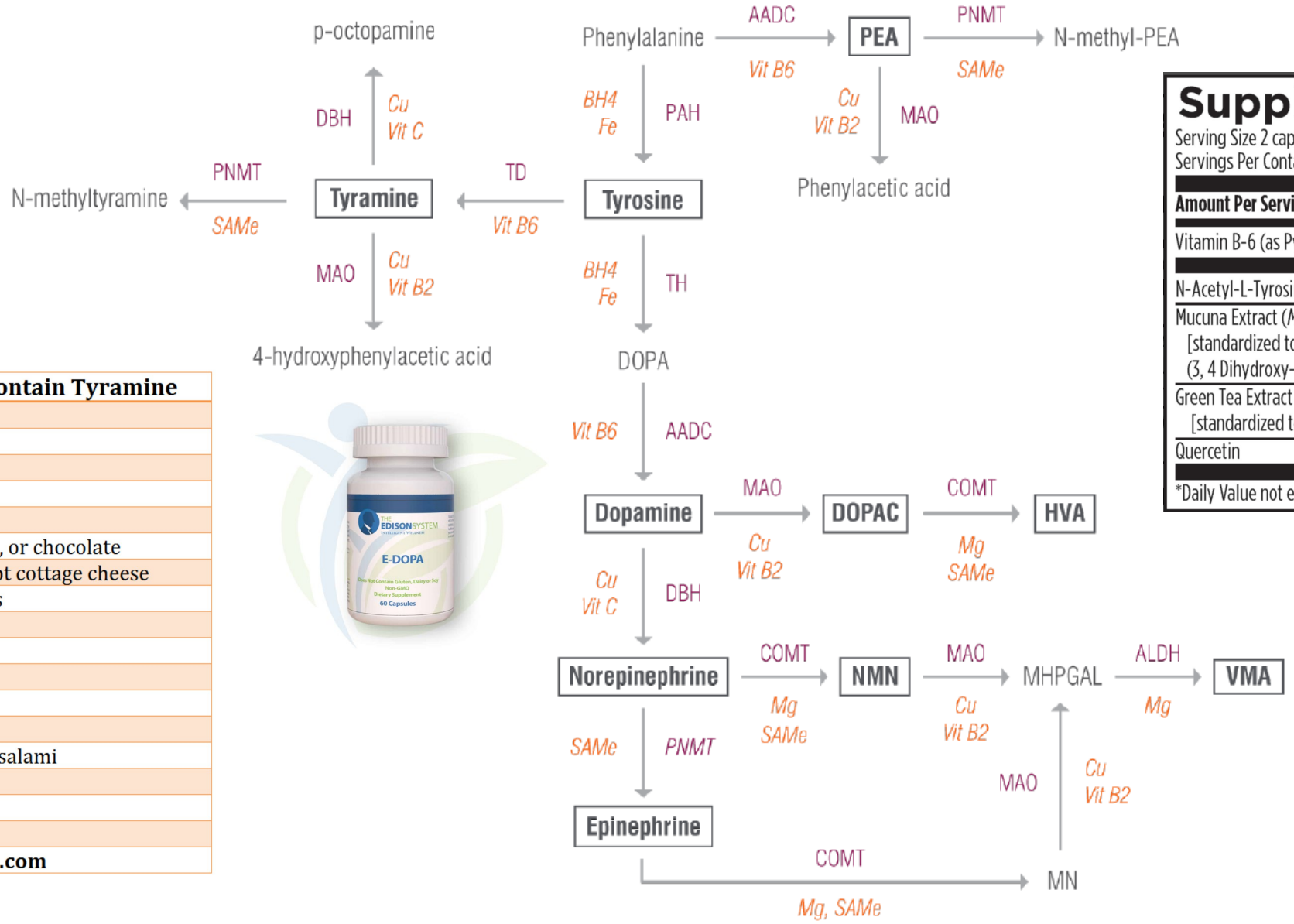
Gender	Last Menses	Height	Waist
Female	04/15/2021	Unspecified	Unspecified
DOB	**Menses Status**	**Weight**	
2/14/1974 (47 yrs)	Pre-Menopausal	205 lb	

TEST NAME	RESULTS | 04/26/21	RANGE
Urinary Inhibitory Neurotransmitters		
Tryptophan	14113 H	2633-12688 µg/g Cr (Optimal 3970-8450)
Serotonin	86.1	47.6-140.3 µg/g Cr (Optimal 61.0-103.2)
5-HIAA	3753	2205-11816 µg/g Cr (Optimal 2988-5850)
GABA	208	167-463 µg/g Cr (Optimal 193-367)
Glycine	227	41-295 mg/g Cr (Optimal 61-159)
Taurine	17.4	7.1-293.1 mg/g Cr (Optimal 24.5-134.1)
Urinary Excitatory Neurotransmitters		
Glutamate	1277	1213-4246 µg/g Cr (Optimal 1515-2710)
Glutamine	86	27-106 mg/g Cr (Optimal 37-71)
Histidine	57.9	10.8-98.9 mg/g Cr (Optimal 19.7-58.4)
Histamine	16.4	3.6-44.3 µg/g Cr (Optimal 5.2-15.3)
N-Methylhistamine	56 L	59-195 µg/g Cr (Optimal 79-140)
PEA	8.3	3.6-38.8 µg/g Cr (Optimal 5.3-16.1)
Tyrosine	11884	3128-15548 µg/g Cr (Optimal 4790-10278)
Tyramine	437	187-910 µg/g Cr (Optimal 279-588)
Dopamine	112	103-282 µg/g Cr (Optimal 144-240)
DOPAC	472 L	495-2456 µg/g Cr (Optimal 658-1449)
HVA	4038	3025-9654 µg/g Cr (Optimal 3737-7048)

Neurotransmitter	Function
Dopamine	Acts as the "feel good" reward mechanism of the brain; enhances sensations
Acetylcholine	Stimulates muscles, especially the gastrointestinal system
Norepinephrine	Increases the sympathetic nervous system (heart rate, blood pressure, respiratory system)
Serotonin	Affects emotion, mood, and perception
GABA (gamma aminobutyric acid)	Affects motor control, vision, and anxiety
Glutamate	Affects learning, memory, and cognition
Endorphins	Causes pain reduction and pleasure

NEURO-TRANSMITTERS REPORT

Catecholamines & Metabolites



Foods to Avoid That Contain Tyramine
Avocados
Bananas
Beef or chicken liver
Brewer's yeast
Broad beans
Caffeine, such as in coffee, tea, or chocolate
Cheese, especially aged, except cottage cheese
Meat extracts and tenderizers
Overripe fruit
Papaya
Pickled herring
Raisins
Red wine, beer, sherry
Sausage, bologna, pepperoni, salami
Sour cream
Soy sauce
Yogurt
NCLEXQuiz.com

Supplement Facts

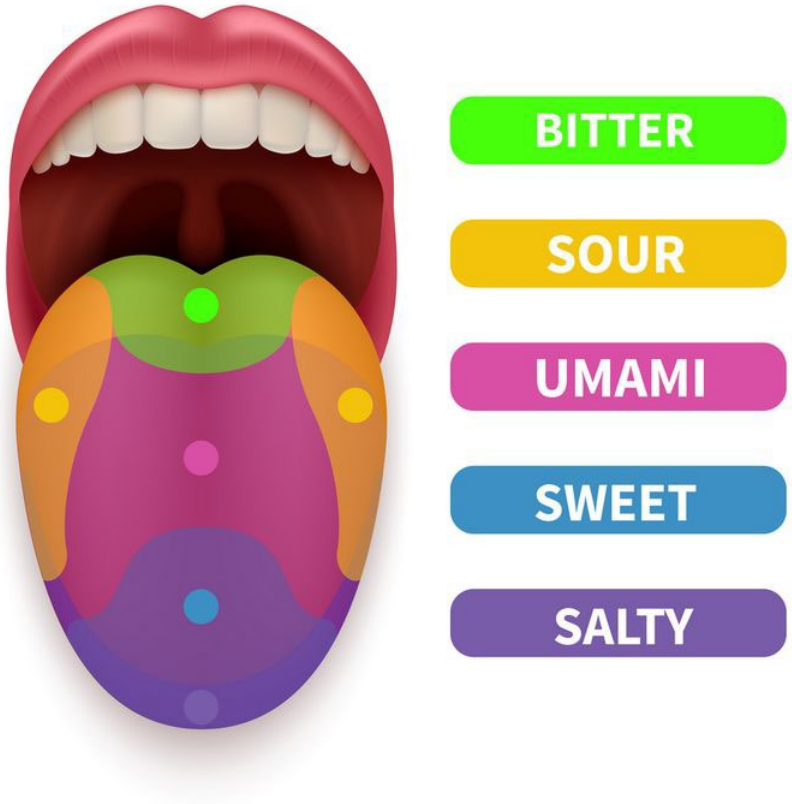
Serving Size 2 capsules
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin B-6 (as Pyridoxal-5-Phosphate)	5 mg	294%
N-Acetyl-L-Tyrosine	750 mg	*
Mucuna Extract (*Mucuna pruriens*)(seed) [standardized to contain 60% L-Dopa (3, 4 Dihydroxy-L-Phenylalanine)]	425 mg	*
Green Tea Extract (*Camellia sinensis*)(leaves) [standardized to contain 98% polyphenols and 45% EGCg]	100 mg	*
Quercetin	100 mg	*

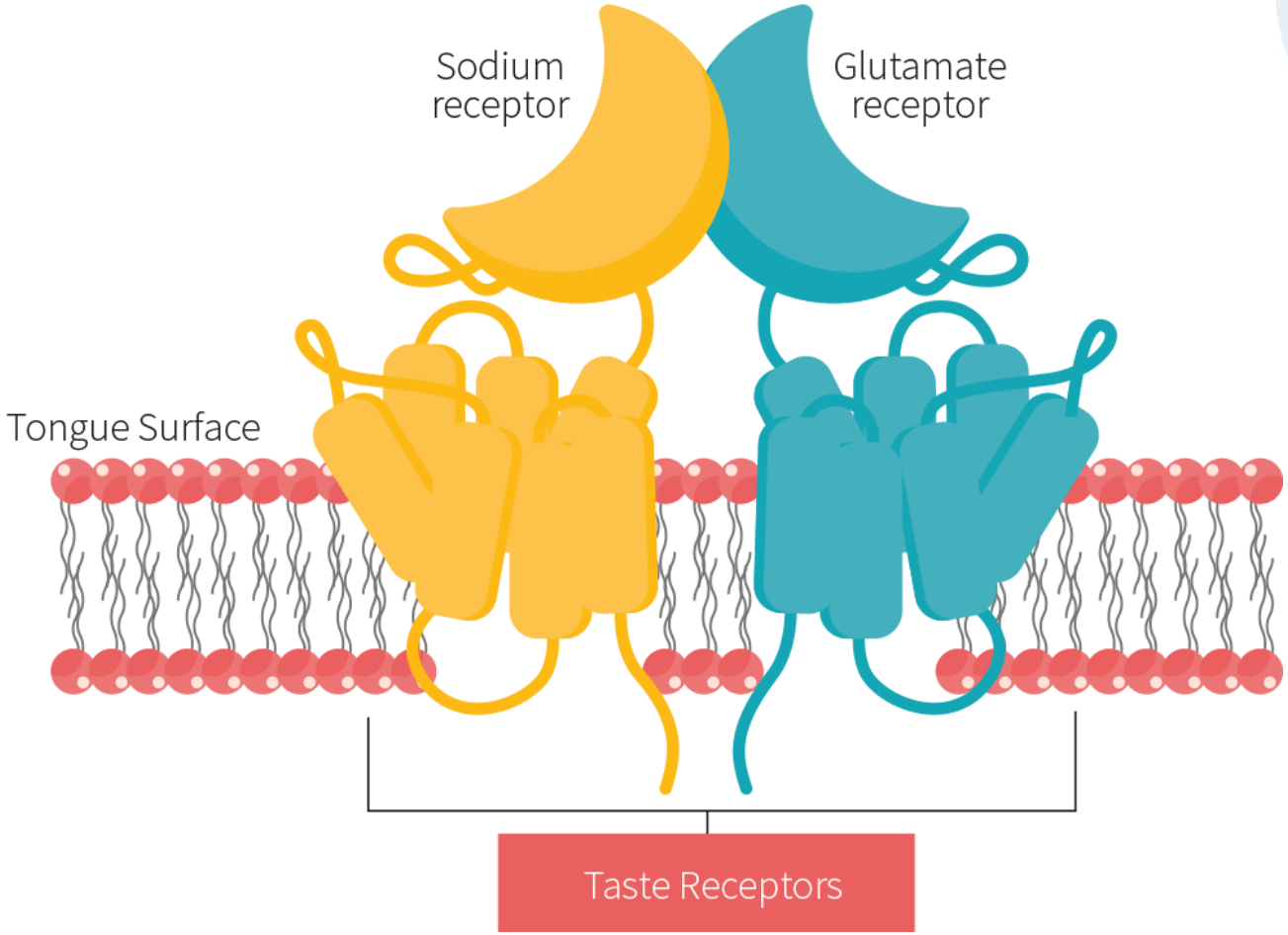
*Daily Value not established.

VITALLEO HEALTH

Glutamate/GABA, Glycine, Histamine & Taurine



MSG and taste bud interactions



Well Aligned

Published in final edited form as:
Cell Metab. 2019 October 01; 30(4): 630–655. doi:10.1016/j.cmet.2019.09.001.

NAD^+ in Brain Aging and Neurodegenerative Disorders

Abstract

NAD^+ is a pivotal metabolite involved in cellular bioenergetics, genomic stability, mitochondrial homeostasis, adaptive stress responses, and cell survival. Multiple NAD^+-dependent enzymes are involved in synaptic plasticity and neuronal stress resistance. Here, we review emerging findings that reveal key roles for NAD^+ and related metabolites in the adaptation of neurons to a wide range of physiological stressors and in counteracting processes in neurodegenerative diseases, such as those occurring in Alzheimer's, Parkinson's, and Huntington diseases, and amyotrophic lateral sclerosis. Advances in understanding the molecular and cellular mechanisms of NAD^+-based neuronal resilience will lead to novel approaches for facilitating healthy brain aging and for the treatment of a range of neurological disorders.

Published in final edited form as:
Cell Metab. 2019 October 01; 30(4): 630–655. doi:10.1016/j.cmet.2019.09.001.

NAD+ in Brain Aging and Neurodegenerative Disorders

NAD+ Has Numerous Functions in Cells

The SIRTs are NAD^+-dependent enzymes that regulate a wide spectrum of cellular pathways involved in health and disease (Chalkiadaki and Guarente, 2015; Imai et al., 2000). For example, SIRT1 consumes NAD^+ to regulate glycolysis, gluconeogenesis, and mitochondrial homeostasis via the balance between mitochondrial biogenesis and mitophagy and adaptive responses of neurons to exercise and metabolic/excitatory challenges (Bonkowski and Sinclair, 2016; Cheng et al., 2016; Fang, 2019).

Published in final edited form as:
Cell Metab. 2019 October 01; 30(4): 630–655. doi:10.1016/j.cmet.2019.09.001.

NAD+ in Brain Aging and Neurodegenerative Disorders

NAD+ in Normal Brain Aging

During normal aging, lower NAD^+ levels are observed in tissues of various organisms including humans, mice, and *C. elegans*. Using a non-invasive ^{31}P magnetic resonance (MR)-based *in vivo* NAD assay, Zhu et al. demonstrated an age-dependent reduction of NAD^+ levels, NAD^+/NADH, and total NAD(H) contents in intact human brain from healthy volunteers (Zhu et al., 2015). In mice, there was a nearly 40% decrease of NAD^+ levels in the hippocampus in 10- to 12-month-old mice compared with 1-month-old mice (Stein and Imai, 2014).

Published in final edited form as:
Cell Metab. 2019 October 01; 30(4): 630–655. doi:10.1016/j.cmet.2019.09.001.

NAD^+ Has Numerous Functions in Cells

NAD^+ is a vital redox cofactor for metabolism and ATP production, and a key substrate for at least four families of enzymes involved in healthspan and longevity (Fang et al., 2017; Gomes et al., 2013; Verdin, 2015). NAD^+ plays an essential role in glycolysis and the citric acid (TCA) cycle, by its ability to accept hydride equivalents, forming NADH during ATP production (Krebs, 1970; Wallace, 2012). NADH is one of the central electron donors in oxidative phosphorylation (OXPHOS) in the mitochondria, providing electrons to the electron transport chain (ETC) to generate ATP (Krebs, 1970; Wallace, 2012). The ratio of

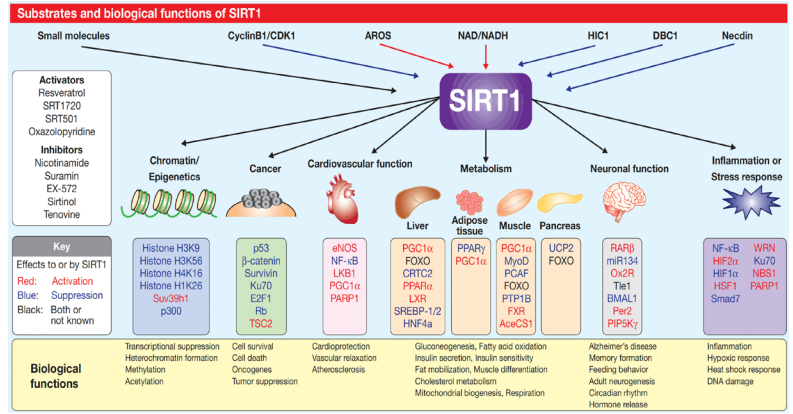
Published in final edited form as:
Cell Metab. 2019 October 01; 30(4): 630–655. doi:10.1016/j.cmet.2019.09.001.

NAD^+ Depletion in Mitochondrial Dysfunction.—Mitochondria isolated from animal and post-mortem human brain tissues show an age-dependent rise in mitochondrial functional heterogeneity, increased oxidative damage, reduced function of the ETC, disrupted membrane potential, impaired Ca^{2+} handling, and/or an accumulation of dysfunctional mitochondria (Lin and Beal, 2006; Mattson et al., 2008; Sorrentino et al., 2017). Mitochondria generate ATP to support neuronal activities including neurotransmission and Ca^{2+} homeostasis and are a source of signals that regulate nuclear-mitochondrial communication and even the arbitration of neuronal survival and death (Mattson et al., 2008).

Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2020, Article ID 6782872, 19 pages
https://doi.org/10.1155/2020/6782872

Review Article

The Beneficial Roles of SIRT1 in Neuroinflammation-Related Diseases



Sirtuins are the class III of histone deacetylases whose deacetylate of histones is dependent on nicotinamide adenine dinucleotide (NAD+). Among seven sirtuins, SIRT1 plays a critical role in modulating a wide range of physiological processes, including apoptosis, DNA repair, inflammatory response, metabolism, cancer, and stress. Neuroinflammation is associated with many neurological diseases, including ischemic stroke, bacterial infections, traumatic brain injury, Alzheimer's disease (AD), and Parkinson's disease (PD). Recently, numerous studies indicate the protective effects of SIRT1 in neuroinflammation-related diseases. Here, we review the latest progress regarding the anti-inflammatory and neuroprotective effects of SIRT1. First, we introduce the structure, catalytic mechanism, and functions of SIRT1. Next, we discuss the molecular mechanisms of SIRT1 in the regulation of neuroinflammation. Finally, we analyze the mechanisms and effects of SIRT1 in several common neuroinflammation-associated diseases, such as cerebral ischemia, traumatic brain injury, spinal cord injury, AD, and PD. Taken together, this information implies that SIRT1 may serve as a promising therapeutic target for the treatment of neuroinflammation-associated disorders.

An Inflamed Brain- Sabotage Happiness and Content

Individuals with major depressive disorder often have elevated levels of inflammatory biomarkers, such as C-reactive protein (CRP), and proinflammatory cytokines, such as IL-1β and IL-6.

CRP and these cytokines can directly influence mood and emotion.

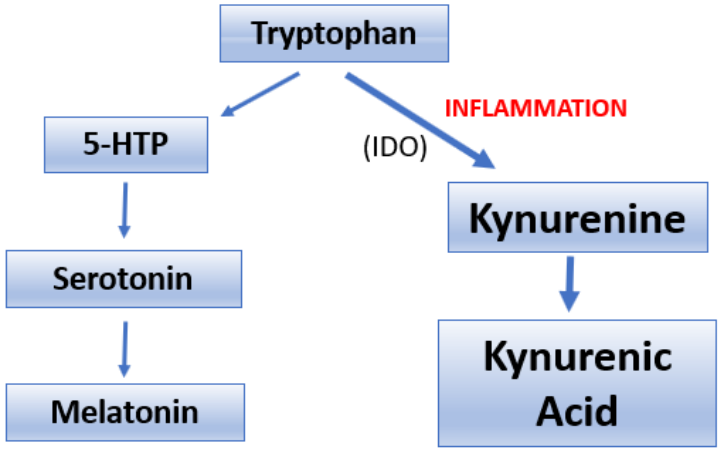
Inflammation can indirectly impact mood by influencing tryptophan metabolism. The body can convert the amino acid tryptophan into the feel-good neurotransmitter serotonin and the sleep-inducing-hormone melatonin, or it can convert tryptophan to kynurenine.

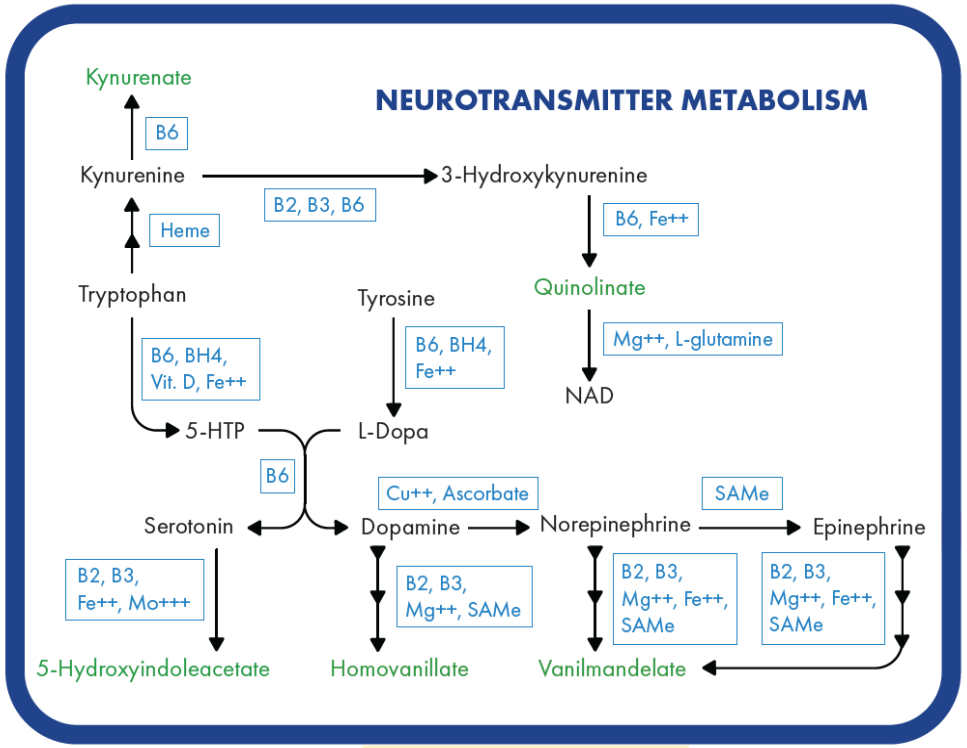
Chronic low-grade inflammation, such as can happen in patients with major depressive disorder (MDD), can activate the tryptophan-degrading enzyme, indoleamine 2,3-dioxygenase (IDO), leading to decreased tryptophan levels and upregulation of the kynurenine-pathway.

Psychosom Med. 2009;71(2):171-186. | Depress Anxiety. 2013;30(4):297-306.
Brain Behav Immun. 2013;31:128-133. | Brain Behav Immun. 2015;46:55-59.
Nat Rev Neurosci. 2008;9(1):46-56.

Inflammation & Tryptophan Metabolism

When tryptophan is metabolized through the kynurenine pathway, the body has less access to serotonin and melatonin, which are both essential for mood and sleep. Furthermore, the kynurenine pathway generates potentially neurotoxic metabolites, such as such as 3-hydroxykynurenine and quinolinic acid.





OAP/EPP TEST

Brain Behav Immun. 2015;46:55-59. | J Psychosom Res. 2017;99:1-7.

Life Sciences 250 (2020) 117583

Contents lists available at ScienceDirect

Life Sciences

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

COVID-19: Melatonin as a potential adjuvant treatment

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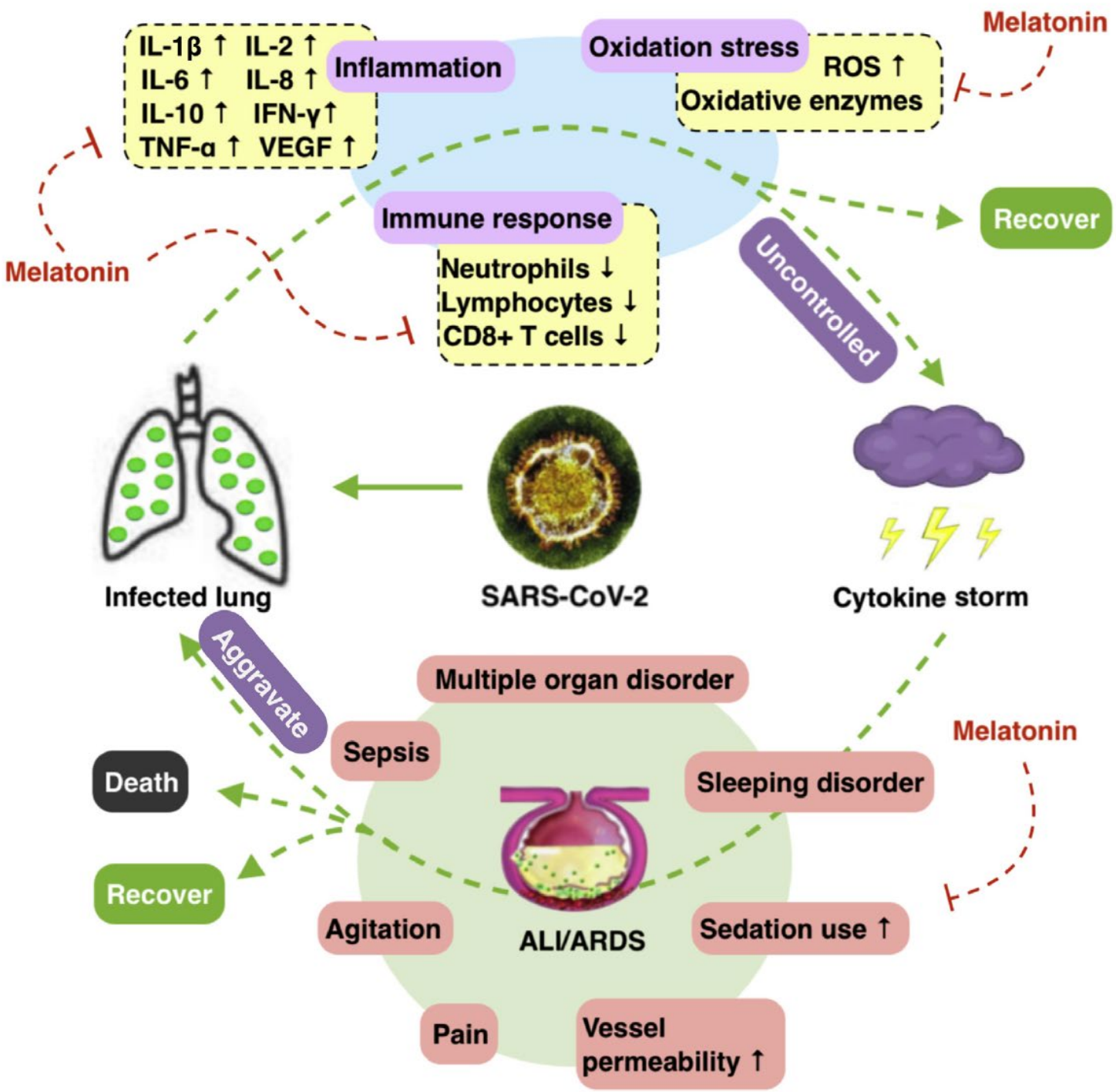
[b] Department of Cell Systems and Anatomy, UT Health San Antonio, San Antonio, TX 78229, USA

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Melatonin
Oxidation-reduction
Cytokines
Immunomodulation

ABSTRACT

This article summarizes the likely benefits of melatonin in the attenuation of COVID-19 based on its putative pathogenesis. The recent outbreak of COVID-19 has become a pandemic with tens of thousands of infected patients. Based on clinical features, pathology, the pathogenesis of acute respiratory disorder induced by either highly homogenous coronaviruses or other pathogens, the evidence suggests that excessive inflammation, oxidation, and an exaggerated immune response very likely contribute to COVID-19 pathology. This leads to a cytokine storm and subsequent progression to acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and often death. Melatonin, a well-known anti-inflammatory and anti-oxidative molecule, is protective against ALI/ARDS caused by viral and other pathogens. Melatonin is effective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality, which might also be beneficial for better clinical outcomes for COVID-19 patients. Notably, melatonin has a high safety profile. There is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients. Additional experiments and clinical studies are required to confirm this speculation.


IL-1β ↑ IL-2 ↑
IL-6 ↑ IL-8 ↑
IL-10 ↑ IFN-γ↑
TNF-α ↑ VEGF ↑
Inflammation
Oxidation stress
ROS ↑
Oxidative enzymes
Melatonin
Melatonin
Immune response
Neutrophils ↓
Lymphocytes ↓
CD8+ T cells ↓
Recover
Uncontrolled
Infected lung
SARS-CoV-2
Cytokine storm
Aggravate
Multiple organ disorder
Sepsis
Death
Recover
Sleeping disorder
Melatonin
Agitation
ALI/ARDS
Sedation use ↑
Pain
Vessel permeability ↑

3. Melatonin & anti-inflammation

Melatonin exerts anti-inflammatory effects through various pathways. Sirtuin-1 (SIRT1) may mediate the anti-inflammatory actions of melatonin by inhibiting high mobility group boxechromosomal protein 1 (HMGB1), and thus down-regulating the polarization of macrophages towards the pro-inflammatory type [26]. In sepsis-induced ALI, the proper regulation of SIRT1 attenuates lung injury and inflammation, in which the application of melatonin might be beneficial [27]. Nuclear factor kappa-B (NF-κB) is closely associated with pro-inflammatory and pro-oxidative responses while being an inflammatory mediator in ALI. The anti-inflammatory effect of melatonin involves the suppression of NF-κB activation in ARDS [28,29]. Melatonin reportedly down-regulate NF-κB activation in T cells and lung tissue [30,31]. The stimulation of NF-E2-related factor 2 (Nrf2) is crucial in protecting lung from injury. In related studies, melatonin induces the up-regulation of Nrf2 with therapeutic effects in hepatoprotection, cardioprotection, etc. [32].

Published in final edited form as:
Cell Mol Life Sci. 2017 November ; 74(21): 3913–3925. doi:10.1007/s00018-017-2617-7.

Melatonin and its metabolites as regulators of bioenergetics of mitochondria

It has been suggested that melatonin could donate electrons to the ETC, thus improving mitochondrial respiration and increasing ATP production [80]. At the same time, mitochondrial ETC may be a target not only for melatonin, but also for its metabolites generated in mitochondria [37, 40] (Fig. 6). It appears that AMK like a melatonin exerts effects on electron flux through the respiratory chain [80]. According to our data, 6-hydroxymelatonin in vitro effectively reduces oxidized cytochrome *c*, thus exhibiting greater reducing potential than melatonin itself (Fig. 6a, b). During mitochondrial respiration, cytochrome *c* supports electron shuttling between complex III (ubiquinol cytochrome *c* oxidoreductase) and complex IV (cytochrome *c* oxidase). Therefore, when an electron is removed from 6-hydroxymelatonin, it becomes available for donation by reduced cytochrome *c* to complex IV, contributing to mitochondrial energy production (Fig. 6c). This

The Link Between Sleep & Depression

Insomnia is a risk factor for depression.

It is thought that insomnia-exacerbated inflammation may be the mechanism of action by which chronic sleep loss can lead to depression.

Depression can also lead to sleep loss, creating a vicious circle.

Inflammation-induced alterations of kynurenine metabolism may explain the association between insomnia and depression. In a study of 68 currently depressed, 26 previously depressed, and 66 never-depressed subjects, only in the currently depressed group was sleep disturbance associated with alterations in kynurenine metabolites.

CRP levels were high only in the subjects with sleep disturbances who were currently depressed.

J Psychosom Res. 2017;99:1-7. | Am J Psychiatry. 2008;165(12):1543-1550.
J Affect Disord. 2011;135(1-3):10-19. | Brain Behav Immun. 2010;24(1):54-57.
Arch Intern Med. 2006;166(16):1756-1762. | Brain Behav Immun. 2015;47:86-92.
Transl Psychiatry. 2016;6(3):e750.

To Sleep

Sleep Apnea, S

Chris D. Meletis, N.D., wi

Sleep apnea is defined as
episodes of upper-airv
hemoglobin oxygen desat
terized by periods of breathing c
reduced breathing (hypopnea). S
and mortality, thus making it a
tion.[1]

Sleep apnea is typically categ
or mixed. Central sleep apnea ir
of respiratory drive resulting f
system initiation, combined wit
respiration. This form of the dis
patients with sleep apnea.[2] Ob
the most common type and is c
airflow despite respiratory effo
tion in the upper airway. Mixec
of lack of respiratory effort anc
way. Sleep disordered breathin
disorders that includes snoring
drome, and OSA.

Preva

In industrialized countries, O
cent of men and 2 percent of wo
with age and studies suggest th
many as 31 percent of elderly
women.[4] Children are also affecte
lence of 0.7–3 percent, with a p
children.[5] Many sources state tha
a result of the difficulty involv
diagnostic procedures.[6]

Sleep apnea greatly affects the
patients and their partners. Snori
precursor to OSA, is common. St
affects 29.5 percent of males and
severity in 2.1 percent of females
nificant enough to cause their
shared with these patients.[7]

Chemoreceptors within the brai
carbon dioxide (CO_2) levels, so tha
these receptors do not compensate
and depth of lung ventilation. This
piratory effort at a time when an i
leading to partial or total collapse o
exchange in the lungs. Ultimate
hypoxia and hypercapnia, which th
drive. Often, however, a severe hy
required to stimulate a respirator
overcome the obstruction and end t

Specifically, the primary initiati
comes from chemoreceptors that a
CO_2 in the aortic arch, brainstem, an
changes in respiration cause chang
which have been shown to affect ca
as ventricular filling, venous retu
natriuretic peptide.[2]

Hypoxia and hypercapnia during
an increase in sympathetic nerve act
many cardiovascular effects includir
tance, vasoconstriction, and increas
ingly, sympathetic nerve activity ha
the daytime as well in patients wit
this increase may be the cause of
arrhythmias.[14]

Diagnosing Sle

The severity of sleep apnea–hyp
ous methods. The number of apne
of sleep can be evaluated with th
(AHI). In addition, the severity of
sleep can be measured via pulse
gasses. The severity of daytime sl
symptom associated with apnea, ca
latency time using the Multiple Sle
sleep latency of less than 10 minute
ness.

Sleep apnea is frequently underdi
80–90 percent of OSA cases go und
that 30 percent of patients with esser
agnosed—and thus untreated—OSA

Diagnosis of OSA includes a thc
examination, using polysomnogra

Health Conditions Linke

- Hypertension
- Atherosclerosis
- Tachycardia
- Bradycardia
- Ventricular ectopy
- Stroke
- Coronary artery disease
- Congestive heart failure
- (
- [
- (
- [
- [
- A
- H

Risk Factor

- Snoring
- Increased body–mass index
- Increased neck circumferenc
- Increasing age
- Male gender
- African-American ethnicity
- Smoking
- Alcohol use
- Menopause

cardiac arrhythmias, sug
caused by an increase in va
disease process. Tracheo-
arrhythmias.[25]

Other arrhythmias founc
sleep apnea include ventri
dia, premature ventricular
and sinus arrest.[27]

Hypertension

Approximately 50 percer
hypertensive, a correlation
effects of obesity on blood p
(BP).[28] Studies indicate that
ty of OSA is directly correlat
severity of both sleep apn
daytime hypertension.
increase in sympathetic a
caused by the induction
fight-or-flight response is b
to be one contributing facto
rise in BP. Treatment of OS
nCPAP has been shown to d
BP during both daytime and

Strokes

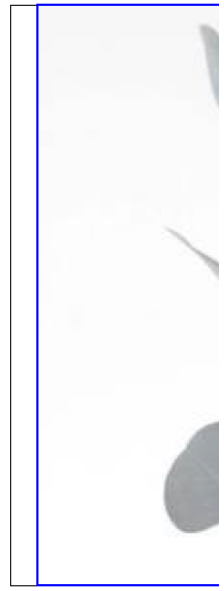
OSA is an independent
strokes or transient ischemic
with untreated OSA experi
rates of stroke morbidity anc
treated with nCPAP.[32]

Diabetes

Sleep apnea is a risk facto
insulin resistance, and typ
nCPAP in individuals with C
increase in insulin sensitivity

Gastroesophageal Reflux Diseas

Gastroesophageal reflux d
individuals with OSA. Stud
also increases with an incr
OSA, treatment of GERD has
of arousals during sleep.[37]



**Eucalyptus (*Eucalyptus globul*

There are many types of s
treating sleep apnea. Most p
ages to the airway or increa
dures include uvulopala
turbinectomy, midline glosse
my, and tracheotomy.[2]

Alternative Treatme

Several lifestyle changes
the severity of sleep apnea
sleep lying on one side. W
correlations of increased E
OSA. Even modest weight l
apnea symptoms; studies ha
increase can cause a 32 pe
percent weight loss could
AHI.[43] Avoidance of alcol
encouraged.

Although specific studies
apnea are generally lacking,
therapies that address the
factors known to exist in s
prove important as adjuncti
larly important, given the
with nCPAP/BiPAP inter

lungs, congestion, and sneezing.) A
able and may be improved by c
bromelain.

Bromelain

Bromelain is a proteolytic enzyr
This enzyme produces anti-infla
antiplatelet aggregation activities.[51]
interferes with the AA pathway, ca
tory eicosanoid production.[52]

Eucalyptus

Historically, eucalyptus (*Eucalypt*
addressing many inflammatory resp
asthma and bronchitis.[53] Eucalyptu
and branches contains 60–90 percen
Studies on eucalyptol show that it ex
mucolytic, and analgesic effects. It i
metabolites and such proinflammato

Stinging Nettle

Stinging nettle (*Urtica dioica*) leal
E, carotenoids, calcium, potassit
quercitin and rutin. This herb has s
effects, and studies suggest that it r
allergic rhinitis.[55] Researchers beli
the nettles' quercitin content, wh
inhibits histamine release.[50]

Beefsteak Plant

The beefsteak plant (*Perilla frute*
ingredients such as rosmarinic acid
is a plant polyphenol found in th
which includes basil (*Ocimum* spp.)
(*Mentha* spp.), rosemary (*Rosmarinus*

Oral supplementation using per
marinic acid has been shown to su
A study confirmed that oral admini
inhibits production of TNF-α and d
and inflammation in mice.[59]

Another study demonstrated tha
with rosmarinic acid is an effectiv
have seasonal allergic rhinoconjunc
luteolin—found in various species c
plant flavonoid that has potent antia

Licorice Root

Licorice (*Glycyrrhiza glabra*) is of
conditions such as GERD and ulc
cyrrhizinated licorice (DGL) stimu
differentiation of glandular cells
stimulating mucous secretion—is
increased mucous secretion in the s
for at least part of licorice's benefic
tains flavonoids that produce anti
working against the ulcer-causing b

Hyaluronic acid, a glycosaminoglycan, could be considered for treatment of snoring and augmentation of airway connective tissue integrity.[62] Because of hyaluronic acid's viscoelastic quality, this substance may work to strengthen the connective tissue surrounding the airway and decrease obstructions.

Diet

Diet can affect inflammation and mucous production. Diets high in fruits and vegetables provide the vitamins and bioflavonoids that reduce allergy symptoms. Diets high in EFAs and low in animal products (such as dairy foods and meat) will decrease inflammation. (Animal products are high in AA and lead to an increase in inflammatory eicosanoids.) In addition, members of the nightshade family—such as potatoes, tomatoes, eggplants, and peppers—may also be proinflammatory in some individuals. Clinical observation suggests avoidance of mucous-forming foods such as dairy foods, bananas, and citrus fruits can be beneficial, although that line of thought is controversial.

Food allergies should also be considered when modifying the diet to decrease apneic episodes. Many individuals have latent food allergies that increase the inflammatory response and cause additional overall stress on the body. Many forms of testing are readily available to measure immunoglobulin (Ig)E and IgG antibodies to common foods.

Environment

Environmental allergies are important airway irritants. It is important to control allergies in order to minimize the nasal and pharyngeal congestion that can help compromise airway patency.

The best way to treat allergies is to advise patients to avoid the substances that trigger symptoms. The environment should be kept as free of potential allergens as possible. Pillows and mattresses should be covered with dust- and mite-proof covers. Bedding should be washed frequently in very hot water. Removal of carpets and items that collect dust in the bedroom may also help avoid dust and dust mites. Bathing and washing hair before bed also is suggested.

Mold anywhere in the home should be treated aggressively. Pets should be kept away from the sleeping areas and should be bathed regularly. High-efficiency particulate absorbing filters at home and work can improve air quality and decrease pollen exposure. Avoidance of cigarette smoke is recommended.

Anecdotal literature suggests other possible—though unproven—treatments for sleep apnea. Nasal sprays, nasal dilators, and magnetic mattresses and pillows are available.[63] Essential oil sprays and gargles to treat snoring have shown efficacy.[64] A case report also suggests hypnosis as an effective treatment for snoring.[65] Snoring has also been reduced by singing exercises in nonobese patients when done correctly and regularly.[66] Biofeedback training to control abnormal breathing while sleeping also has shown promising results. In at least one study, biofeedback reduced the duration of apneic episodes, resulting in higher oxygen saturation levels.[67]

Conclusions

Sleep apnea is a medical condition that warrants thorough study because of the increase in morbidity and mortality in patients who have the condition. It also affects quality of life greatly in many patients and frequently goes undiagnosed. If a patient complains of fatigue, excess sleepiness, lack of restorative sleep, or other unexplained systemic symptoms, a close review of the potential existence of apnea is a must. Given that sleep apnea can mimic and manifest as an accelerated peripheral vascular disease, the presence of premature vascular symptoms such as "classic shiny shin" may serve as a significant sign.

Although there are many treatments that have been proposed to help with sleep apnea, the best approaches remain weight loss and use of positive airflow therapy. Nonetheless, adjunctive therapies can help control the severity of apnea and snoring. □

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Depression and Weight Gain– Accelerated by the Covid-ERA

Obstructive sleep apnea (OSA) is a common sleep disorder that is linked to depression.

OSA occurs when a patient temporarily stops breathing while sleeping, resulting in low oxygen levels. We can live without food for weeks and water for days, but we can only live without air for moments.

OSA does not only occur in obese patients; I have diagnosed mild, moderate, and severe sleep apnea in people who are thin, young, and with no or few classical symptoms.

My philosophy is always "test, don't guess." The standard treatment for OSA is for patients to use a continuous positive airway pressure (CPAP) machine.

Resolving sleep apnea can result in a corresponding decrease in depression. Adults with OSA and coronary artery disease experienced reduced depression scores after 3 months of CPAP treatment, compared to participants not using CPAP.

Sleep. 2018;41(12):180. | Ann Am Thorac Soc. 2019;16(1):62-70.

JBC ARTICLE

Author's Choice

J Biol Chem 2020; 295(52):17986-96.

Coronavirus infection and PARP expression dysregulate the NAD metabolome: An actionable component of innate immunity

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Edited by Craig E. Cameron

Poly(ADP-ribose) polymerase (PARP) superfamily members covalently link either a single ADP-ribose (ADPR) or a chain of ADPR units to proteins using NAD as the source of ADPR. Although the well-known poly(ADP-ribosylating) (PARylating) PARPs primarily function in the DNA damage response, many noncanonical mono(ADP-ribosylating) (MARylating) PARPs are associated with cellular antiviral responses. We recently demonstrated robust up-regulation of several PARPs following infection with murine hepatitis virus (MHV), a model coronavirus. Here we show that SARS-CoV-2 infection strikingly up-regulates MARylating PARPs and induces the expression of genes encoding enzymes for salvage NAD synthesis from nicotinamide (NAM) and nicotinamide riboside (NR), while down-regulating other NAD biosynthetic pathways. We show that overexpression of PARP10 is sufficient to depress cellular NAD and that the activities of the transcriptionally induced enzymes PARP7, PARP10, PARP12 and PARP14 are limited by cellular NAD and can be enhanced by pharmacological activation of NAD synthesis. We further demonstrate that infection with MHV induces a severe attack on host cell NAD^+ and $NADP^+$. Finally, we show that NAMPT activation, NAM, and NR dramatically decrease the replication of an MHV that is sensitive to PARP activity. These data suggest that the antiviral activities of noncanonical PARP isozyme activities are limited by the availability of NAD and that nutritional and pharmacological interventions to enhance NAD levels may boost innate immunity to coronaviruses.

acquired respiratory syndrome coronavirus 2, SARS-CoV-2, is transmitted largely by aerosol and liquid droplets that infect cells of the lung epithelium (2). Severe disease is thought to proceed through a combination of robust viral replication and a cytokine storm in which host inflammation damages multiple organ systems. Although many therapeutic approaches are under investigation, the evidence basis for effective prevention and treatment agents remains limited.

CoV genomes do not encode enzymes needed for ATP generation, nucleotide, amino acid, lipid, or protein synthesis and therefore depend on exploitation of host functions to synthesize and assemble virus (3–5). Cellular and viral energy generation and biosynthetic programs depend on the four NAD coenzymes, NAD^+, NADH, $NADP^+$, and NADPH, which are the central catalysts of metabolism (6). These coenzymes accept and donate electrons in essential, ubiquitous processes of fuel oxidation, lipid, nucleotide, and amino acid biosynthesis, and the generation and detoxification of reactive oxygen species. The specific roles of these coenzymes in viral replication and antiviral defenses are largely unexplored.

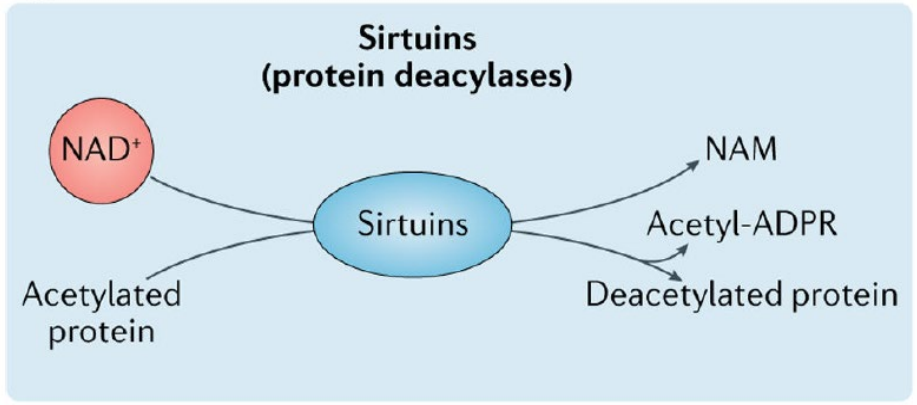
Several members of the PARP superfamily are interferon-stimulated genes that have been implicated in restriction of viral replication through mechanisms that are not well understood (7, 8). With the exception of the enzymatically inactive PARP13 protein, PARP isozymes have an absolute requirement for NAD^+ (9, 10).

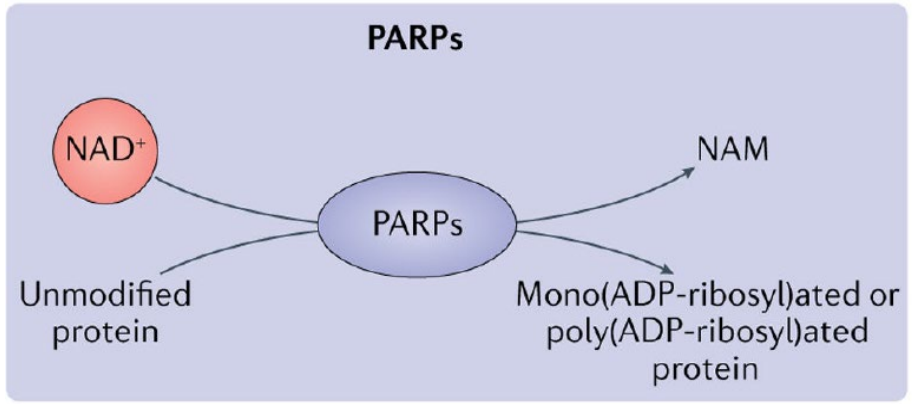
Discussion

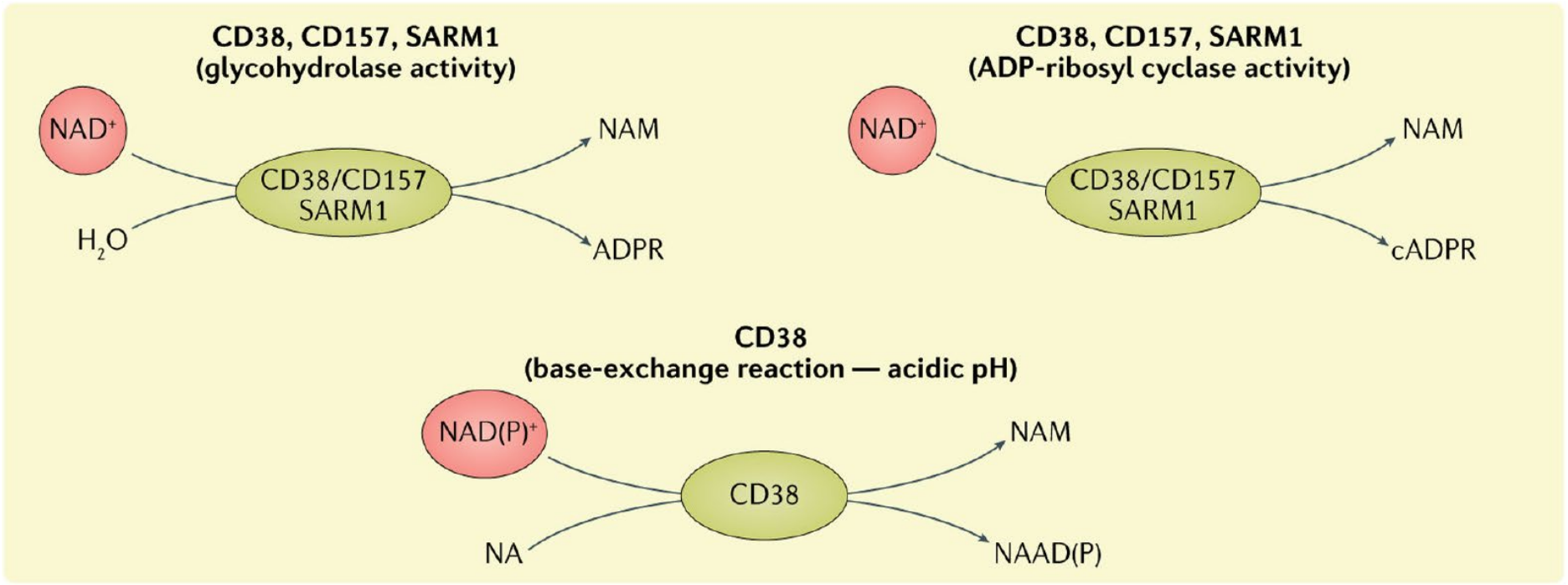
SARS-CoV-2 is a highly infectious agent that constitutes a severe threat to public health (2). Morbidity and mortality data make it clear that age, smoking status, and multiple preexisting conditions greatly increase the frequency of serious illness and death (34). There is an abundance of data from model systems and humans that age and conditions of metabolic stress including obesity and type 2 diabetes (35), smoking (36), heart failure (29), nerve damage (37), and central brain injury (28) challenge the NAD system in affected tissues. Although PARP1 was known to be a significant consumer of NAD^+, we showed that noncanonical PARP isozymes are consistently up-regulated by CoV infections, that PARP10 overexpression can depress the NAD metabolome

J Biol Chem 2020; 295(52):17986-96.

3 NAD Dependent Immune Enzymes







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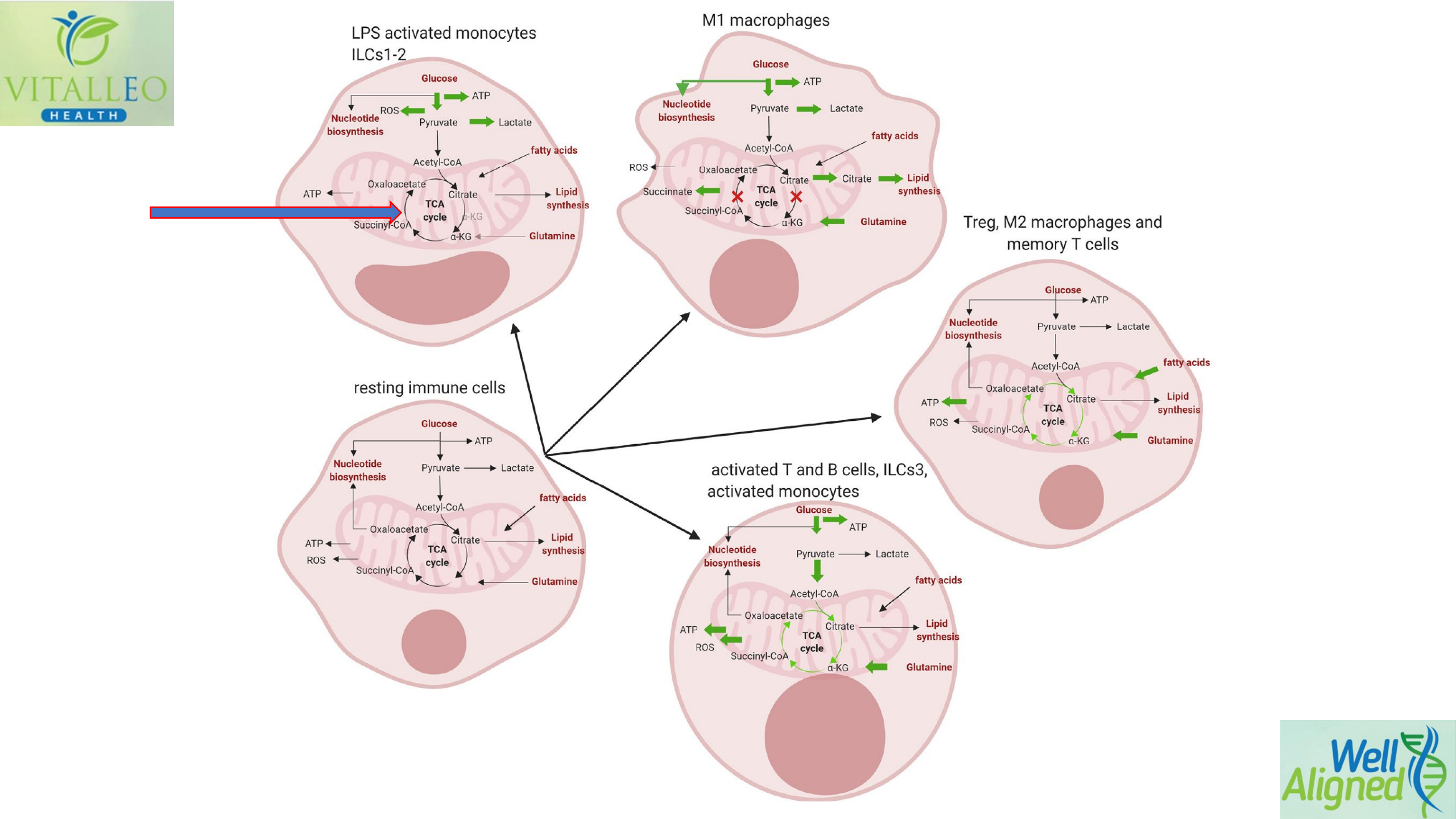
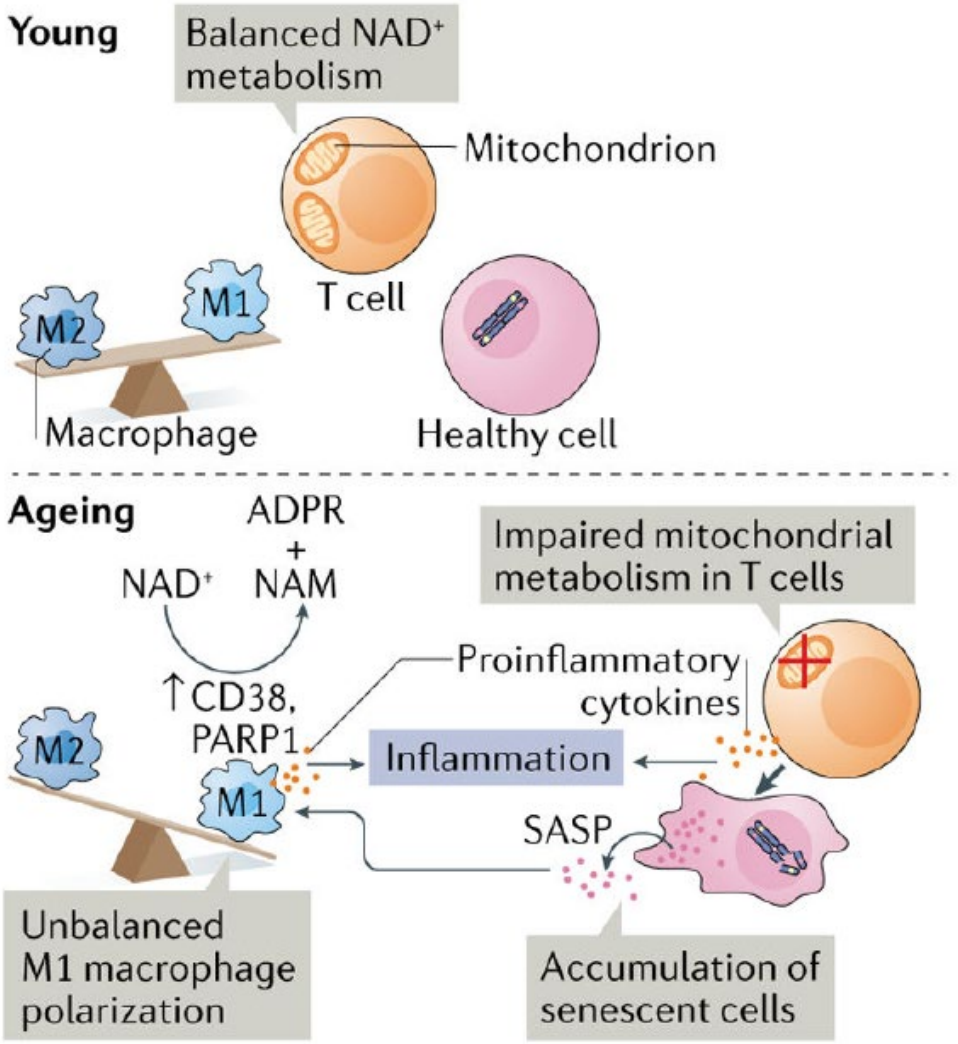

LPS activated monocytes
ILCs1-2
M1 macrophages
Treg, M2 macrophages and
memory T cells
resting immune cells
activated T and B cells, ILCs3,
activated monocytes
Glucose
ATP
ROS
Nucleotide
biosynthesis
Pyruvate
Lactate
Acetyl-CoA
fatty acids
Oxaloacetate
Citrate
Lipid
synthesis
TCA
cycle
α-KG
Succinyl-CoA
Succinnate
Glutamine

Immune Senescence – Morbidity and Mortality Risk



Nat Rev Mol Cell Biol 2021; 22(2):119-141.

Organic Acids In Central Energy Pathways

Marker elevations may suggest nutrient deficiencies in the metabolic pathway

Food Source Proteins
Amino Acids
B_1, B_2, B_3, B_5
Keto Acids
Food Source Carbohydrates
Glucose
B_1, B_2, B_3, B_5, Lipoic Acid
B_1
Lactate
Pyruvate
Fatty Acyl-CoA
B_2, B_3, Carnitine
* Beta-Oxidation
Food Source Fats
Fatty Acids
Carnitine
CoQ10
Hydroxymethylglutarate
Cholesterol
Biotin
Beta-Hydroxyisovalerate
B_1, B_2, B_3, B_5 Lipoic Acid, Mg ++
Alpha-Ketoisocaproate
B_6
Leucine
(amino acid conversion to keto acids)
ASN (amino acid)
Mn++, Mg++ Biotin
B_6
Aspartate
Acetyl-CoA
Acetoacetate
B_3
Beta-Hydroxybutyrate
Oxaloacetate
Citrate
B_3
Malate
cis-Aconitate
Cysteine, Fe++, Glutathione
Isocitrate
B_3, Mg++, Mn++
Fumarate
B_2, Fe++
Succinate
Alpha-Ketoglutarate
GLN
B_3
GLU
B_6
Proline
Histidine
Arginine
Amino Acids
Succinyl-CoA
B_1, B_2, B_3, B_5, Lipoic Acid
B_6
Tyrosine
Phenylalanine
NH3
CO_2
++, K+
Carbamoyl - P
Orotate
Citrulline
Ornithine
UREA CYCLE
Arginosuccinate
Arginine
Urea
Isoleucine
B_6
Food Source Proteins
(amino acid conversion to keto acids)
Alpha-Keto-Beta-Methylvalerate
B_1, B_2, B_3, B_5 Lipoic Acid, Mg ++
Valine
B_6
Propionyl-CoA
Biotin
Alpha-Ketoisovalerate
Methylmalonyl-CoA (Methylmalonate)
B_{12}
Methionine
Cysteine
B_6
GSH
Pyroglutamate
**Alpha-Ketobutyrate
Alpha-Hydroxybutyrate
B_3, B_5
Threonine
Odd chain fatty acids
Cholesterol side chains
NADH, $FADH_2$
Mitochondrial electron transport system
CoQ10
O_2
H_2O
Cellular Energy
ATP
Biosynthetic Reactions

NEUROTRANSMITTER METABOLISM
Kynurenate
B_6
B_2, B_3, B_5
Kynurenine
3-Hydroxykynurenine
B_6
B_1
B_3
Quinolinate
Mg^{++}
Tryptophan (amino acid)
B_3, Fe^{++}
Tyrosine
B_3
NAD
5-HTP
L-Dopa
B_6
Cu++, Ascorbate
Mg++
Serotonin
Dopamine
Norepinephrine
Epinephrine
B_2, B_6
B_2
B_2, Mg++, Fe++
5-Hydroxyindoleacetate
Homovanillate
Vanilmandelate

* Interference with mitochondrial beta-oxidation yields products of incomplete alternate oxidative pathways; adipate, suberate, ethylmalonate and methylsuccinate
** Interferance with alpha-ketobutylate oxidation yeilds subsequent elevation of urinary alpha-hydroxybutyrate

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Host NAD$^+$ metabolism and infections: therapeutic implications

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Abstract

Nicotinamide adenine dinucleotide (NAD$^+$) is both a crucial coenzyme and a cosubstrate for various metabolic reactions in all living cells. Maintenance of NAD$^+$ levels is essential for cell energy homeostasis, survival, proliferation and function. Mounting evidence points to NAD$^+$ as one of the major modulators of immuno-metabolic circuits, thus regulating immune responses and functions. Recent studies delineate impaired host NAD$^+$ metabolism during chronic infections and inflammation, suggesting NAD$^+$ replenishment as an avenue to ameliorate deleterious inflammatory responses. Here, we discuss aspects of NAD$^+$ biosynthesis and consumption, NAD$^+$ biology during infections and how NAD$^+$ metabolism can be intervened with pharmacologically to enhance the host's immunological fitness against pathogens.

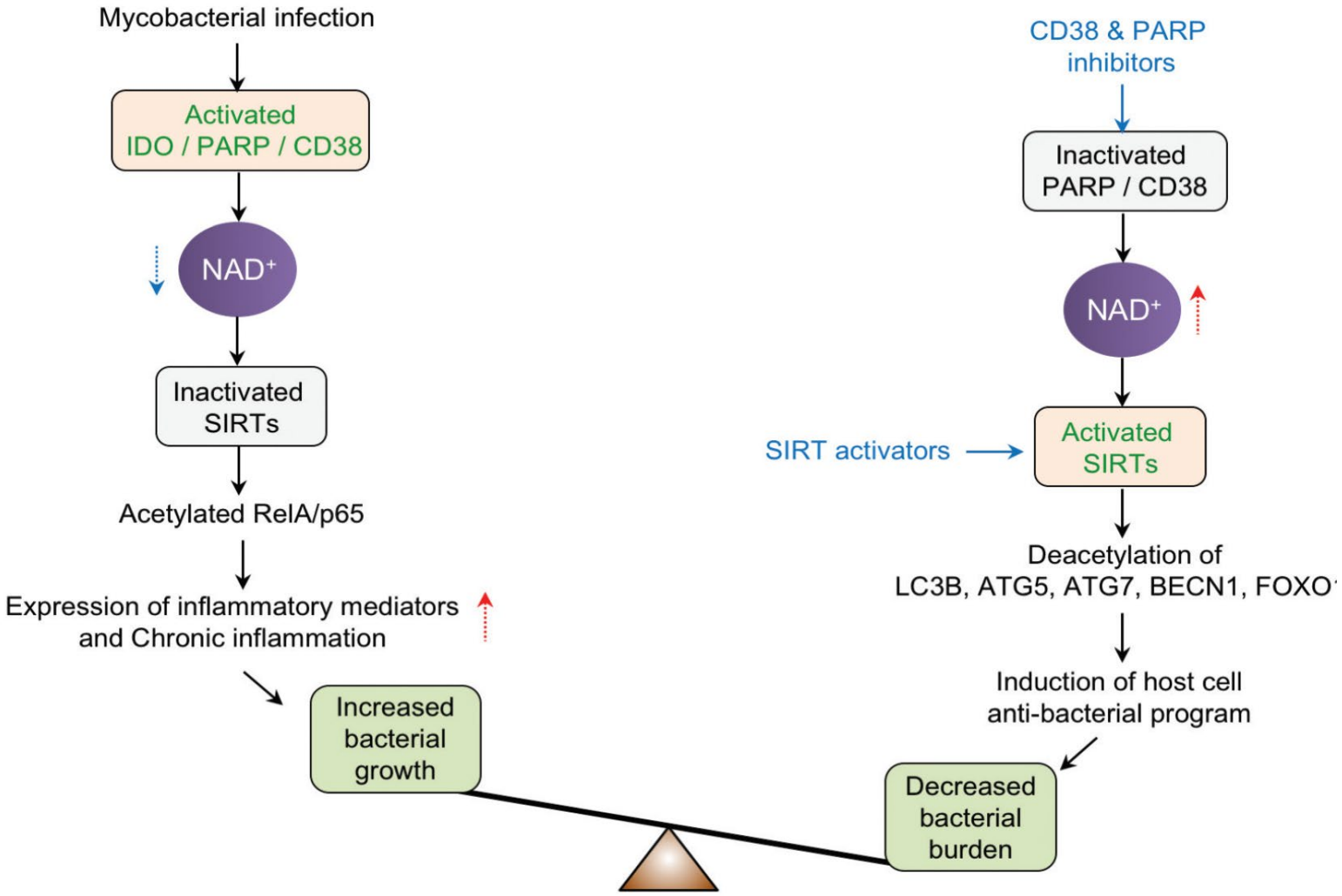
Keywords: bacteria, immunity, immuno-metabolism, NAD$^+$

NAD^+ Modulates Immune Cells

This modulation of NAD^+ levels is predicted to affect effector functions of immune cells and, consequently, affect the clearance or persistence of infections. NAD^+ levels are largely dependent on the TRP-catabolizing enzyme IDO and the NAD^+-consuming enzymes SIRTs, PARPs and CD38 (cluster of differentiation 38). These enzymes play important roles in energy metabolism, cell survival, proliferation and effector functions, making them potential targets for designing host-directed therapies (HDT).

International Immunology 2018; 31(2):59-67.

NAD+ is Pivotal to Fuel Critical Immune Pathways



International Immunology 2018; 31(2):59-67.

Mitochondria as central hub of the immune system

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ARTICLE INFO

Keywords:
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Mitochondrial function
Cell fate
And immune cells

ABSTRACT

Nearly 130 years after the first insights into the existence of mitochondria, new rolesassociated with these organelles continue to emerge. As essential hubs that dictate cell fate, mitochondria integrate cell physiology, signaling pathways and metabolism. Thus, recent research has focused on understanding how these multifaceted functions can be used to improve inflammatory responses and prevent cellular dysfunction. Here, we describe the role of mitochondria on the development and function of immune cells, highlighting metabolic aspects and pointing out some metabolic- independent features of mitochondria that sustain cell function.

1. Introduction

Cellular metabolism has been an extensively explored field during the past decade. The understanding of how cells use energy to perform their functions has attracted the attention of scientists, especially with regard to metabolic-related diseases such as obesity, diabetes, and cancer [1–4]. Classically, these conditions not only change whole-body metabolism, but also impair the inflammatory responses. Thus, immunometabolism has emerged as a potential new field of inquiry in order to investigate how the metabolic alterations affect immune cells.

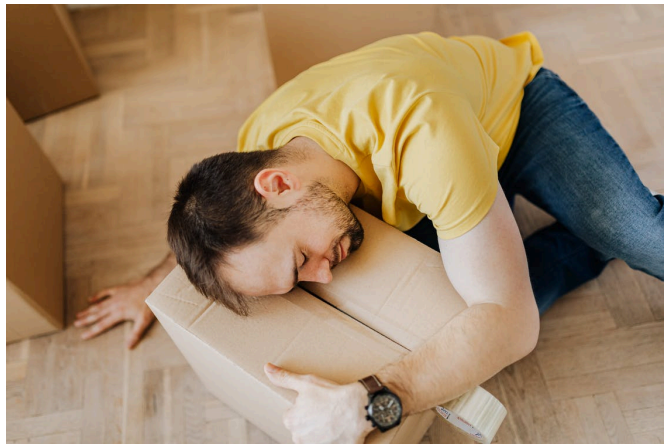
The immune system comprises a family of heterogeneous cells with multiple roles during homeostasis and inflammation in a tissue-specific manner. Recent studies have shown that different immune cell subtypes use distinct metabolic programs to perform their functions. For instance, effector T cells prioritize aerobic glycolysis during anabolic metabolism to balance the synthesis of macromolecules and the generation of energy to support it [5]. Conversely, memory T cells, as well as regulatory T cells (Treg), prioritize fatty acid oxidation (FAO also called β-oxidation) to support the energy demand for survival and function [5].

As first hypothesized by Richard Altmann in 1890 [6], the generation of useful metabolic energy is provided mainly by mitochondria in virtually all eukaryotic cells. However, the concept that the mitochondria are only powerhouses of cells has changed due to a myriad of other roles this membrane-bound organelle can perform. In immune cells, for instance, mitochondria can also regulate cell development, activation, proliferation, differentiation, and death [7,8], which directly impact cell fate and fitness. Moreover, mitochondria are dynamic organelles and can change their morphology and position in the cells through coordinated cycles of fission and fusion to regulate their own and functions and cell metabolism [9]. This process is called mitochondrial dynamics. Another important aspect of the mitochondrial physiology is the local production of oxidants or more commonly referred to as “reactive oxygen species” (mtROS). They were first described as byproducts of the electron transport chain (ETC) and implicated in oxidative damage [10–13], but are also important signaling molecules for cell activation when produced in low quantities [10,14–16].

Thus, the importance of mitochondria goes beyond energy production. Mitochondria can orchestrate immunity by modulating both metabolic and physiologic states in different types of immune cells. In this review, we will focus on how mitochondria drive the development and function of immune cells, highlighting their main metabolic features and pointing out other metabolism-independent roles of mitochondria that sustain cell function.

Redox Biology 2019; 26:101255.

How Many Cells? How Low an NAD^+ or ATP LEVEL?



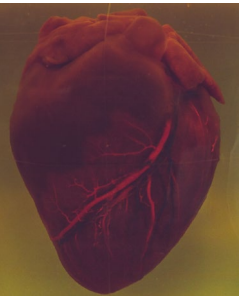
How Low a Thyroid Function?

How Diminished a Gonadal Function?

How Great an Adrenal Fatigue?

How Much Sleep Deprivation?

How Significant an Infection?



How Diminished a Mitochondrial Function?

NO's Role in Relieving Depression & Anxiety

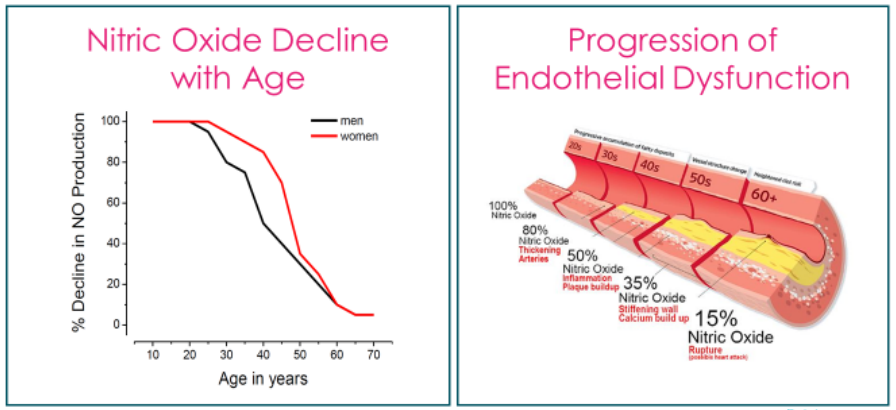
Imbalanced levels of the neurotransmitter, nitric oxide (NO), are associated with anxiety and depression, due to NO's role as a regulator of neuroinflammation.

NO is thought to influence the release of other neurotransmitters. In doing so, it is involved in brain cell function, such as plasticity and development, and may also increase blood flow to the brain due to its vasodilating actions.

Abnormalities in NO signaling correlate with major depressive disorder, and certain polymorphisms in the neuronal nitric oxide synthase gene (NOS1) are linked to MDD.

Aging Process:

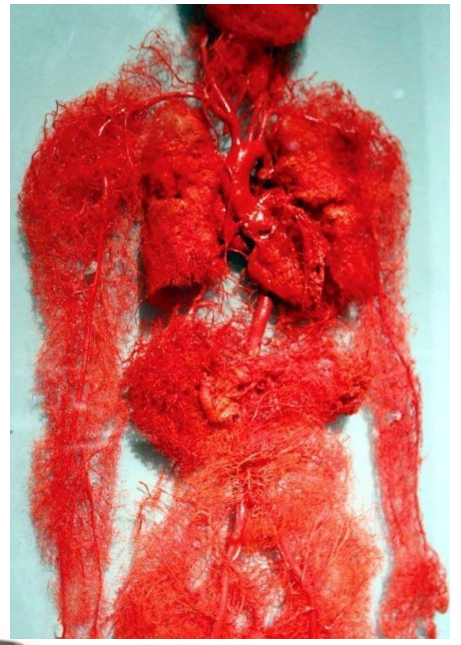
- Decrease of NAD^+
- Decrease of ATP
- Decrease of Nitric Oxide (NO)
- Decrease of Melatonin



Berkeley Life Professional

Psychopharmacol Bull. 2001;35(1):24-41. | Curr Mol Med. 2016;16(2):206-215.

What Size Diameter Blood Vessels Do You Want Irrigating Your BODY?



- ✔ Large Diameter Supply
- ✔ High Water Flow
- ✔ Hydrant Ready

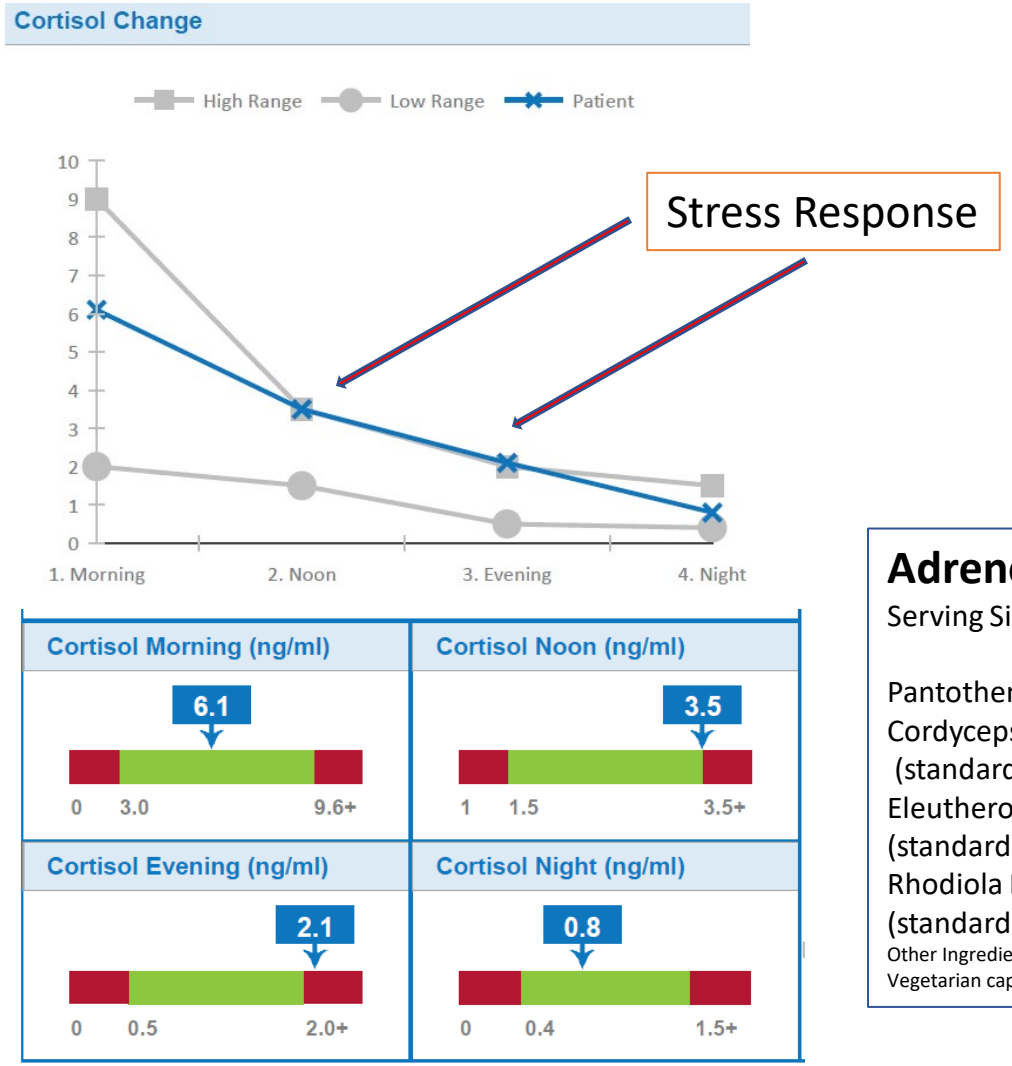
Well Aligned

Brain Drain from Chronic Pain

Chronic pain driven by neuroinflammation is clinically relevant. Neuroinflammation associated with pain has been found in patients with chronic low back pain, fibromyalgia, complex regional pain syndrome (CRPS), osteoarthritis, and chronic radicular pain [8–11]. Animal studies have demonstrated that chronic pain arises from the activation of the microglia and astrocytes in the dorsal horn of the spinal cord, leading to increased production of pro-inflammatory mediators [12]. The release of these inflammatory mediators by microglia and astrocytes initiate and enhances pain transmission via the activation of projection neurons [13]. Glial cell modulators may substantially reduce the release of pro-inflammatory cytokines and increase the release of anti-inflammatory cytokines, as well as improve the pain state and overall quality of life of the patients. Specifically, they modify the balance between anti- and pro-inflammatory cytokines. Multiple glial cell modulators, such as fluorocitrate, ibudilast, minocycline, naltrexone, and propentofylline [14,15], have been assessed in clinical trials. However, the development of drugs targeting neuroinflammation is still in its infancy and needs to be further advanced.

Pharmaceuticals 2021; (14)777:1-33.

Stress and Cortisol



Stress Response (high cortisol levels)

Serving Size 2 Vegetarian Capsules

Thiamine 10 mg
Riboflavin 10 mg
Niacinamide 10 mg
Vitamin B6 10 mg
Folic Acid 200 mcg
Vitamin B12 100 mcg
Relora®500 mg

Other ingredients: Cellulose and vegetable stearate.
Relora® is a registered trademark of NPI, LLC.
U.S. Patent No. US 6,582,735.

Adreno Care Plus (overall support and during low levels too)

Serving Size 2 Capsules

Pantothenic Acid (as calcium D-pantothenate)	100 mg
Cordyceps (Cordyceps sinensis) (mycelium) (standardized to 7% cordycepic acid)	400 mg
Eleuthero Extract (Eleutherococcus senticosus) (root) (standardized to 0.8% eleutherosides)	200 mg
Rhodiola Extract (Rhodiola rosea) (root) (standardized to 5% rosavins)	50 mg

Other Ingredients:
Vegetarian capsule (hydroxypropyl methylcellulose, water), microcrystalline cellulose, ascorbyl palmitate, and silicon dioxide.

- **Nicotinamide Riboside**
- Adrenal Support
  - **Adreno-Care Plus**
  - **Stress Response**
  - **CBD**

frontiers in Endocrinology

REVIEW
published: 29 July 2016
doi: 10.3389/fendo.2016.00106

Adrenal Mitochondria and Steroidogenesis: From Individual Proteins to Functional Protein Assemblies

In this paper, we discuss this functionalization, beginning with the tissue zonation of the adrenal cortex and how this impacts steroidogenic output. We then discuss the cellular biology of steroidogenesis, placing special emphasis on the mitochondria. Mitochondria are classically known as the "powerhouses of the cell" for their central role in respiratory adenosine triphosphate synthesis, and attention is given to mitochondrial electron transport, in both the context of mitochondrial respiration and mitochondrial steroid metabolism. Building on work demonstrating functional assembly of large protein complexes in respiration, we further review research demonstrating a role for multimeric protein complexes in mitochondrial cholesterol transport, steroidogenesis, and mitochondria–endoplasmic reticulum contact. We aim to highlight with this review the shift in steroidogenic cell biology from a focus on the actions of individual proteins in isolation to the actions of protein assemblies working together to execute cellular functions.

Supplement Facts

Serving Size 2 Capsules
Servings Per Container 60

Amount Per 2 Capsules		% Daily Value
Pantothenic acid (as calcium D-pantothenate)	100 mg	2,000%
Cordyceps (*Cordyceps sinensis*) (mycelium) (standardized to 7% cordycepic acid)	400 mg	*
Eleuthero Extract (*Eleutherococcus senticosus*) (root) (standardized to 0.8% eleutherosides)	200 mg	*
Rhodiola Extract (*Rhodiola rosea*) (root) (standardized to 5% rosavins)	50 mg	*

*Daily Value not established.

Other ingredients: Vegetarian capsule (hydroxypropyl methylcellulose, water), microcrystalline cellulose, ascorbyl palmitate, and silicon dioxide.

J Int Soc Sports Nutr. 2013 Aug 7;10(1):37. doi: 10.1186/1550-2783-10-37.

Effect of Magnolia officinalis and Phellodendron amurense (Relora®) on cortisol and psychological mood state in moderately stressed subjects

Shawn M Talbott [1], Julie A Talbott, Mike Pugh

Affiliations + expand

PMID: 23924268 PMCID: PMC3750820 DOI: 10.1186/1550-2783-10-37

Free PMC article

Abstract

Results: After 4 weeks of supplementation, salivary cortisol exposure was significantly ($p<0.05$) lower (-18%) in the Relora group compared to Placebo. Compared to Placebo, the Relora group had significantly better ($p<0.05$) mood state parameters, including lower indices of Overall Stress (-11%), Tension (-13%), Depression (-20%), Anger (-42%), Fatigue (-31%), and Confusion (-27%), and higher indices of Global Mood State (+11%) and Vigor (+18%).

VITALLEO HEALTH

Supplement Facts

Serving Size 2 Vegetarian Capsules
Servings Per Container 30

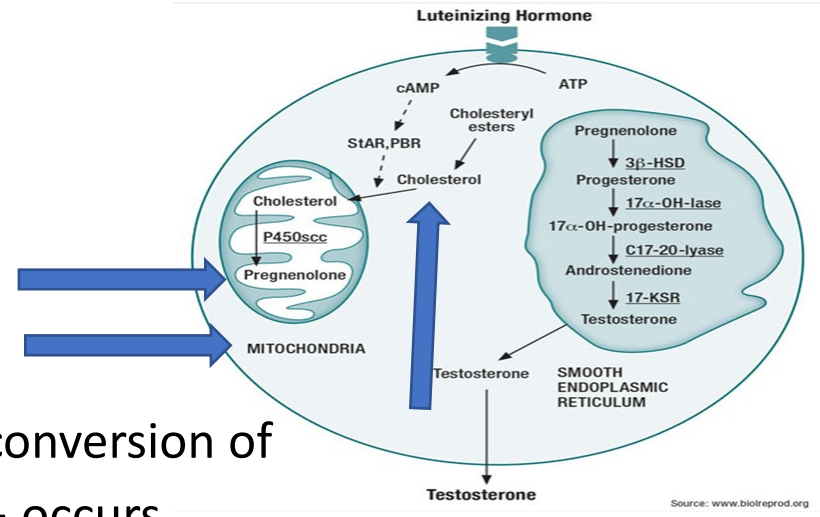
	Amount Per Serving	%DV
Thiamine (as thiamine mononitrate)	10 mg	833%
Riboflavin	10 mg	769%
Niacin (as niacinamide)	10 mg	63%
Vitamin B_6 (as pyridoxine HCl)	10 mg	588%
Folate (as folic acid)	333 mcg DFE (200 mcg folic acid)	83%
Vitamin B_{12} (as cyanocobalamin)	100 mcg	4,167%
Relora® (a proprietary blend of a patented** extract from *Magnolia officinalis* (bark) and a proprietary extract from *Phellodendron amurense* (bark))	500 mg	*

*Daily Value (DV) not established

Other ingredients: Microcrystalline cellulose, hydroxypropyl methylcellulose (capsule) and vegetable stearate

Well Aligned

Mitochondrial Function and Anabolism



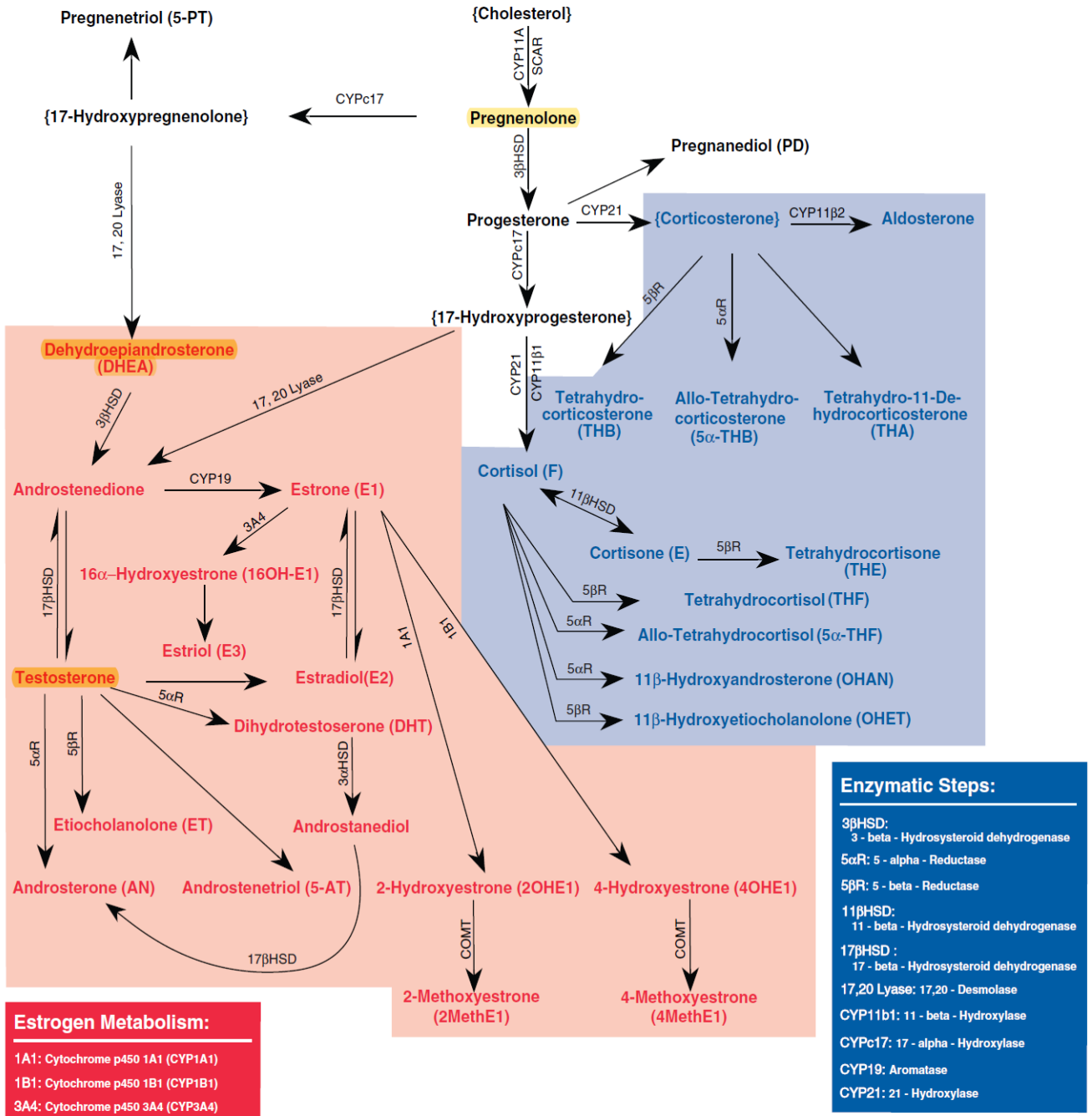
The mitochondria give birth to all steroid hormones.

Steroid hormone biosynthesis begins in the mitochondria because the conversion of cholesterol to pregnenolone — the precursor to all steroid hormones — occurs through the activity of the cytochrome P450 side-chain cleavage enzyme located on the inner mitochondrial membrane.

The electron transport chain of mitochondria is involved in testosterone production in the Leydig cells and manipulation of this pathway has been shown to increase production of testosterone.

Mol Cell Endocrinol. 2013 Oct 15;379(1-2):74-84. | Proc Natl Acad Sci USA. 2011 Jun 21;108(25):10139-43.

PLoS One. 2012; 7(9): e45829. | Andrology. 2014 May 12.



Estrogen Metabolism:

- 1A1: Cytochrome p450 1A1 (CYP1A1)
- 1B1: Cytochrome p450 1B1 (CYP1B1)
- 3A4: Cytochrome p450 3A4 (CYP3A4)
- COMT: Catechol-O-Methyl-transferase

Enzymatic Steps:

- 3βHSD: 3 - beta - Hydrosysteroid dehydrogenase
- 5αR: 5 - alpha - Reductase
- 5βR: 5 - beta - Reductase
- 11βHSD: 11 - beta - Hydrosysteroid dehydrogenase
- 17βHSD : 17 - beta - Hydrosysteroid dehydrogenase
- 17,20 Lyase: 17,20 - Desmolase
- CYP11b1: 11 - beta - Hydroxylase
- CYPc17: 17 - alpha - Hydroxylase
- CYP19: Aromatase
- CYP21: 21 - Hydroxylase

A Tired Brain = A Tired Patient?

Composite Summation of:

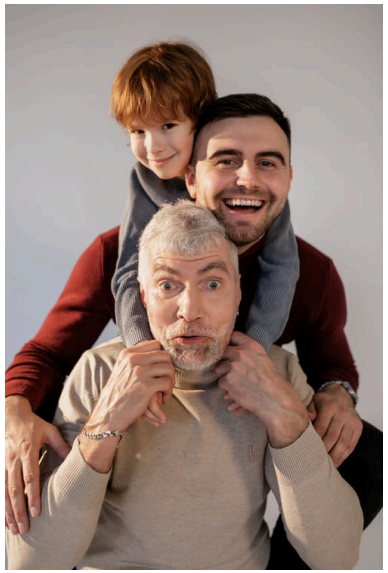
Cellular energy production and utilization

Endocrine production and function

- Gonadal
- Adrenal
- Thyroid

Immune/Inflammatory Homeostasis

Repair vs. Apoptosis



OVERALL RESILIENCE to ALLOSTATIC LOAD

Review > Reprod Fertil Dev. 2001;13(7-8):567-76. doi: 10.1071/rd01077.

The irritable male syndrome

Abstract

The irritable male syndrome (IMS) is a behavioural state of nervousness, irritability, lethargy and depression that occurs in adult male mammals following withdrawal of testosterone (T). The negative mood state has been described in men following withdrawal of androgens and is a striking feature in male seasonally breeding mammals associated with the end of the mating season. The Soay ram provides an animal model for IMS. Rams exposed to alternating 16-week periods of long and short days inactivate the reproductive axis in response to the switch to long days; the rapid decrease in T secretion provokes the symptoms of IMS. The animals appear agitated and fearful, and the incidence of physical wounding owing to fractious inter-male fighting peaks at this time. Androgen and oestrogen receptors expressed in cells in the preoptic area and ventromedial/arcuate nuclei appear to relay the effects of T on behaviour and gonadotrophin secretion, and melatonin receptors expressed in the premammillary area relay the effects of melatonin/photoperiod. Changes in the activity of hypothalamic opioidergic, dopaminergic and serotonergic neural networks may dictate the interactive effects of T and photoperiod. The working hypothesis is that IMS is a transition state associated with low hypothalamic amine levels triggered, in part, by the withdrawal of opioid peptides.

Introduction

A dysregulated response to inflammation can be a major cofactor in the pathogenesis of many chronic human conditions. Brain inflammation can affect metabolic and molecular pathways that influence neurotransmitter systems which affect neurocircuits that affect behaviour, resulting in psychiatric disorders. This review will explore research that suggests that clues to the aetiology of premenstrual disorders including premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS) can be found by looking at neuroinflammation expressed via the GABAergic system.

Premenstrual Dysphoric Disorder (PMDD)

PMDD is classified as a Mood Disorder within the DSM-5 and is characterised by affective symptoms, including irritability, depression, anxiety and suicidality which arise in the luteal phase of the menstrual cycle and resolve soon after the onset of menses.[1]

Brain inflammation and PMDD

All women of reproductive age experience cycles of inflammation. The immune system has an important role in female reproductive function and CRP levels are positively associated with symptom severity. [2] Prostaglandins in women's reproductive organs are known to raise inflammation at menstruation and the use of naproxen (an NSAID) and sumatriptan (a triptan) is effective in the treatment of adult migraines, a common premenstrual symptom. [3] Does neuroinflammation influence the severe mood changes of PMDD? Inflammation is being investigated as an etiologic factor of mood disorders so it seems logical that it has a role in PMDD. [4]

Evidence from recent observational studies

In a recent cross-sectional study both emotional and physical premenstrual symptom scores were associated with levels of inflammatory factors. Levels of IL-12 and interferon-gamma were more than twice as high in PMS cases.[5] A cross-sectional analysis of a longitudinal study showed there was a significant relationship of specific groups of premenstrual symptoms with elevated hs-CRP levels of >3 mg/L.[6] Women with PMS have a higher risk of subsequently developing hypertension and inflammation levels in women are reduced depending on how much partnered sexual activity women have. [7,8] Changing levels of inflammation affecting behaviour during menstrual cycles may represent an evolutionary mechanism which conferred an advantage in early humans but now results in a greater incidence of depression.[9,10]

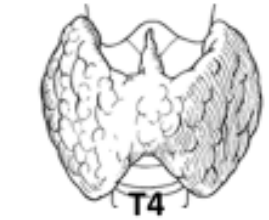
A potential mechanism - the GABAergic system

The research points to alterations in the function of the GABA-A receptor. GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter in the central

United Kingdom of Great Britain and Northern Ireland

Corresponding Author:
Emma Bannister, 3 Combe Park, Bath, BA1 3NP.
Email: hannahlouiseshort@gmail.com

Assessment of Production, Transport, Sensitivity, and Excretion of Thyroid Hormones



Factors that contribute to proper production of thyroid hormones
- Nutrients: iodine, tyrosine, zinc, vitamins: E, B2, B3, B6, C
- Antioxidants

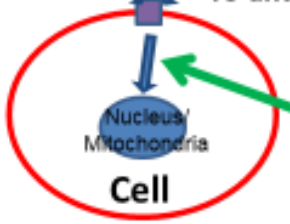
Factors that inhibit proper production of thyroid hormones
- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, Hg, Cd, Pb
- Autoimmune disease: Celiac

Factors that increase conversion of T4 to RT3
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications

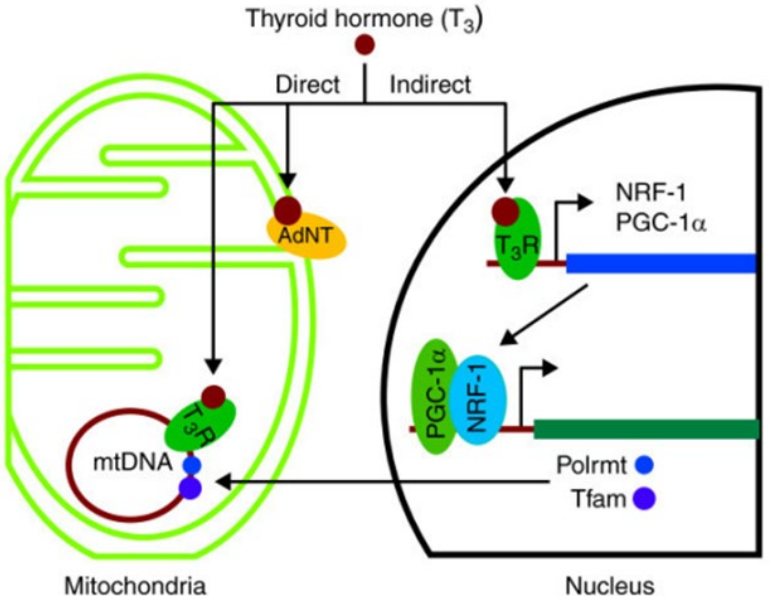
Factors that increase conversion of T4 to T3
- Selenium
- Zinc

RT3 T3

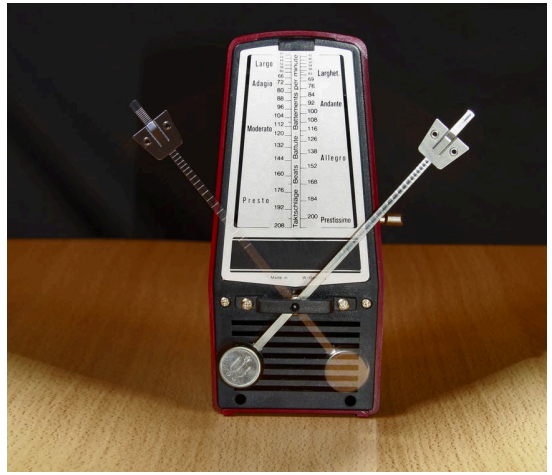
T3 and RT3 compete for binding sites



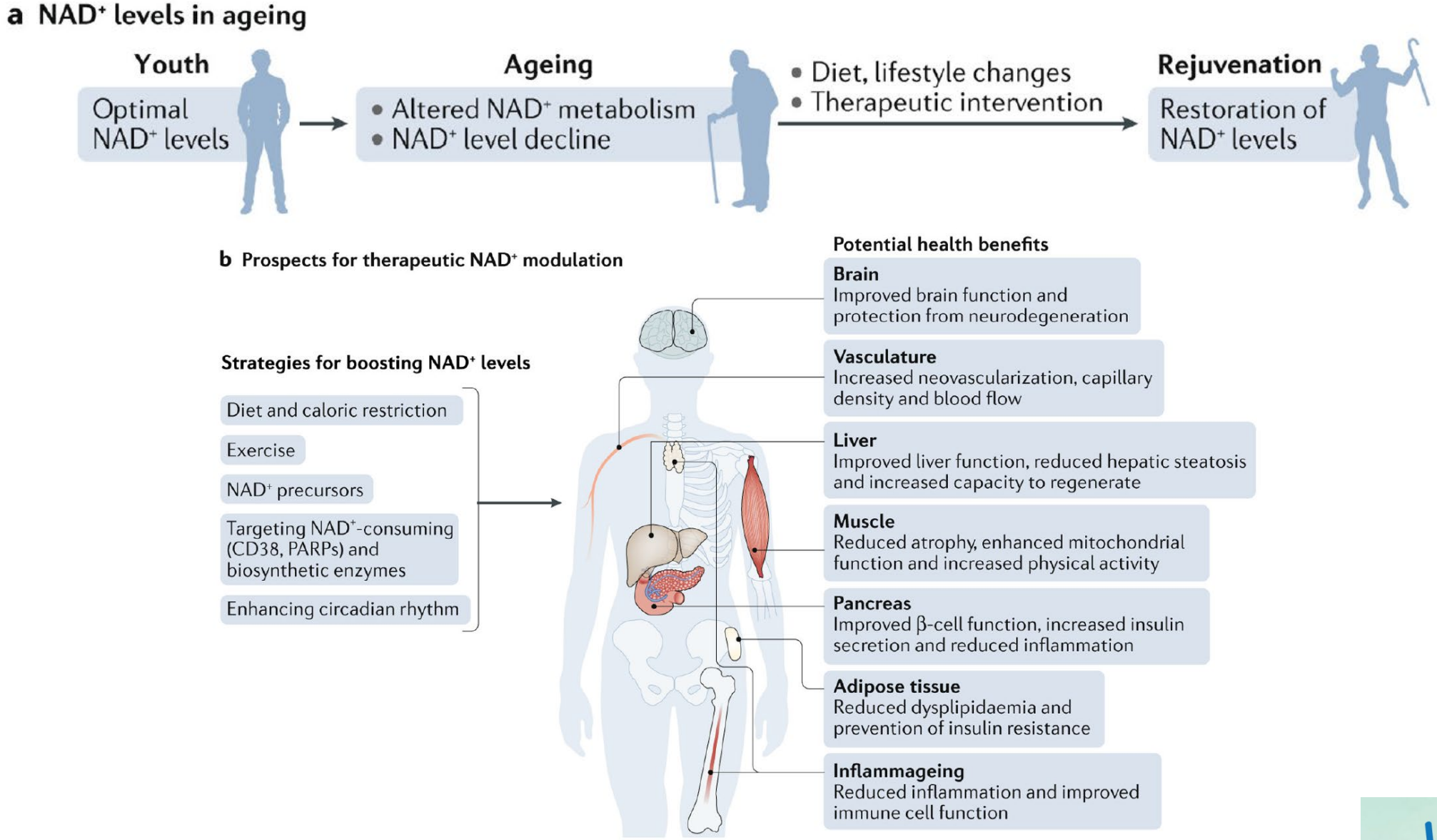
Factors that improve cellular sensitivity to thyroid hormones
- Vitamin A
- Exercise
- Zinc



Leigh-Brown *et al. Genome Biology* 2010, 11:215

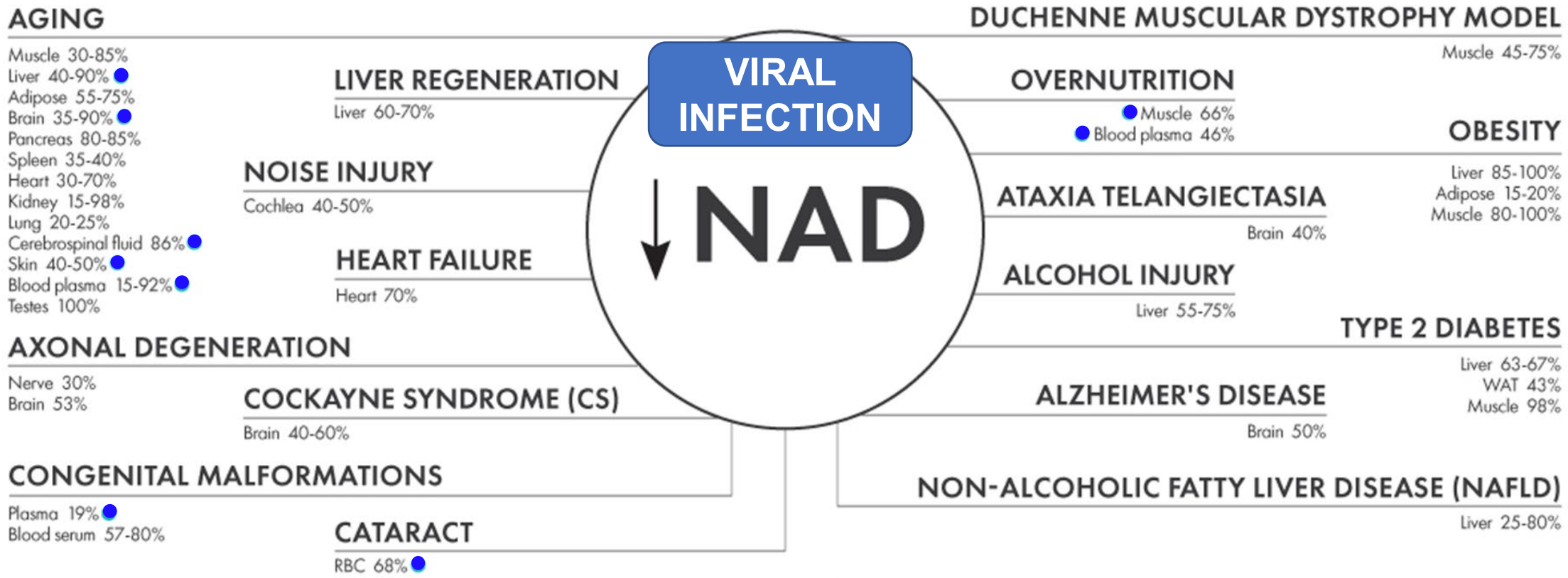


Well Aligned



Nat Rev Mol Cell Biol 2021; 22(2):119-141.

NAD+ Levels are Not Constant Through a Lifetime



● HUMAN STUDY

Cited Monograph Available Upon Request

NAD+ Full Body Therapeutic Considerations

Published in final edited form as:
Cell Metab. 2018 March 06; 27(3): 529–547. doi:10.1016/j.cmet.2018.02.011.

Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence

Luis Rajman[1], **Karolina Chwalek**[1], and **David A. Sinclair**[1,2,#]

[1]Paul F. Glenn Center for the Biological Mechanisms of Aging, Department of Genetics, Harvard Medical School, Boston, MA 02115, USA

[2]Laboratory for Ageing Research, Department of Pharmacology, School of Medical Sciences, The University of New South Wales, Sydney NSW 2052, Australia

Summary

Nicotinamide adenine dinucleotide (NAD), the cell's hydrogen carrier for redox enzymes, is well known for its role in redox reactions. More recently, it has emerged as a signaling molecule. By modulating NAD^+ sensing enzymes, it controls hundreds of key processes from energy metabolism to cell survival, rising and falling depending on food intake, exercise and the time of day. NAD^+ levels steadily decline with age, resulting in altered metabolism and increased disease susceptibility. Restoration of NAD^+ levels in old or diseased animals can promote health and extend lifespan, prompting a search for safe and efficacious NAD-boosting molecules. Such molecules hold the promise of increasing the body's resilience, not just to one disease, but to many, thereby extending healthy human lifespan.

eTOC Blurb

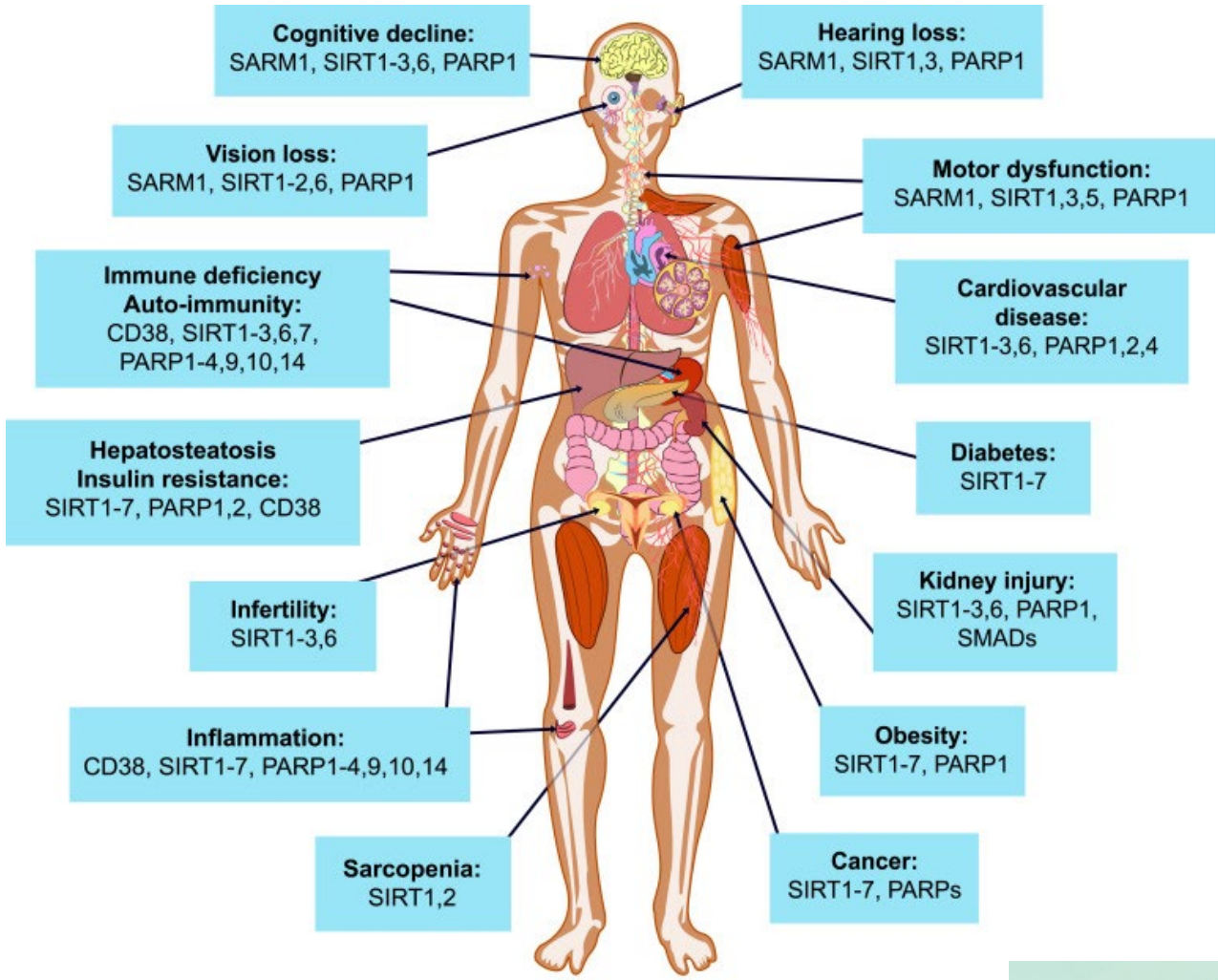
Nicotinamide adenine nucleotide (NAD+) has emerged as a key regulator of cellular processes that control the body's response to stress. Rajman et al. discuss NAD boosters, small molecules that raise NAD+ levels, which are now considered to be highly promising for the treatment of multiple diseases and the potential extension of human lifespan.

Keywords

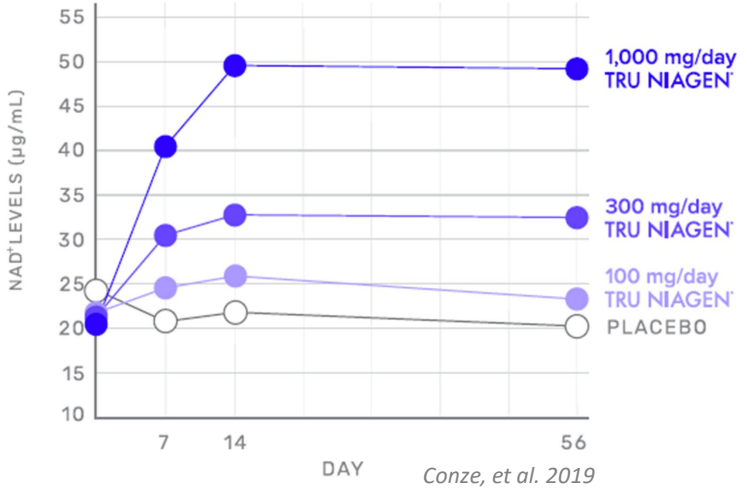
aging; epigenetics; sirtuins; chromatin; epigenetics; PARP1; cancer; cardiovascular disease; inflammation; nicotinamide riboside; nicotinamide mononucleotide; CD38; STAC

The rise, fall, and rise of NAD

Nicotinamide adenine dinucleotide (NAD) is one of the most important and interesting molecules in the body. It is required for over 500 enzymatic reactions



LARGEST PUBLISHED NIAGEN® CLINICAL, SCIENTIFIC REPORTS



Conze, et al. 2019

Design:

- 8-week, randomized, double-blind, placebo-controlled, parallel arm trial
- 140 healthy overweight adults
- NR 100 mg, 300 mg, or 1000 mg QD
- Measured kinetics and dose-dependent effects of chronic Niagen® supplementation

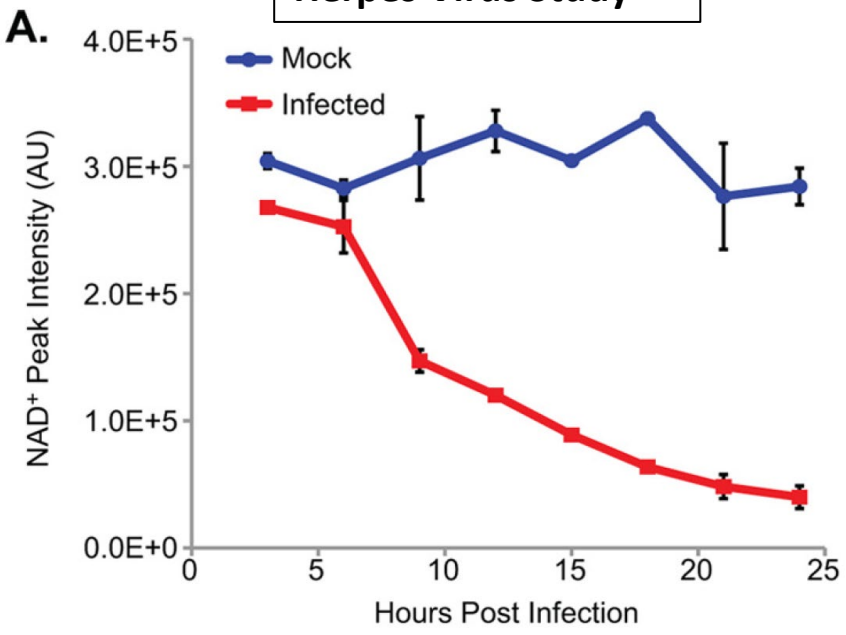
Results:

- On average, **300 mg/day** experienced a statistically significant **51% increase** in whole blood NAD^+ within two weeks.
- Increase was maintained throughout the remainder of the 8-week study **1000 mg/day** led to a **142% increase** in NAD^+ levels increases also sustained through the remainder of the study
- Validated safety and efficacy, when used consistently over time

Results directly support the NAD-boosting efficacy of TRUNIAGEN® PRO at 300 mg QD and demonstrates a dose response

- Titanium Immune
- Vit D3/K2 Melatonin
- NAC
- Quercetin

Herpes Virus Study



Medical Hypotheses 144 (2020) 110044

Contents lists available at ScienceDirect

Medical Hypotheses

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

Conclusion

The SARS-CoV-2 hyperinflammatory response is associated with high mortality. A deficiency of NAD^+, in the context of an elevated CD38, may be the primary factor related to the SARS-Cov-2 disease spectrum and the risk of mortality, as subclinical nutritional deficiencies may be unmasked by any significant increase in oxidative stress.

NAD^+ levels decline with age and are also reduced in conditions associated with oxidative stress as occurs with hypertension, diabetes and obesity. These same groups have also been observed to have high mortality following infection with COVID-19. Further consumption of NAD^+ in a pre-existent depleted state is more likely to cause progression to the hyperinflammatory stage of the disease through its limiting effects on the production of SIRT1.

Given that activation of SIRT1 is dependent on the availability of NAD^+ and zinc and that high levels of oxidative stress deplete NAD^+, thereby decreasing SIRT1 activity, nutritional support with NAD^+ precursors and SIRT1 activators, could minimise disease severity if administered prophylactically and or therapeutically. The significance of this hypothesis, if proven, has far-reaching consequences in the management of COVID-19 especially in third world countries, where resources and finances are limited.

Nutrients. 2021 Mar; 13(3): 976.

Journal of Virology (2012) 86(15): 8259–8268.

VITALLEO HEALTH

Supplement Facts

Serving Size: 2 Capsules
Servings Per Container: 30

Amount Per Serving		% DV
Vitamin A (as Palmitate)	825 mcg	92%
Vitamin C (Liposomal; as Ascorbic Acid)	300 mg	333%
Zinc (as Picolinate)	20 mg	182%
Astragalus Root Extract	250 mg	**
Fucoidan	200 mg	**
Olive Leaf Extract (Std. to 20% Oleuropein)	150 mg	**
Berberine HCl	100 mg	**
Cat's Claw Extract (*Uncaria tomentosa*)	100 mg	**
Citrus Bioflavonoids	100 mg	**
Oregano Oil Powder (Std. to 55-80% Carvactol)	100 mg	**
Quercetin Dihydrate	100 mg	**
Rosemary Oil	10 mg	**

**Daily Value (DV) not established

Other Ingredients: Methylcellulose Capsule, Sunflower Lecithin, Phosphatidylcholine

Well Aligned

Remember Way Back When--- There Were Buffets and Family Gatherings?

Food as Medicine for the Body and Microbiome

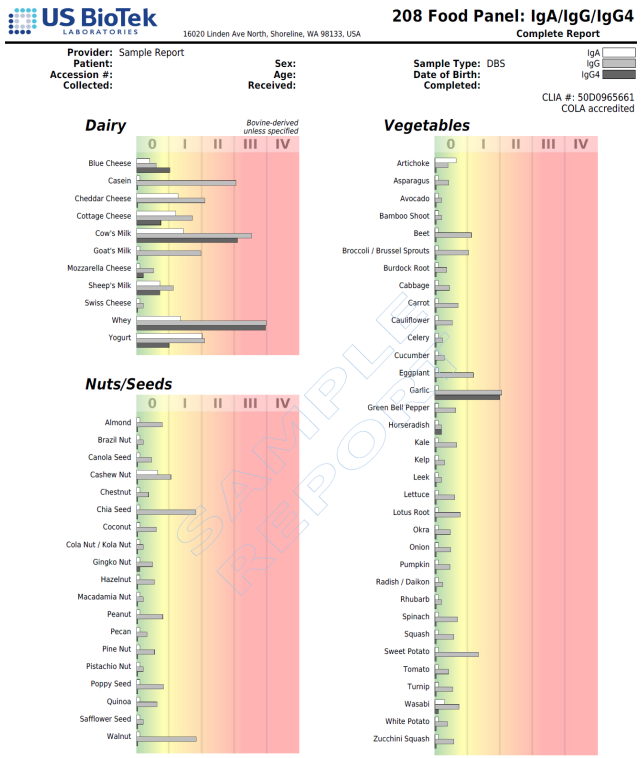
"The complement system is primarily activated by the recognition of pathogens (or non-self) by the pattern recognition molecules of this system."

Viral Exposure

&

Seasonal Allergies

IgG Food Sensitivities



Frontiers in Microbiology, June 2017, Volume 8; Article 1117.

Review paper

Role of Immunoglobulin G Antibodies in Diagnosis of Food Allergy

The role of IgG cells in triggering defence reactions to food allergens

IgG antibodies comprise 70–75 immunoglobulins in the serum and are the fundamental antibodies of secondary immune response. Four subclasses of immunoglobulin G are distinguished: the IgG1, IgG2, IgG3, and IgG4 subclasses amount to 66%, 23%, 7%, and 4% of the IgG antigen pool, respectively. The IgG1–3 immunoglobulins are able to activate the complement, while the IgG4 do not show such abilities. The IgG antibodies are

Adv Dermatol Allergol 2016; XXXIII (4): 253-256.

Table 1 | Properties of human IgG subclasses.

	IgG1		IgG2		IgG3		IgG4	
General								
Molecular mass (kD)	146		146		170		146	
Amino acids in hinge region	15		12		62[a]		12	
Inter-heavy chain disulfide bonds	2		4[b]		11[a]		2	
Mean adult serum level (g/l)	6.98		3.8		0.51		0.56	
Relative abundance (%)	60		32		4		4	
Half-life (days)	21		21		7/~21[a]		21	
Placental transfer	++++		++		++/++++[a]		+++	
Antibody response to:								
Proteins	++		+/–		++		++[e]	
Polysaccharides	+		+++		+/–		+/–	
Allergens	+		(–)		(–)		++	
Complement activation								
C1q binding	++		+		+++		–	
Fc receptors								
FcγRI	+++[c]	65[d]	–	–	++++	61	++	34
FcγRIIa$_{H131}$	+++	5.2	++	0.45	++++	0.89	++	0.17
FcγRIIa$_{R131}$	+++	3.5	+	0.10	++++	0.91	++	0.21
FcγRIIb/c	+	0.12	–	0.02	++	0.17	+	0.20
FcγRIIIa$_{F158}$	++	1.2	–	0.03	++++	7.7	–	0.20
FcγRIIIa$_{V158}$	+++	2.0	+	0.07	++++	9.8	++	0.25
FcγRIIIb	+++	0.2	–	–	++++	1.1	–	–
FcRn (at pH < 6.5)	+++		+++		++/+++[a]		+++	

Front. Immunol., 2014(10):1-17.

Simple Overview of Viral Illness Immunology

frontiers in Microbiology

REVIEW
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Complement Evasion Strategies of Viruses: An Overview

*Palak Agrawal, Renuka Nawadkar, Hina Ojha, Jitendra Kumar and Arvind Sahu**

Complement Biology Laboratory, National Centre for Cell Science, Savitribai Phule Pune University, Pune, India

Being a major first line of immune defense, the complement system keeps a constant vigil against viruses. Its ability to recognize large panoply of viruses and virus-infected cells, and trigger the effector pathways, results in neutralization of viruses and killing of the infected cells. This selection pressure exerted by complement on viruses has made them evolve a multitude of countermeasures. These include targeting the recognition molecules for the avoidance of detection, targeting key enzymes and complexes of the complement pathways like C3 convertases and C5b-9 formation – either by encoding complement regulators or by recruiting membrane-bound and soluble host complement regulators, cleaving complement proteins by encoding protease, and inhibiting the synthesis of complement proteins. Additionally, viruses also exploit the complement system for their own benefit. For example, they use complement receptors as well as membrane regulators for cellular entry as well as their spread. Here, we provide an overview on the complement subversion mechanisms adopted by the members of various viral families including *Poxviridae*, *Herpesviridae*, *Adenoviridae*, *Flaviviridae*, *Retroviridae*, *Picornaviridae*, *Astroviridae*, *Togaviridae*, *Orthomyxoviridae* and *Paramyxoviridae*.

Frontiers in Microbiology, June 2017, Volume 8; Article 1117

Food Induced Inflammation + Viral Induced Inflammatory Processes Unnecessary Burden

As a result the immune complexes are phagocytosed and then destroyed in the reticuloendothelial system. Simultaneously, the inflammatory process caused by the immune reaction between sIgG and food antigens might facilitate further damage and increased permeability of the digestive tract mucosa to food antigens. Therefore, the presence of specific IgG antibodies directed against food allergens reflects natural defence reactions of a body to allergens penetrating due to the damage of the epithelial barrier.

Adv Dermatol Allergol 2016; XXXIII (4): 253-256.

Immune Effect of Complement Products

1. Opsonization→ via C3b→ Activate Neutrophils + Macrophage → Phagocytosis

2. Cell Lysis→ Membrane Attack Complex (via C5b6789) → Rupture Bacterial Cell Wall

3. Chemotaxis→ via C5a→ Attracts Neutrophils + Macrophage to where Antigen is Present

4. **Activation of Mast Cells→ via C3a, C4a, C5a →Activate Mast Cells + Basophils→ Releases Histamine, Serotonin, etc.**

VITALLEO HEALTH

Springtime Burden

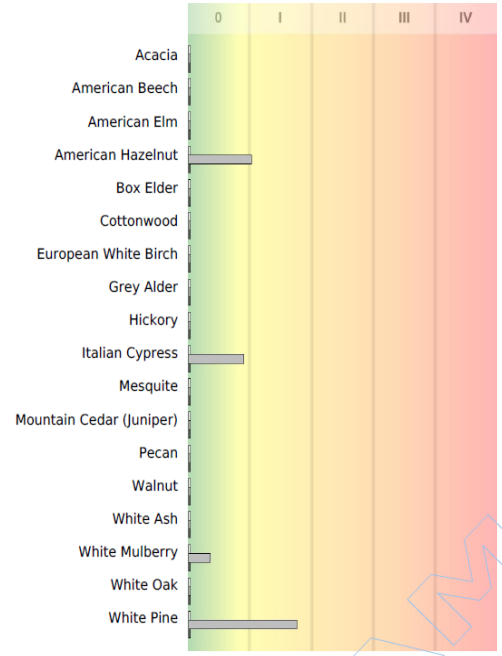
+

Food Reactivity

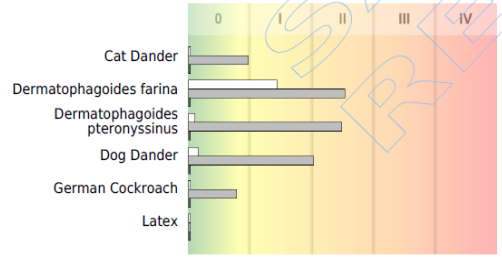
+

Infectious Agents

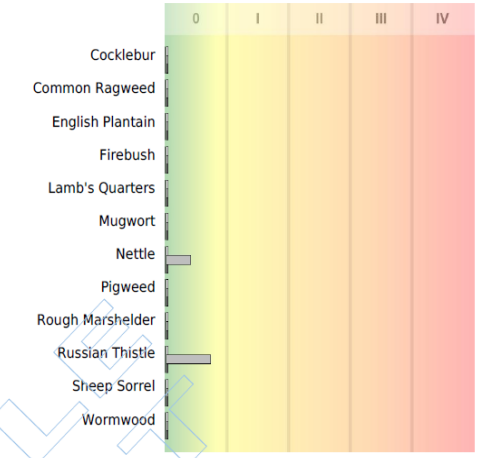
Trees



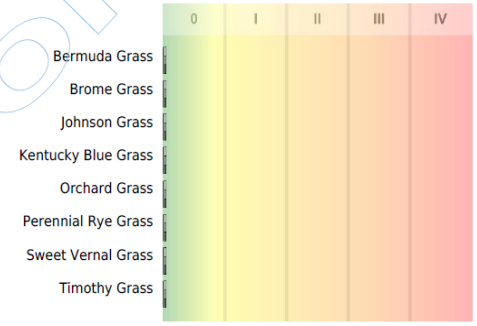
Indoor



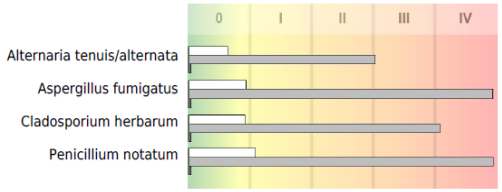
Weeds



Grasses



Molds

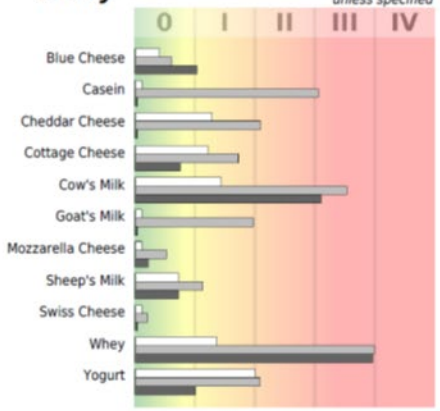


Well Aligned

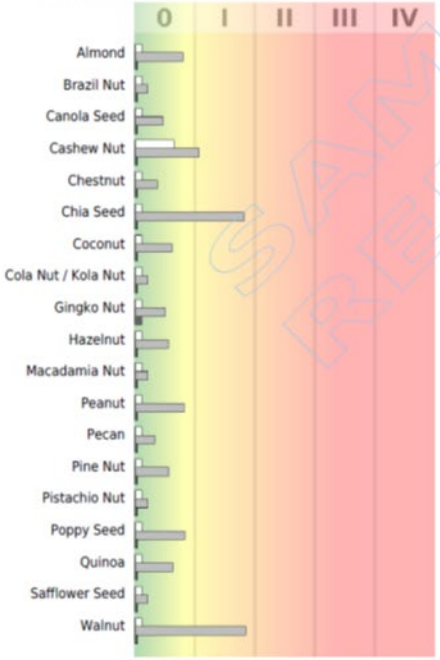
VITALLEO HEALTH

Dairy

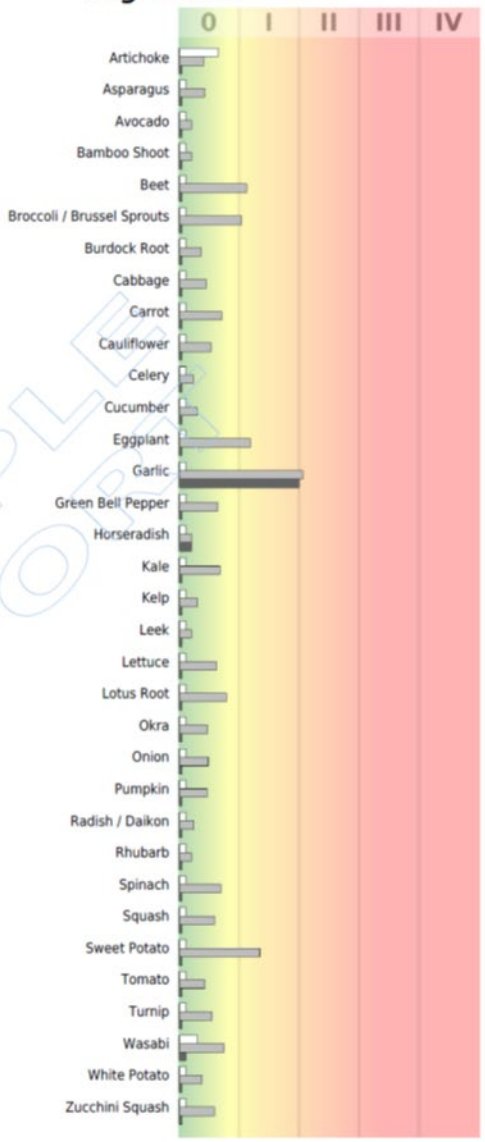
Bovine-derived unless specified

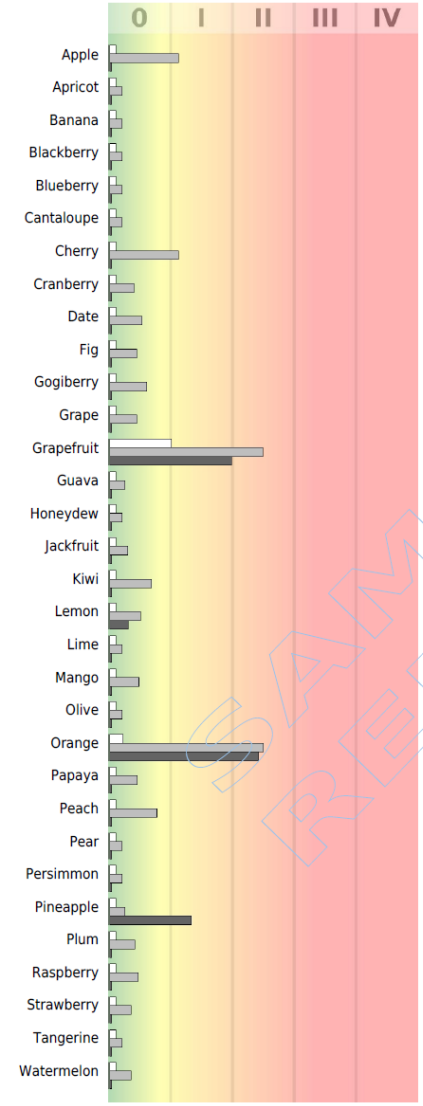


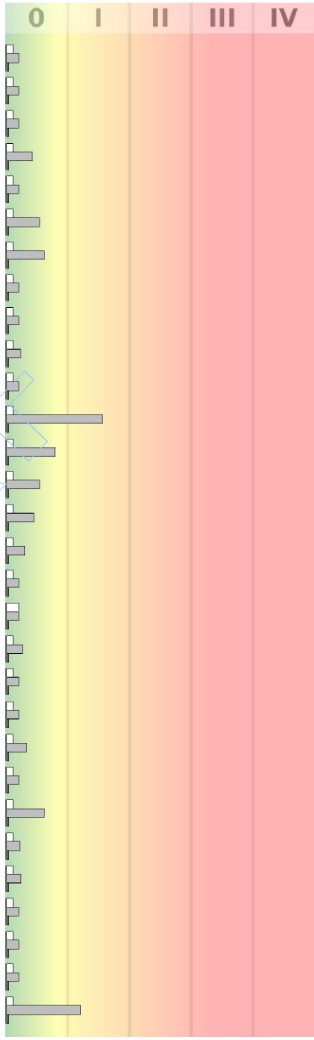
Nuts/Seeds



Vegetables



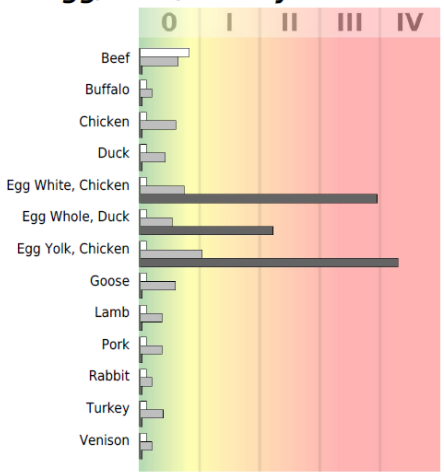




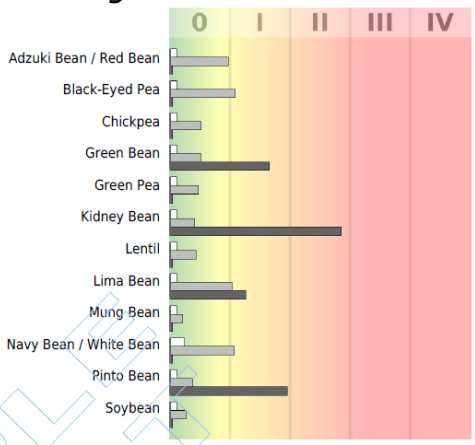
Well Aligned

VITALLEO HEALTH

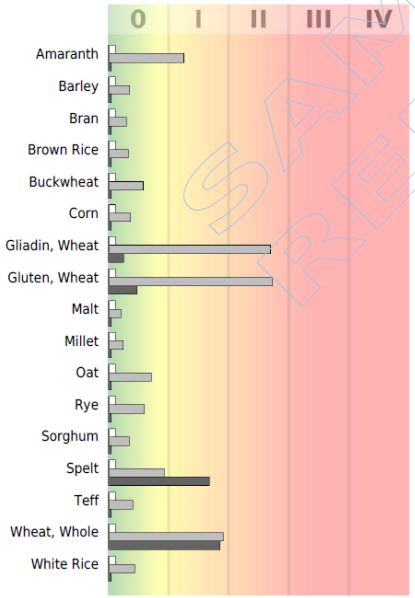
Egg/Meat/Poultry



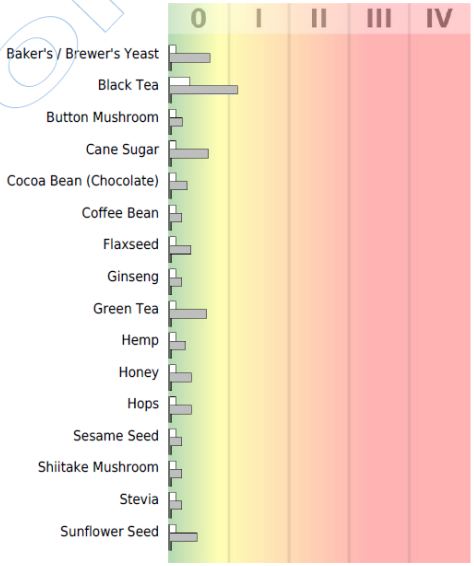
Legumes



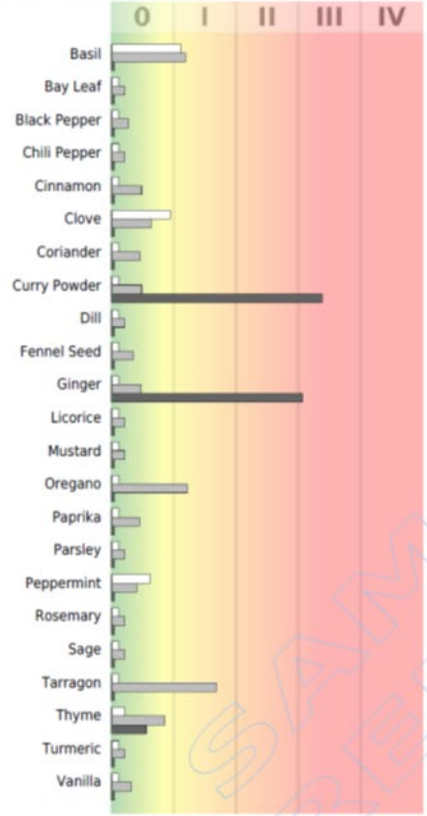
Grains



Miscellaneous



Herbs/Spices



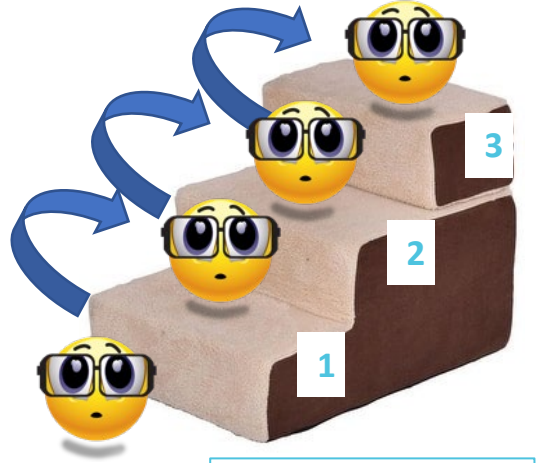
Candida Screen

Well Aligned

360 Degree Exposure
Surrounded by and from Within

It’s All About Total Burden!

IgG – Delayed Reaction



Reactive Food

Tuesday → 72 hours

Wednesday → 72 hours

Thursday → 72 hours

Little Scores can become BIG

3 Day Stacked Effect

What IgG Testing Tells Us

- It is a “Sensitivity Test”, NOT an Allergy Test (which is IgE)
- It is the most prevalent antibody in the bloodstream
- Other immunoglobulins to consider: IgA and/or IgG4 or IgE

Table 1: IgG Food Reactivity & Clinical Findings

Condition	Type of Study	Findings
Migraine	**Double-blind, randomized, crossover trial**	Exclusion of foods to which the patients had raised IgG antibodies led to a significantly reduced number of headache days and migraine attacks.
Asthma	**Case report**	Elimination of foods that elicited an IgG response resulted in a reduction in asthma symptoms, less dependence on medications, and improved quality of life.
Sleep	**Randomized, controlled trial**	Elimination of foods that triggered an IgG reaction along with health coaching to help with meal planning was associated with improved sleep in overweight/obese subjects.

Cephalalgia. 2010;30(7):829-37. | Glob Adv Health Med. 2015 Jan;4(1):62-6.
J Altern Complement Med. 2019 Feb;25(2):241-8.

Table 1: IgG Food Reactivity & Clinical Findings….

Condition	Type of Study	Findings
Irritable Bowel Syndrome	**Double-blind, randomized, controlled parallel study**	Patients with IBS experienced a pronounced reduction in severity of symptoms and improved quality of life when eating an elimination diet based on an IgG test compared to a sham diet.
	Retrospective Patient Chart Review	Patients with ulcerative colitis or Crohn's disease had significantly higher IgG antibody levels compared with healthy controls.
	Age-Matched Healthy Controls Study	IBS patients had significantly higher titers of IgG antibody to crab, egg, shrimp, soybean, and wheat than controls. FD patients had significantly higher titers of IgG antibody to egg and soybean than controls.
	Open label pilot study	IBS patients who had failed standard medical treatments experienced improvement in pain, stool frequency, and quality of life after they were put on a food elimination and rotation diet based upon IgG testing.

Gut. 2004 Oct;53(10):1459-64. | PLoS One. 2014 Nov 13;9(11):e112154.
Clin Exp Allergy. 2007 Jun;37(6):823-30. | J Am Coll Nutr. 2006 Dec;25(6):514-22.

Role of Immunoglobulin G Antibodies in Diagnosis of Food Allergy

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Antibody response to:								
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Polysaccharides	+		+++		+/–		+/–	
Allergens	+		(–)		(–)		++	
Complement activation								
C1q binding	++		+		+++		–	
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Simple Overview of Viral Illness Immunology

frontiers in Microbiology

REVIEW
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Complement Evasion Strategies of Viruses: An Overview

*Palak Agrawal, Renuka Nawadkar, Hina Ojha, Jitendra Kumar and Arvind Sahu**

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Frontiers in Microbiology, June 2017, Volume 8; Article 1117.

Food Induced Inflammation + Viral Induced Inflammatory Processes Unnecessary Burden

As a result the immune complexes are phagocytosed and then destroyed in the reticuloendothelial system. Simultaneously, the inflammatory process caused by the immune reaction between sIgG and food antigens might facilitate further damage and increased permeability of the digestive tract mucosa to food antigens. Therefore, the presence of specific IgG antibodies directed against food allergens reflects natural defence reactions of a body to allergens penetrating due to the damage of the epithelial barrier.

Adv Dermatol Allergol 2016; XXXIII (4): 253-256.

A Glimpse of the Scientific Literature

> . . . The complement system is owning to direct neutralization of cell-free viruses, lysis of virus infected cells, induction of antiviral state, and boosting of virus specific immune responses due to recognition of effector fragments of complement along with viral antigens by immune cells.

Frontiers in Microbiology, June 2017, Volume 8; Article 1117

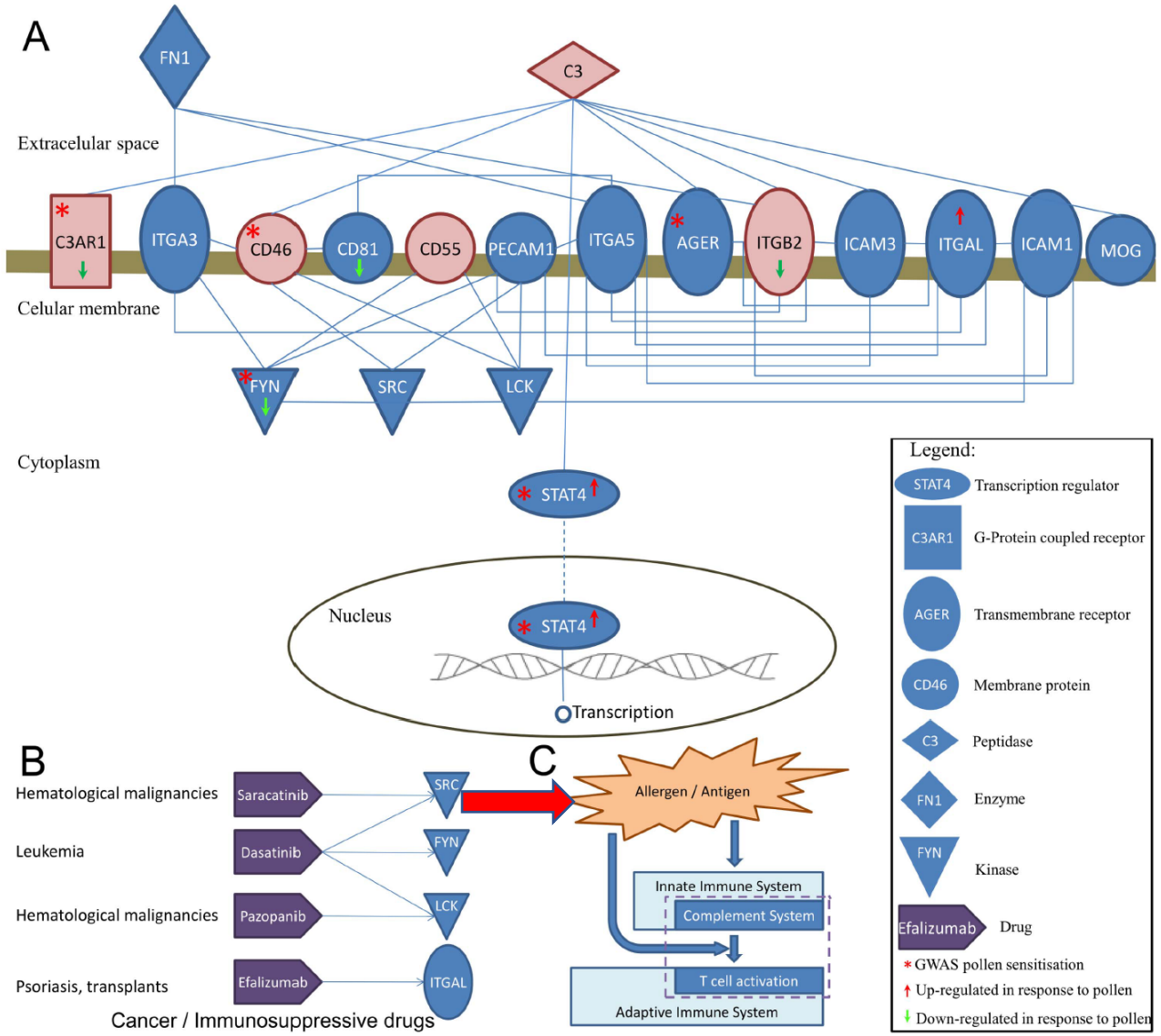


Figure 3. Inter-pathway interactions analysis identifies disease network linking complement system to CD4+ T cell activation. (A) INPAR network has 19 genes that link Complement system to CD4+ T cell activation. Blue nodes correspond to genes involved in T cell activation while red nodes correspond to genes involved in the complement system. (B) Drug target network analysis of the INPAR-N showing that several immunosuppressive drugs target the INPAR-N network genes, particularly the Src family of tyrosine kinases, including Src, Fyn, Lck. (C) Allergens trigger the innate immune system that in turn triggers the adaptive immune system. INPAR-N includes complement system proteins that interact with T cell membrane proteins.

doi:10.1371/journal.pone.0074821.g003

Immune Effect of Complement Products

1. Opsonization→ via C3b→ Activate Neutrophils + Macrophage → Phagocytosis

2. Cell Lysis→ Membrane Attack Complex (via C5b6789) → Rupture Bacterial Cell Wall

3. Chemotaxis→ via C5a→ Attracts Neutrophils + Macrophage to where Antigen is Present

4. **Activation of Mast Cells→ via C3a, C4a, C5a →Activate Mast Cells + Basophils→ Releases Histamine, Serotonin, etc.**

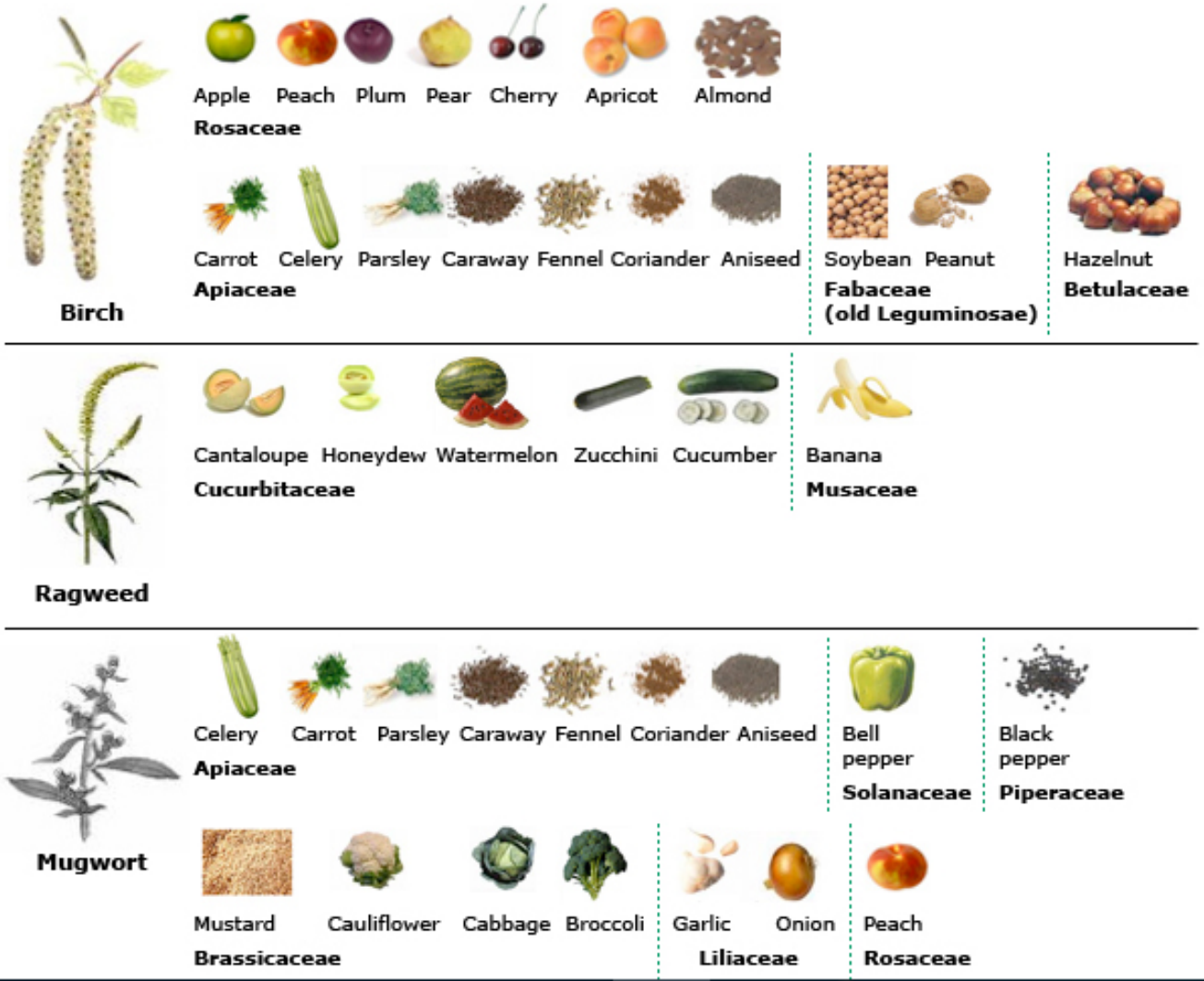
Birch Cross-Reactivity

- In the Western developed world, birch pollen allergy is the form of allergic rhinitis most likely to be accompanied by food allergies.

- **Up to 80 percent of people who suffer from birch pollen allergies also have food allergies.**

Acta Clin Belg. 2012 Sep-Oct;67(5):317-21.

Cross-reactivity patterns in oral allergy syndrome (pollen-food allergy syndrome)



Takeaway Points

- Cross-reactivity can be seen in people who are allergic to pollen and have allergy symptoms when exposed to certain food groups.
- **In adults, up to 60 percent of all food allergic reactions occur because of cross-reactions between food and pollen.**
- Birch pollen cross-reacts with hazelnuts, apples, celery, carrot and soy.

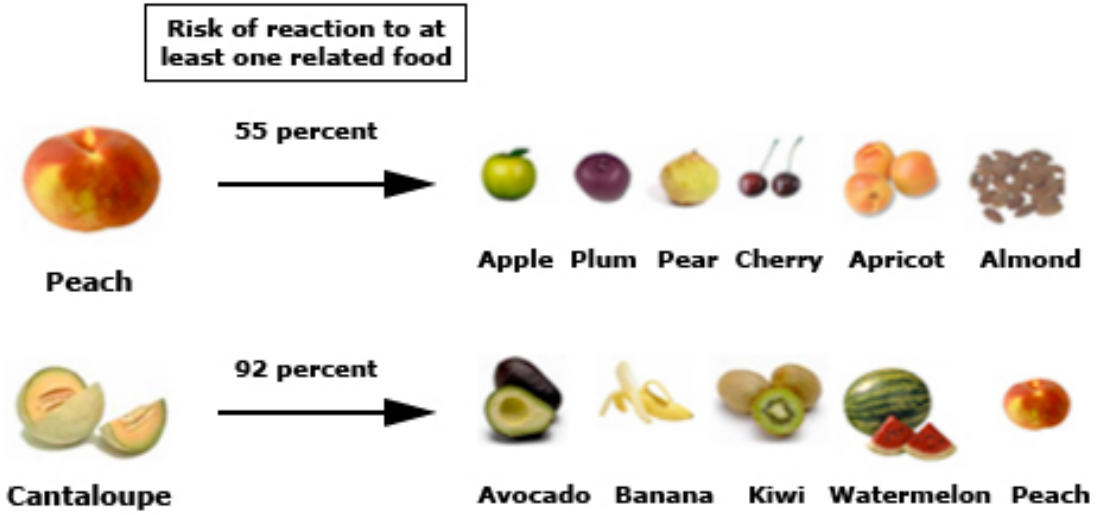
www.texasallergyexperts.com/oralallergy.html

Clin Exp Allergy. 2007;37:261-9.

Not So Peachy

Seventy-five percent of patients who suffer from peach allergy recognize the peach LTP, which is to blame for food cross-reactivities—especially those related to fruits and nuts—as well as pollens from mugwort and plane trees.

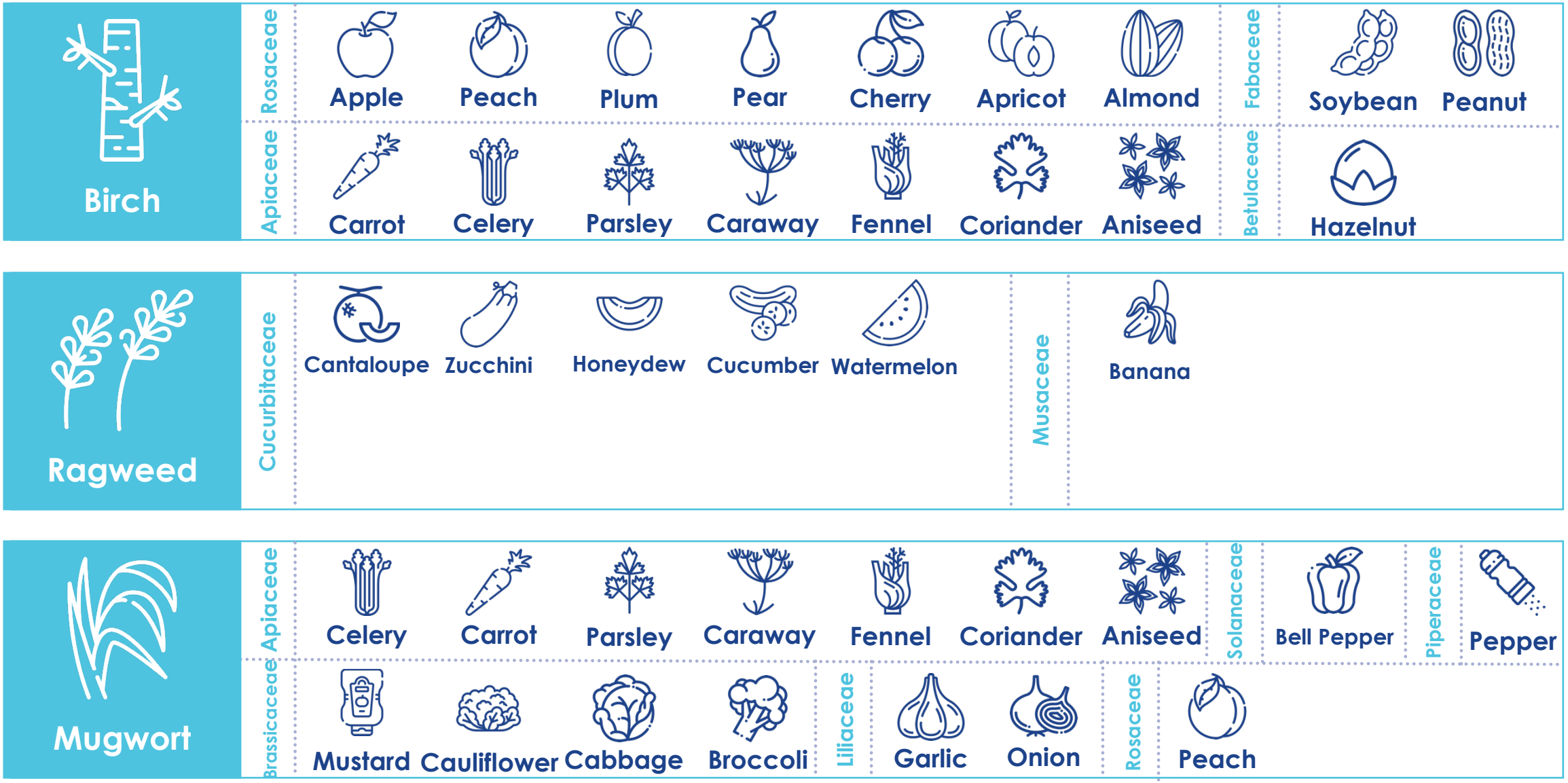
Knowing which foods cross-react with pollen sources is critical for diagnosing patients and improving the treatment of their allergies.



www.texasallergyexperts.com/oralallergy.html

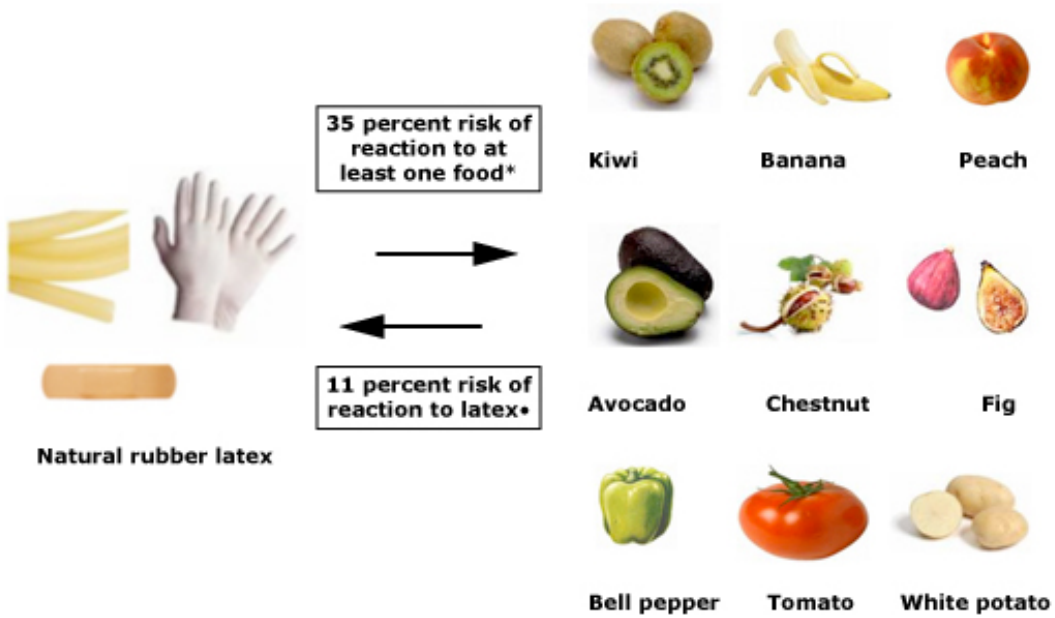
Clin Exp Allergy. 2007;37:261-9.

Cross-Reactivity Patterns



Latex Cross-Reactivity

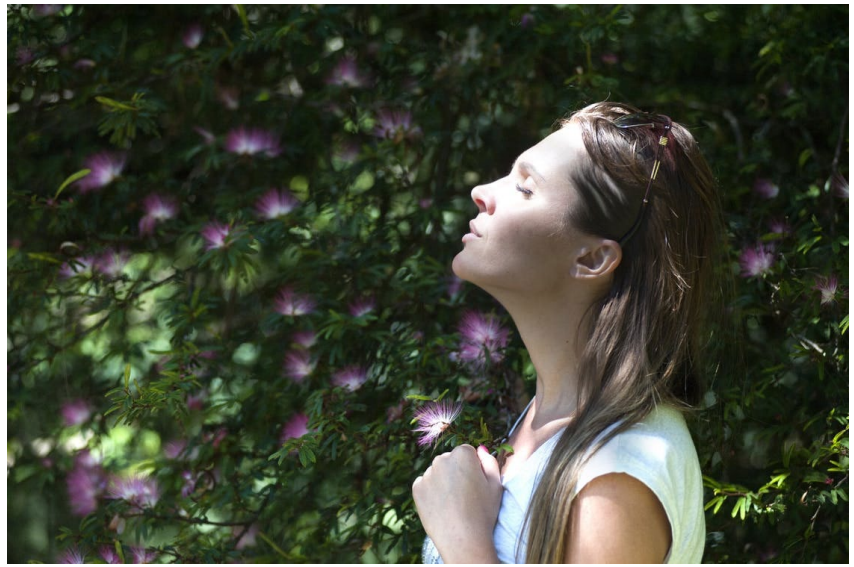
- Allergy to latex is common and well-known. About 50 to 60 percent of people who are allergic to latex also have "latex-fruit syndrome," where they develop adverse reactions after consuming cross-reacting vegetables and fruits.
- The most common foods to cross-react with latex are bananas, avocados, chestnuts and kiwis. Latex also cross-reacts with chickpeas and bell peppers.



Int J Immunopathol Pharmacol. 2012 Apr-Jun;25(2):445-53. | Rev Prat. 2006 Feb 15;56(3):289-95.
Food Chem. 2013 May 1;138(1):13-8. | Clin Exp Allergy. 2004 Nov;34(11):1739-46.

Total Ingestion of Allergenic Exposures

- Remembering up to 60 percent of all food allergic reactions occur because of cross-reactions between food and pollen.



J Dtsch Dermatol Ges. 2008 Jul;6(7):573-83.

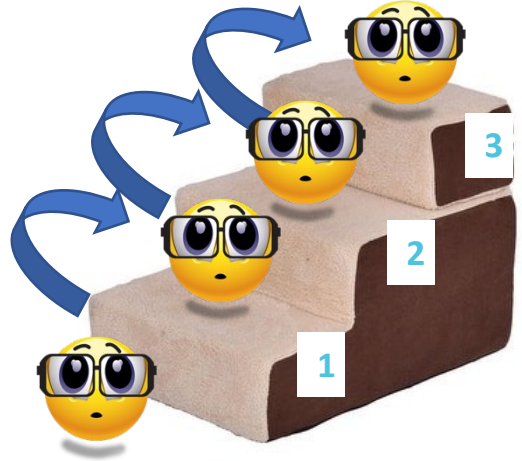
It is All About Total Burden!!!

Time to AVOID the Final Straw that Breaks the Camel's Back

Cross-Reactivity Master List

Allergen	Possible Cross-Reactive Items
Alder Pollen	Almond, Apple, Celery, Cherry, Hazelnut, Parsley, Peach, Parsley, Pear
Almond	Alder, Birch, Elm, Hazelnut, (all other nuts)
Aniseed	Mugwort
Apple	Birch, Alder, Celery, Cherry, Elm, Hazelnut, Mugwort, Peach, Pear, Potato, Ragweed, Rye-Grass, Tomato
Apricot	Alder, Birch, Elm, Hazelnut
Ash Pollen	Birch, Lilac, Olive Tree, Privet, Timothy Grass
Avocado	Banana, Kiwi, Latex
Banana	Avocado, Birch pollen, Kiwi, Latex, Melon
Basil	Alder, Birch, Elm, Hazelnut
Bermuda Grass	Celery, Cocksfoot, Olive, Rapeseed, Sunflower (Other grass species)
Birch Pollen	Almond, Aniseed, Apple, Apricot, Buckwheat, Carrot, Caraway, Celery, Cherry, Coriander, Cumin, Dill, Fennel, Hazelnut, Honey, Kiwi, Nectarine, Parsley, Parsnip, Pear, Peach, Peanut, Peppers, Persimmons, Plum, Potato, Prune, Soybean, Spinach, Tomato, Walnut, Wheat, (all tree nuts) & (possibly all foods in Birch Weeping)
Birch Weeping	Aniseed, Apple, Ash pollen, Banana, Beech pollen, Caraway, Carrot, Celery, Chamomile, Cherry, Chestnut, Coriander, Curry, Elm, Fennel seed, Hazelnut, Hornbeam, Kiwi, Latex, Lychee, Mango, Mugwort, Olive, Orange, Paprika, Parsley, Peach, Pear, Pepper, Potato, Soybean, Tomato, (all tree nuts) & (possibly all foods in Birch Pollen)
Brazil Nut	Alder, Birch, Elm, Hazelnut, (all other nuts)
Caraway Seeds	Alder, Birch, Elm, Mugwort, Hazelnut
Cantaloupe	Avocado, Banana, Peach, Kiwi, Watermelon
Carrots	Birch Weeping, Celery, Mugwort, Cucumber, Lettuce, Mango, Melon
Chamomile	Mugwort
Cherry	Alder, Apple, Birch Weeping, Elm, Hazelnut, Peach

Complement Burden of:
IgG Foods+ Cross-Reactivity+ Virus



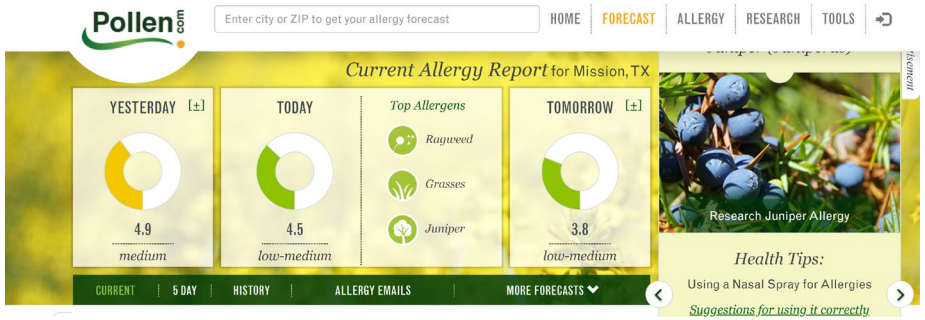
Tuesday → 72 hours

Wednesday → 72 hours

Thursday → 72 hours

Little Scores can become **BIG**

3 Day Stacked Effect



Vitamin D and Immune Competence

Seven Steps to Help Fortify and Minimize Viral Risk

1. First and foremost stay calm and get your rest!!!
2. Wash your hands and portable electronic devices!!!
3. Stay Hydrated.

   →Mucous membranes were designed to be moist.
4. Use Common Sense. Steer clear of the "Spray-Zone"
5. Break the Face-Touching Habit

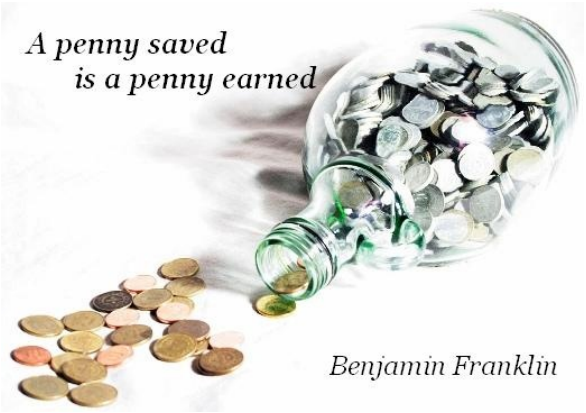
   →USA Today found that the average person touches their face 23 times an hour.
6. Eat Well to Be Well- Avoid Food Sensitivities and Allergies (also low histamine diet)
7. Supplementing your Diet with Botanicals and Vitamins

   →Vitamins D, Vitamin C, Zinc, Selenium (**NAD+ as Nicotinamide Riboside®**)

   →N-Acetyl Cysteine (clearing mucus and glutathione precursor); Glutathione, **Lipoic Acid**

   →**Anti-Viral/Anti-Bacterial- Botanicals and Nutraceuticals**

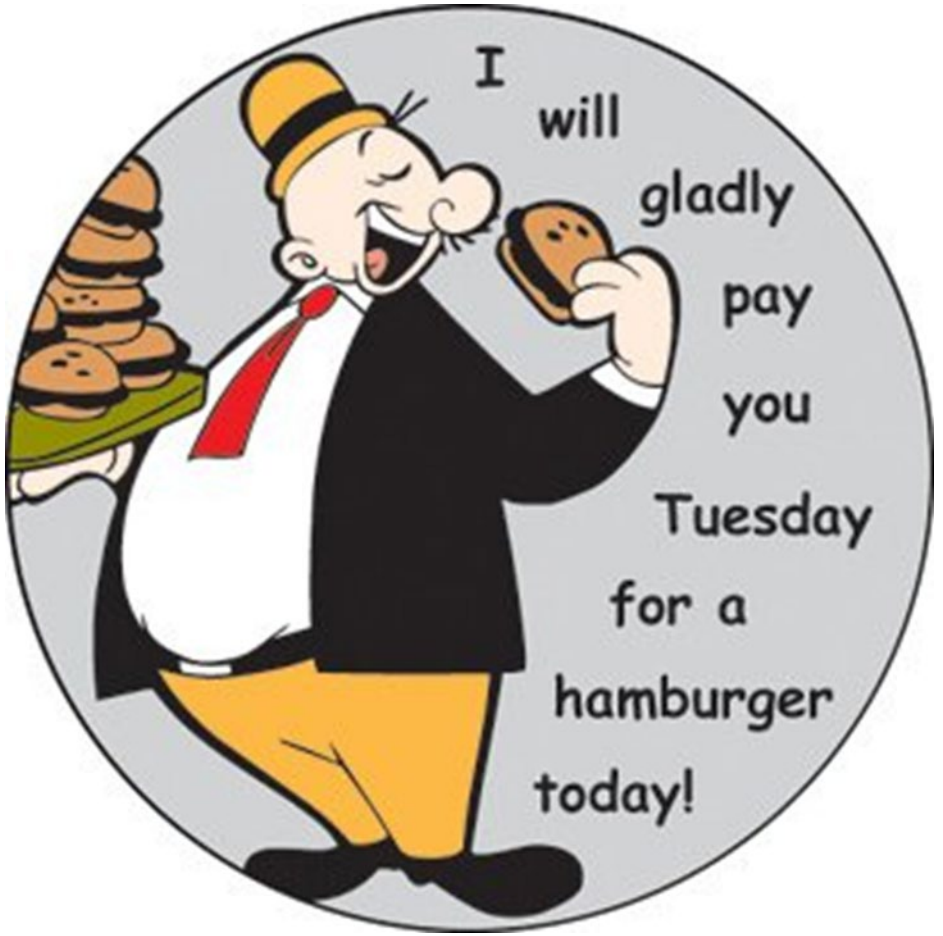
What is the Take Away?



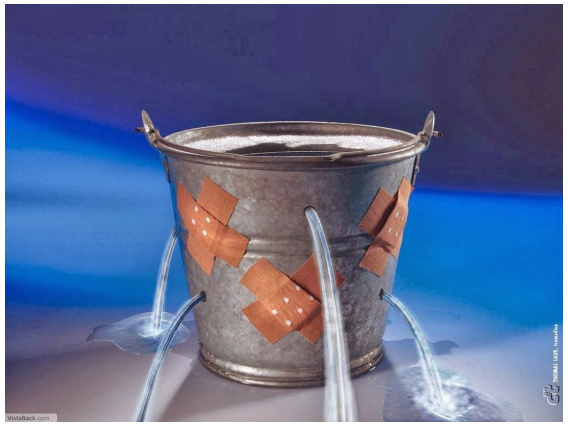
Testing and Supplements

- Organic Acid Test
- Adrenal Testing
- Male/Female Panel

- Edison Multi
- AdrenoCare plus
- Stress Response
- Melatonin
- TruNiagen – NAD
- Titanium Immune

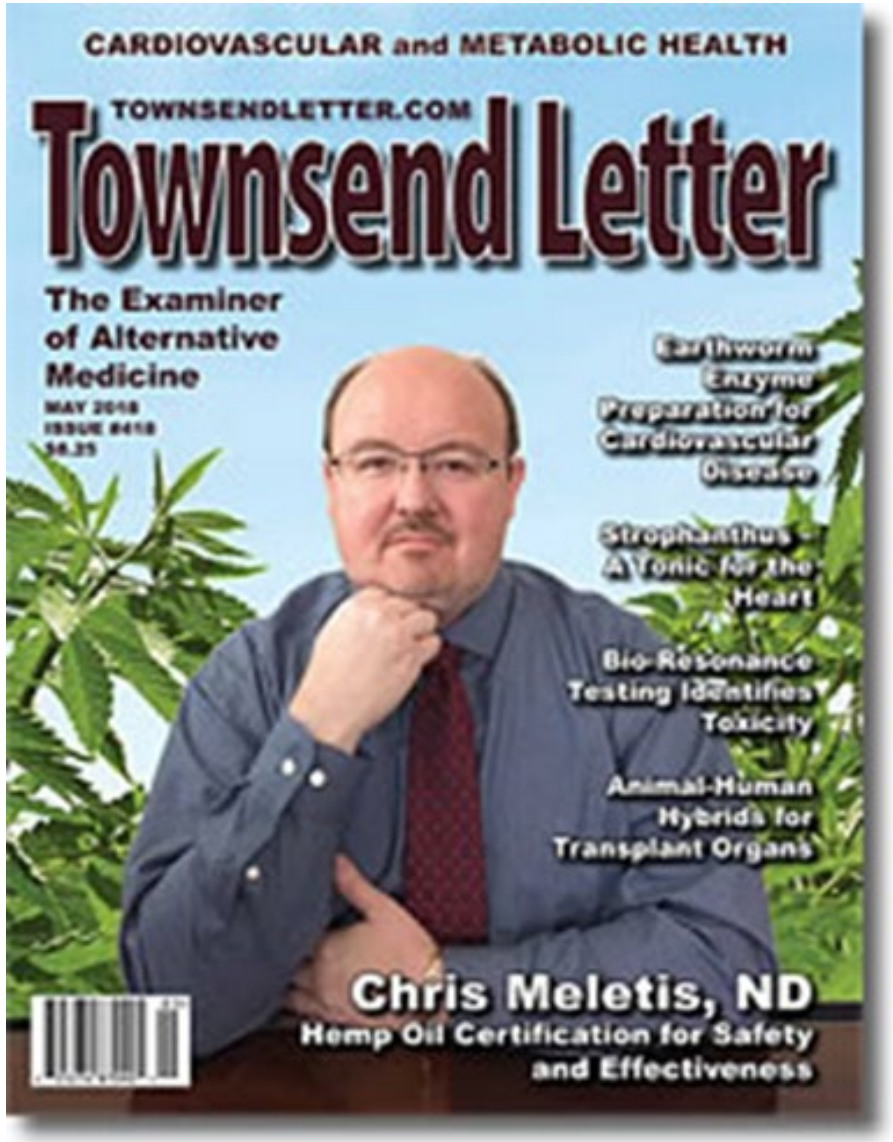


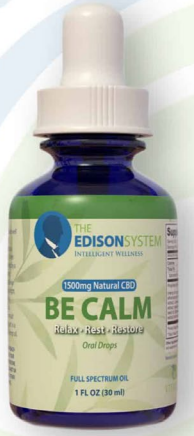
Testing NOT GUESSING!!!




Field Trip Time!!!
Diving Into the Weeds

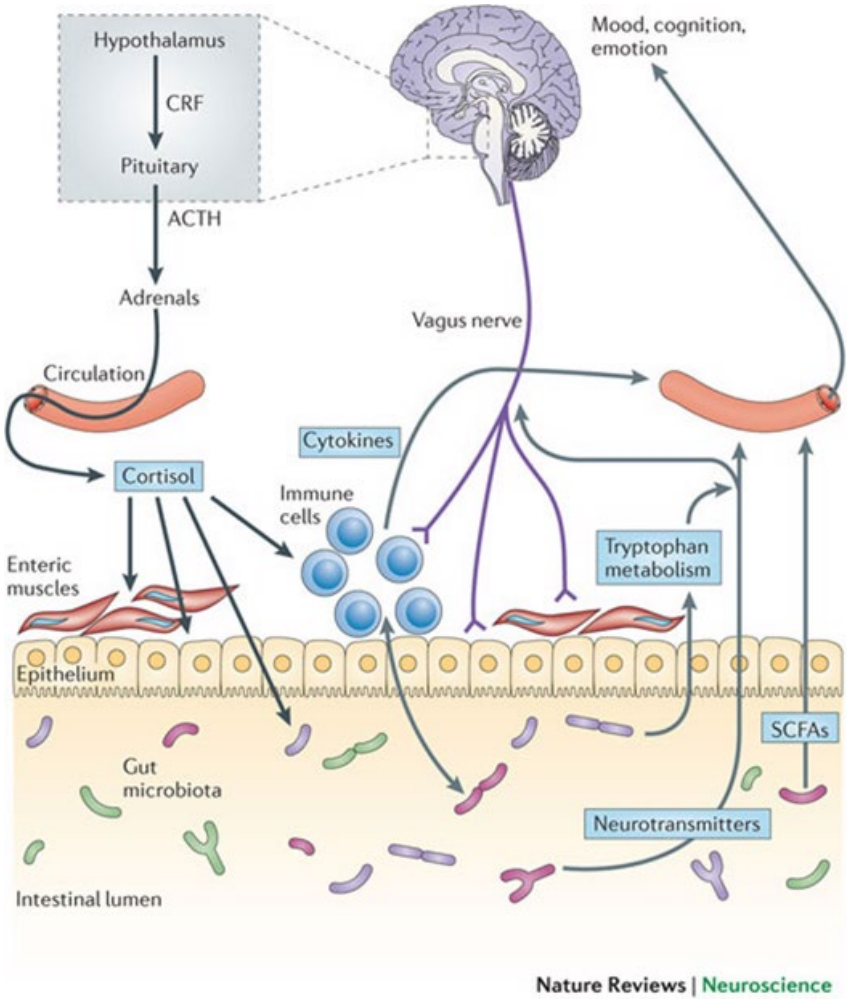
VITALLEO HEALTH





Well Aligned

Supporting the Endocannabinoid System for Enhanced HPA Axis Function, Neurochemistry and Other Essential Clinical Outcomes



What Is The Endocannabinoid System?

- The endocannabinoid system is a natural system in the body that regulates mood, sleep, appetite, memory and many other aspects of health.
- Your body makes natural endocannabinoids on its own. But there are also phytocannabinoids that act on this same system.
- Cannabidiol (CBD), found in hemp oil and *Cannabis sativa*, is one of those phytocannabinoids.
- **Many of CBD's beneficial effects on the body are due to its ability to regulate the endocannabinoid system.**

An Endogenous Gatekeeper

- The endocannabinoid system is known to play an important role in regulating immunity and scientists consider it to be one of the “gatekeepers” of the immune system.

- The endocannabinoid system includes receptors known as cannabinoid receptors 1 and 2 (CB1 and CB2) as well as the endogenous cannabinoids **anandamide** (AEA) and 2-arachidonoylglycerol **(2-AG)** and enzymes that influence the production of these endocannabinoids.

- There’s scientific evidence that cells of the immune system express both CB1 and CB2, although CB2 concentrations are higher than CB1.

Front Immunol. 2017 Nov 10;8:1487.
Free Radic Biol Med. 2011 Sep 1;51(5):1054-61.

The Endocannabinoid System: The Key To Feeling More at Peace

When your endocannabinoid system is working properly it actually keeps your HPA axis working its best, too.

The endocannabinoid system can act like a gatekeeper of the HPA axis, preventing it from becoming overactive and churning out too much cortisol.

It can also prevent the HPA axis from becoming underactive.

Integration of endocannabinoid signaling into the neural network regulating stress-induced activation of the hypothalamic-pituitary-adrenal axis.
Curr Top Behav Neurosci. 2009;1:289-306.

Functional interactions between stress and the endocannabinoid system: from synaptic signaling to behavioral output.
J Neurosci. 2010;30(45):14980-14986.

Allostatic Load and Impact on Homeostasis

Neuroendocrinology Letters Volume 35 No. 3 2014

Clinical endocannabinoid deficiency (CECD) revisited:

Can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

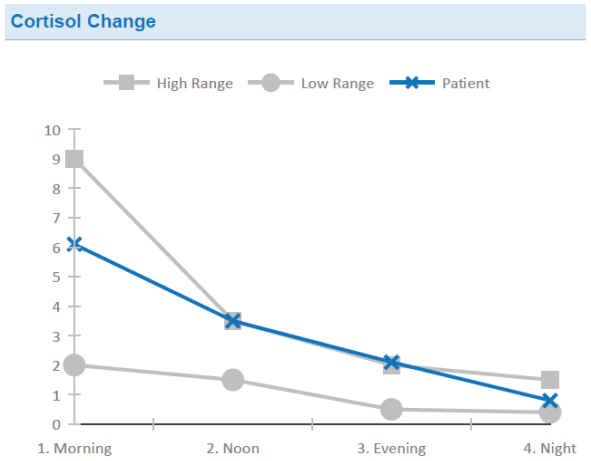
Abstract

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.

RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestional mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.

CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.



Cani

Attention-deficit
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Attention deficit di
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**The Role of the Endoc
System in ADHD and A**

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In last month's *Tow*
Chris Meletis discussed
Center for Cannabis
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Chief Medical Officer–U
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cannabis, Dr. Meletis
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These articles can
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Insights fr
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Cannabinoid-

by Chris D

This is the third and final installment
a series of articles discussing cannabinc
rich hemp oil and a new certificat
program for dietary supplem
manufacturers and healthc
practitioners offered by the Internatio
Center for Cannabis Therapy (ICCT).
Chief Medical Officer–USA of the IC
a Czech Republic-based partnership
qualified doctors and scientists w
specialize in the medical application
cannabis, Dr. Meletis is an expert
the clinical applications and resea
supporting the use of cannabinc
rich hemp oil and its effects on
endocannabinoid system. Last mon
we discussed the endocannabin
system, its role in health, and how
endocannabinoid system interacts w
the adrenals, sex hormones, and g
We also shared pre-clinical and clini
research and Dr. Meletis' observatic
about the use of cannabinoid-rich he
oil in clinical practice, with an emphasis
the management of pain and inflammat
and how to balance the endocannabin
system without overwhelming
receptors. In this article, we'll addr
the use of cannabinoid-rich hemp
in applications such as Alzheime
disease, depression, anxiety, irrita
bowel syndrome, stroke, schizophrer
autoimmunity, and epilepsy, amc
other uses. We'll also discuss the role
cannabinoids in the gut-brain axis.

Healthcare practitioners who w
to delve deeper into the benefits
cannabinoid-rich hemp oil, understa
the legal ramifications of prescrib

Cannabidiol's Promising Role in Muscle and Visceral Pain

by Chris D. Meletis, ND, and Kimberly Wilkes

The endocannabinoid system within our bodies regulates many aspects of health, including pain control. This system is comprised of endocannabinoids produced within the body, including anandamide (arachi-donylethanolamide) and 2-arachidonylglycerol (2-AG), which are able to activate receptors in the endocannabinoid system. The presence of this system was an intriguing discovery, as it indicated our bodies produce substances similar to cannabis that are able to switch endocannabinoid receptors on and off.

Two important receptors in this system that are involved in pain management are cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2).[1] Activation of CB_2 receptors suppresses the pain response to thermal and mechanical stimuli,[2,3] thermal and tactile hypersensitivity produced by peripheral inflammation,[3-5] and neuropathic pain.[6] As with endocannabinoids produced in the body, phytocannabinoids such as Δ^9-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa* plant, and cannabidiol (CBD), a non-psychoactive component, are able to activate endocannabinoid receptors.

Endocannabinoids can indirectly work through the same receptors as opioid drugs to control pain. CB_2 receptors indirectly stimulate opioid receptors found in primary afferent pathways.[7] Furthermore, CB_1 expression is weak in the areas of the brain stem that regulate respiration. This suggests that respiratory depression, a potentially fatal adverse effect of opioid drugs, would not occur when using phytocannabinoids as painkillers.[1]

An extensive amount of evidence points to the endocannabinoid system's role in the management of pain caused by a wide spectrum of conditions. This article will focus exclusively on endocannabinoid and phytocannabinoid regulation of two common types of pain: muscle and visceral pain.

Musculoskeletal Pain, Fibromyalgia, and Temporomandibular Disorders

Chronic widespread musculoskeletal pain is a common disorder, occurring in approximately 10% of the population.[8] A subgroup of patients with this type of pain have fibromyalgia, which occurs in 3% to 5% of the population.[8] In women with musculoskeletal pain, levels of the endocannabinoids oleoylethanolamide and stearoylethanolamide were altered compared with healthy controls.[9]

Endocannabinoid alterations are thought to play a role in fibromyalgia and its frequent comorbidities such as migraines and irritable bowel syndrome.[10] A hallmark of fibromyalgia is sore muscles. The pain usually occurs in similar locations in different patients suffering from this disorder. Studies indicate there is an association between fibromyalgia and endocannabinoid deficiency and this deficiency may play a role in the sore muscles of this condition.[10-12] For this reason, cannabinoids are thought to be useful in chronic pain conditions such as myofascial pain syndrome and temporomandibular joint pain (TMJ).[10]

CBD has analgesic and anti-inflammatory effects that may prove beneficial in disorders that involve muscle pain.[13] CBD was first isolated in 1940, but it is only relatively recently that its full potential was realized due to studies showing its antioxidative, anti-inflammatory, and neuroprotective effects.[14] Some of these actions are independent of the CB_1 and CB_2 receptors.[15]

In studies using rodent models of inflammation, CBD reduces the migration and infiltration of inflammatory cells (neutrophils).[16] Cannabinoids are also thought to reduce inflammation by increasing the generation of eicosanoids, signaling molecules involved in regulating inflammation and pain.[17] In addition, CBD lowers production of the inflammatory cytokine TNFα and reduces fatty acid amidohydrolase (FAAH) activity, an enzyme that degrades the anti-inflammatory endocannabinoid anandamide.[17] CBD's reduction in FAAH causes a raise in anandamide production.[17] In animal and cell culture studies, CBD has demonstrated an anti-inflammatory effect that is several hundred times greater than aspirin.[13] CBD's analgesic properties are due to mechanisms that include acting as a lipoxygenase inhibitor, increasing the release of prostaglandin (PGE2) from synovial cells, and blocking production of leukotriene B4 in human polymorphonuclear cells.[13]

Modulating Our Zen

The fact the endocannabinoid system is a gatekeeper of the HPA axis is probably one of the reasons why several studies have shown that CBD oil supports calm and relaxed feelings in subjects undergoing a simulated public speaking test.

CBD also promotes a restful night's sleep. (**REST**oration)

This makes sense since an overactive HPA axis and high nighttime cortisol level will interfere with getting enough shut eye.

Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis.
Psychopharmacology (Berl). 2020;237(4):1121-1130.

Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease.
J Psychopharmacol. 2020;34(2):189-196.

Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients.
Neuropsychopharmacology. 2011;36(6):1219-1226.

Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol.* 1981;21(S1):417s-427s.

THE INTRICATE LINK BETWEEN GLUCOCORTICOIDS AND ENDOCANNABINOIDS AT STRESS-RELEVANT SYNAPSES IN THE HYPOTHALAMUS

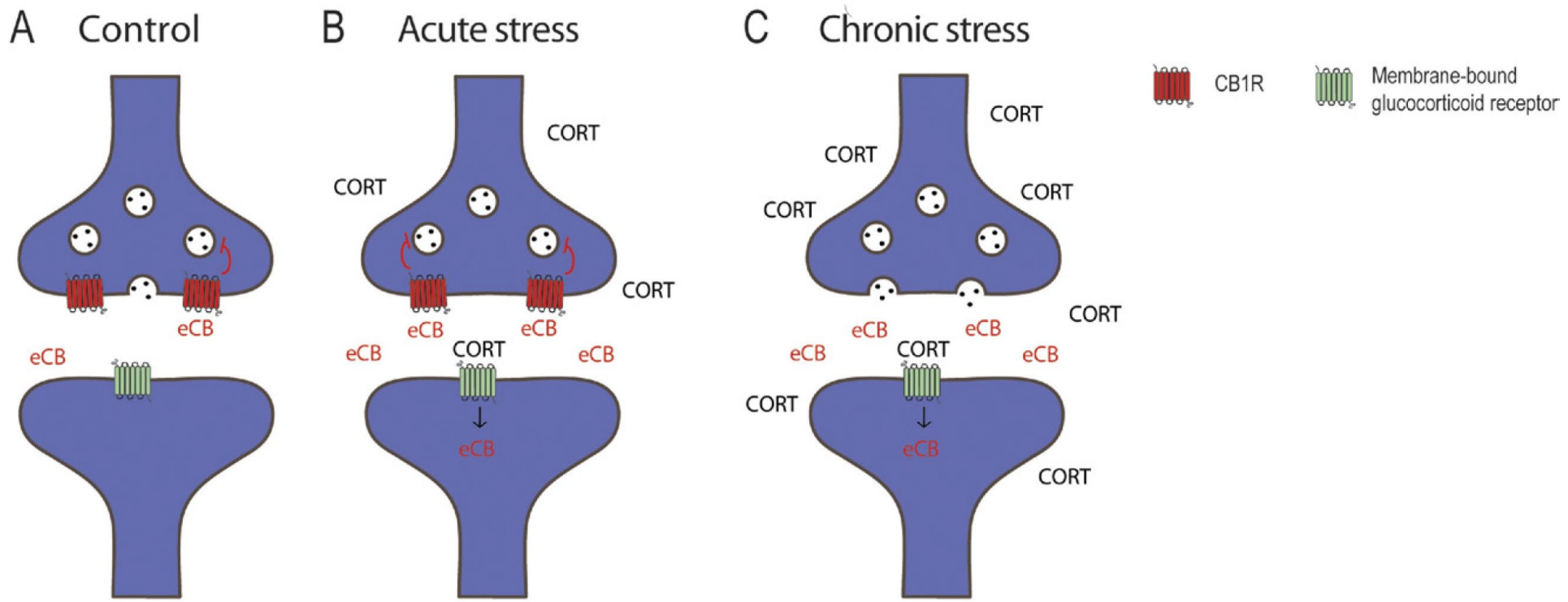


Fig. 1. In the hypothalamus, the severity of stress has different effects on eCB signaling. (A) eCBs inhibit neurotransmitter release under basal conditions. (B) Acute stress triggers eCB production and CB1R signaling through CORT-mediated activation of membrane-bound glucocorticoid receptors. (C) Chronic or repeated stress produces a functional down-regulation in CB1R signaling.

Neuroscience 2012(204):31-37.

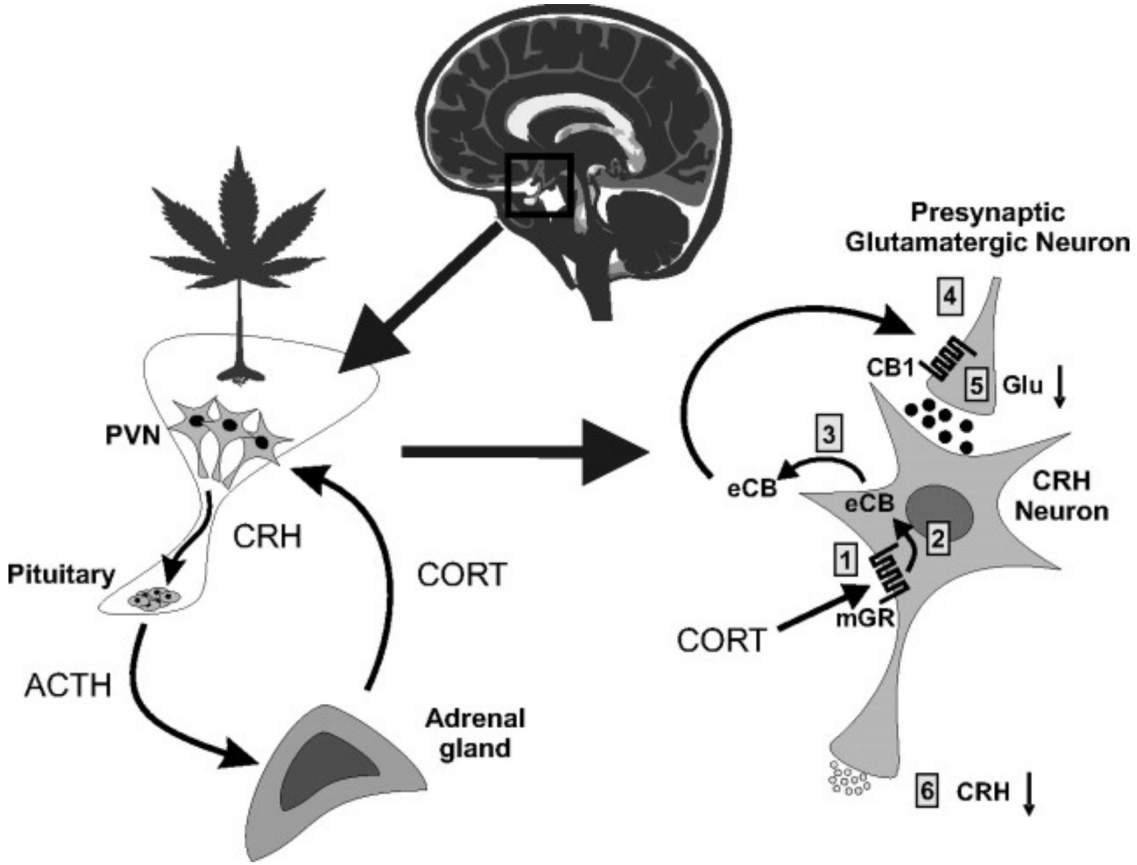
THE INTRICATE LINK BETWEEN GLUCOCORTICOIDS AND ENDOCANNABINOIDS AT STRESS-RELEVANT SYNAPSES IN THE HYPOTHALAMUS

CONCLUSIONS

There is overwhelming evidence that the eCB system and the HPA axis are inextricably linked. The data reviewed above highlight two key interactions: stress and glucocorticoids can trigger eCB synthesis and CB1R signaling to constrain HPA axis activity under acute conditions, whereas chronic or repeated stress leads to a functional down-regulation in CB1R signaling.

Neuroscience 2012(204):31-37.

Fast-Feedback Inhibition of HPA Axis via eCB

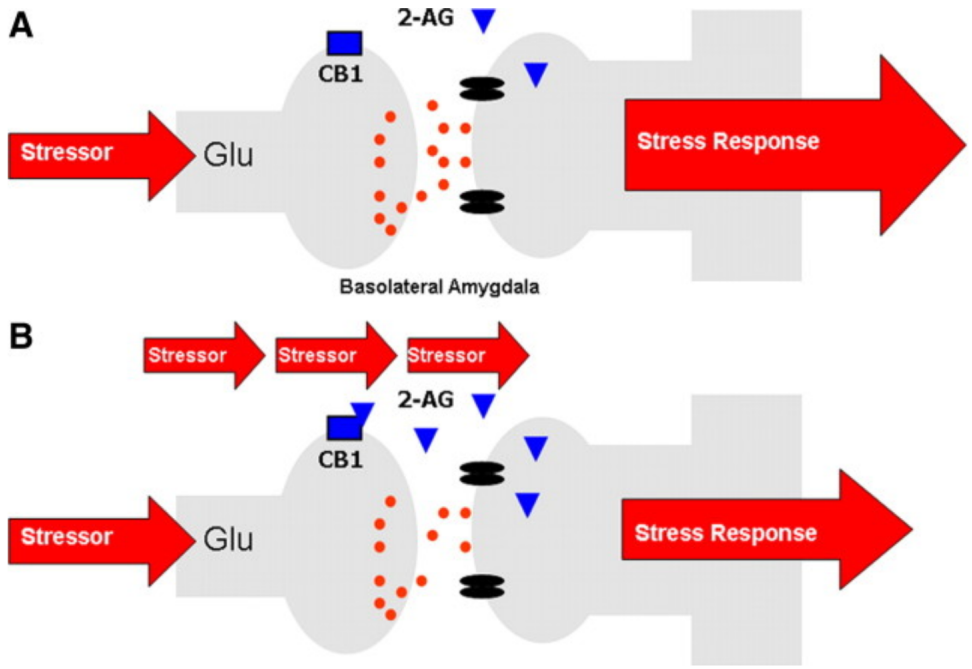


Fast-feedback inhibition of the HPA axis via glucocorticoid-induced eCB release in the hypothalamus. Left, Stress activation of the HPA axis consists of CRH secretion from PVN neurons and CRH-evoked ACTH secretion from the pituitary, which, in turn, stimulates corticosteroid (CORT) release from the adrenal cortex and CORT feedback onto the PVN. Right, In PVN CRH neurons, CORT binds to a membrane-associated glucocorticoid receptor (mGR) (1), which causes eCB synthesis in CRH neurons (2) and retrograde eCB release (3); eCB binds to presynaptic CB1 receptors on glutamate terminals (4) and inhibits glutamate release (5) onto the CRH neurons, suppressing the excitatory synaptic drive and decreasing CRH neuron activity and CRH release (6), which suppresses HPA axis activation.

J Neurosci. 2010 Nov 10; 30(45): 14980–14986.

An Intricate Ballet of the HPA Axis and Endocannabinoids

Figure 3.



A, In response to acute stress, there is little to no change in 2-AG within the BLA. ***B***, Repeated stress exposure, however, primes 2-AG signaling within the BLA such that in response to stressor presentation, there is a phasic and limited increase in 2-AG signaling within the BLA which suppresses glutamatergic inputs to the BLA, decreasing the outflow of the amygdala and driving habituation of the stress response. A similar phenomenon may also subserve behavioral plasticity, such as fear extinction, to aversive stimuli.

J Neurosci. 2010 Nov 10; 30(45): 14980–14986.

Calming Effect During Everyday Mild Stress and Frustration

- Ongoing psychological stress is linked to a decline in immunity.
- CBD is involved in a healthy stress response.*
- Unlike endogenous cannabinoids, which work on the CB_1 receptor, CBD supplementation leads to direct activation of the 5-HT1A serotonin receptor.*
- CBD stress-relieving properties are also related to its ability to modulate cerebral blood flow in brain regions involved in anxiety including the amygdala, hippocampus, hypothalamus and cingulate cortex.*

Psychol Bull. 2004 Jul;130(4):601-30. | J Psychopharmacol. 2011 Jan;25(1):121-30.
Perm J. 2016 Fall;20(4):16-005. | Curr Neuropharmacol. 2017;15(2):291-9.

Controlling the Chatter

- When people become stressed or fearful, they often develop bad memories of the events that caused their painful experiences. If this has happened to you, you might even try to avoid situations that you fear might be as emotionally painful as those you experienced in the past, what's known as fear conditioning.

- If you're stressed all the time, you might also start to feel depressed. A balanced endocannabinoid system and the way it interacts with the HPA axis plays a role in offsetting these two effects of stress.

- CBD oil—through its interaction with the endocannabinoid system—is known to reduce fear conditioning and boost mood.

Endocannabinoids and stress. *Stress.* 2011;14(4):384-397.

Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology (Berl).* 2013;226(4):781-792.

Cannabidiol: A Potential New Alternative for the Treatment of Anxiety, Depression, and Psychotic Disorders. *Biomolecules.* 2020;10(11).

A Changing Brain Chemistry--Be Happy No Worries

- The fact that CBD interacts with dopamine receptors is evidence that the endocannabinoid system is involved in regulating mood during stress.

- CBD's ability to promote a more relaxed and happy mood during stress is likely due at least in part to its effects on dopamine receptors

Cannabidiol is a partial agonist at dopamine D2High receptors, predicting its antipsychotic clinical dose.
Transl Psychiatry. 2016;6(10):e920.

Cannabinoids and the endocannabinoid system in reward processing and addiction: from mechanisms to interventions.
Dialogues Clin Neurosci. 2020;22(3):241-250.

The Stress of Pain

- Being in pain and feeling stressed often go hand in hand. If you're in pain, that in and of itself will cause you to become stressed.
- And ongoing stress leads to inflammation, which makes you more vulnerable to pain. CBD can impact our body's natural inflammatory response.
- **This is circling back to cortisol since cortisol is an anti-inflammatory hormone. CBD's effects on the HPA axis and its ability to help the body produce healthy amounts of cortisol may be the reason why there's a good amount of evidence it may support a healthy pain response.**

- Remember that stress is about the total burden, often referred to as the allostatic load.

- Psychological stress can lead to physical problems, and it's good to recognize this as you seek out ways to calm your stress and feel more at peace.
- HPA axis and its ability to help the body produce healthy amounts of cortisol may be the reason why there's a good amount of evidence it may support a healthy pain response.

Use of cannabidiol (CBD) for the treatment of chronic pain. *Best Pract Res Clin Anaesthesiol.* 2020;34(3):463-477.

Clinicians' Guide to Cannabidiol and Hemp Oils. *Mayo Clin Proc.* 2019;94(9):1840-1851.

Cannabidiol for Pain Treatment: Focus on Pharmacology and Mechanism of Action. *Int J Mol Sci.* 2020;21(22).

CBD 101 – Beyond CB1 and CB2 Receptors

- Cannabidiol (CBD), a non-psychoactive component of *Cannabis sativa*, is a phytocannabinoid that acts on the endocannabinoid system and may have the ability to maintain a balanced and healthy immune system.*

- Transient receptor potential vanilloid 2 (TRPV2), a protein that facilitates the communication of cells with their extracellular environment, plays an important role in healthy immune system function.

- CBD activates TRPV2 and also influences other transient receptor potential (TRP) channels involved in supporting immunity.*

Elife. 2019 Sep 30;8. pii: e48792.

REVIEW ARTICLE

The Important Role of the Endocannabinoid System and the Endocannabinoidome in Gut Health

Chris Meletis, ND

ABSTRACT

The endocannabinoid system is an endogenous pathway comprised of the cannabinoid receptors 1 and 2 (CB_1 and CB_2), their endogenous ligands known as endocannabinoids, and the enzymes responsible for their synthesis and degradation. The endocannabinoidome extends this system to include other receptors such as TRPV1, PPARα, GPR55 and 5-HT_{1A}. An extensive amount of research is now linking the endocannabinoidome to intestinal health through fascinating mechanisms that include endocannabinoid receptor expression in the gut and interplay with the intestinal microbiota. A dysregulated endocannabinoid system may lead to inflammatory bowel disease and colon cancer. (*Altern Ther Health Med.* 2019;25(S2):24-27.)

in gut health including its influence on the microbiota and the potential benefits of its modulation in the intestines. The intestinal involvement of the endocannabinoid system in inflammatory bowel disease, colon cancer, and even atherosclerosis will be reviewed.

THE ENDOCANNABINOID SYSTEM IN THE GUT

Findings that the receptors involved in the endocannabinoid system are expressed in the gastrointestinal tract indicate that this system is intricately involved in gut health and intestinal disorders. The endocannabinoid system is comprised of the cannabinoid receptors 1 and 2 (CB_1 and CB_2), their endogenous ligands known as endocannabinoids, and the enzymes responsible for their synthesis and degradation.[1] The two primary endocannabinoids are anandamide and 2-arachidonoylglycerol (2-AG). In addition to the CB_1 and CB_2 receptors, other receptors such as transient receptor potential cation channel subfamily V

Activation of the CB_2 receptor in these patients may ameliorate colitis-related inflammation.[3,5] Furthermore, in rats exposed to lipopolysaccharides (LPS), increased endotoxin-related intestinal transit was inhibited by activation of CB_2 receptors.[6]

The non-CB receptors GPR55 and TRPV1, which are also present in the GI tract, may play an important role in non-CB_1/CB_2 receptor effects of cannabinoids in the gut. An abundance of evidence indicates that the endocannabinoid anandamide activates TRPV1 and GPR55 receptors.[7,8] The receptors PPARα and PPARγ, which are also present in the GI tract, are activated by phytocannabinoids, synthetic cannabinoids, and endogenous cannabinoids and may regulate many of the analgesic and anti-inflammatory effects of cannabinoid treatment.[9] For this reason, these non-CB receptors are considered to be a component of an expanded endocannabinoid system.[1] The term endocannabinoidome has been used to refer to the combination of the direct

Maintaining a Healthy Gut Microbiota

- A large proportion of the immune system is located in the GI tract, where there are large numbers of organized lymphoid tissue and scattered innate and adaptive effector cells.
- The gut microbiota, the collection of organisms—good and bad—found in the intestines play an important role in helping the body have a balanced immune response.
- Excessive inflammation in the gut can lead to intestinal permeability, gut microbiota dysbiosis, and an impaired intestinal immune response.
- One way the body counteracts this is through the endocannabinoid system.
- Like endogenous cannabinoids, CBD also has been found to support a healthy intestinal inflammatory response in human trials.* The key message here is that keeping the gut healthy supports overall immunity.*

Nat Rev Immunol 14, 667-685 (2014). | Gut Microbes. 2012 Jan 1; 3(1): 4-14.
Br J Pharmacol. 2004 Apr;141(8):1335-45. | Nat Rev Endocrinol. 2016 Mar;12(3):133-43.
Inflamm Bowel Dis. 2018 Mar 19;24(4):714-24.

De-Stress to Avoid Dis-Stress (Distress)

- In human trials, CBD was found to reduce mild stress in people giving a speech.*
- Researchers observed the effects of different doses of CBD and placebo in 57 healthy male participants performing a simulated public speaking test.*
- In this double-blind study, subjects were given oral CBD at doses of 150 mg, 300 mg, or 600 mg or a placebo prior to the public speaking test. (supra-physiological and absorption question?!)
- Compared with the placebo, 300 mg of CBD led to the subjects being more calm and relaxed during the speech.

Braz J Psychiatry. 2019 Jan-Feb;41(1):9-14.

Susceptibility and Immune Modulation

- Recently, the endocannabinoid system has attracted attention due to a number of studies that confirm its role in modulating immune health in a variety of interesting ways.

- Cannabinoids that act on this system play a role in the function of T and B lymphocytes as well as natural killer cells and macrophages.

- Cannabinoids also support the health of people living in a world where viruses and bacteria are prevalent. In vivo and cell culture studies show that cannabinoids modulate the production and function of immune cytokines as well as support the activity of other immune-related cells such as macrophages and T helper cells (Th1 and Th2).

J Neuroimmunol. 1998 Mar 15;83(1-2):102-15.

It is ALL ABOUT Susceptibility 2018 - Revisited

ABSTRACT In every epidemic some individuals become sick and some may die, whereas others recover from illness and still others show no signs or symptoms of disease. These differences highlight a fundamental question of microbial pathogenesis: why are some individuals susceptible to infectious diseases while others who acquire the same microbe remain well? For most of human history, the answer assumed the hand of providence. With the advent of the germ theory of disease, the focus on disease causality became the microbe, but this did not explain how there can be different outcomes of infection in different individuals with the same microbe. Here we examine the attributes of susceptibility in the context of the "damage-response framework" of microbial pathogenesis. We identify 11 attributes that, although not independent, are sufficiently distinct to be considered separately: microbiome, inoculum, sex, temperature, environment, age, chance, history, immunity, nutrition, and genetics. We use the first letter of each to create the mnemonic MISTEACHING, underscoring the need for caution in accepting dogma and attributing disease causality to any single factor. For both populations and individuals, variations in the attributes that assemble into MISTEACHING can create an enormity of combinations that can in turn translate into different outcomes of host-microbe encounters. Combinatorial diversity among the 11 attributes makes identifying "signatures" of susceptibility possible. However, with their inevitable uncertainties and propensity to change, there may still be a low likelihood for prediction with regard to individual host-microbe interactions, although probabilistic prediction may be possible.

So Much More than CB1 and CB2 Receptors

- Endocannabinoids can bind to and activate other receptors besides cannabinoid receptors.
- These other receptors include the transient receptor potential vanilloid 1 (**TRPV1**) channel, peroxisome proliferator-activated receptor (**PPAR**) α and γ, and the orphan G protein-coupled receptor **GPR55**.
- All of these receptors are widely expressed in immune cells. In addition, the ability of endocannabinoids to regulate immunity in several types of immune cells is due to their actions on **PPAR**α and **PPAR**γ.
- The GPR55 receptor also is specifically expressed on immune cells known as monocytes and natural killer (NK) cells.

Cannabis Cannabinoid Res. 2016;1(1):59-66.

The Endocannabinoid System, Stress, and Immunity

- The endocannabinoid system consists of endocannabinoids that act on the same receptors as hemp-based CBD.
- One interesting study investigated the effects of long-term space flight on stress and immunity in cosmonauts. The study found that space flight did not elevate cortisol levels.
- Blood levels of the endocannabinoid system spiked during space flight, suggesting a biological stress response. At the same time, space flight altered the immune system.
- There was a significant increase in white blood cell counts in the cosmonauts. Immune cells such as neutrophils, monocytes, and B cells increased by 50% while natural killer cell levels fell by nearly 60% shortly after landing. Lymphocyte percentages did not change before and after flight, but were high in-flight.

Front Physiol. 2019 Feb 19;10:85.

Researchers are Curious of CBD Applications*

Br J Pharmacol. 2020 Jun 10;10.1111/bph.15157. doi: 10.1111/bph.15157. Online ahead of print.

The potential of cannabidiol in the COVID-19 pandemic

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Affiliations + expand

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Free PMC article

Abstract

Identifying drugs effective in the new coronavirus disease 2019 (COVID-19) is crucial, pending a vaccine against SARS-CoV2. We suggest the hypothesis that cannabidiol (CBD), a non-psychotropic phytocannabinoid, has the potential to limit the severity and progression of the disease for several reasons:- (a) High-cannabidiol Cannabis sativa extracts are able to down-regulate the expression of the two key receptors for SARS-CoV2 in several models of human epithelia, (b) cannabidiol exerts a wide range of immunomodulatory and anti-inflammatory effects and it can mitigate the uncontrolled cytokine production responsible for acute lung injury, (c) being a PPARγ agonist, it can display a direct antiviral activity and (d) PPARγ agonists are regulators of fibroblast/myofibroblast activation and can inhibit the development of pulmonary fibrosis, thus ameliorating lung function in recovered patients. We hope our hypothesis, corroborated by preclinical evidence, will inspire further targeted studies to test cannabidiol as a support drug against the COVID-19 pandemic.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Remember it is More than Adrenal Fatigue

Neuroendocrinology Letters Volume 35 No. 3 2014

Clinical endocannabinoid deficiency (CECD) revisited:

Can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

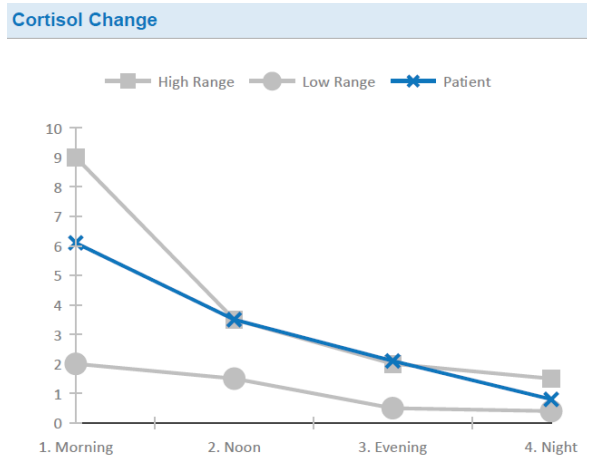
Abstract

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.

RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestional mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.

CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.



Supporting Immune System with Cannabidiol

- Studies show that CBD may play a role in supporting various aspects of immunity.
- ***In vitro*** studies have shown it has actions of interest to people who want to maintain immune health in the liver.
- Animal studies also suggest CBD oil may support an overall healthy immune response.

Pharmacognosy Res. 2017 Jan-Mar;9(1):116-8.
Eur J Pharmacol. 2012 Dec 15;697(1-3):158-64.
J Nat Prod. 2008 Aug;71(8):1427-30.

Inflammation and Immune System

In a mouse model of asthma, CBD reduced inflammation and lung fibrosis. In a similar animal study, scientists triggered the development of asthma in rats.

They later injected CBD into the animals' abdominal areas. CBD reduced the levels of the inflammatory cytokines IL-4, IL-5, IL-13, IL-6 and TNF-α. It did not reduce levels of the anti-inflammatory cytokine IL-10.

Eur J Pharmacol. 2019;843:251-259.
Mediators Inflamm. 2015; 2015:538670.

Not All HEMP and CBD Products are Created Equal

TAMING THE WILD WILD WEST OF THE HEMP OIL MARKET

Certification program brings standards to the booming CBD industry **BY DR. CHRIS D. MELETIS, ND**

Cannabinoid-rich hemp oil has emerged as a promising botanical therapeutic with both clinical experience and published studies to support its use.

The Stanley Brothers are largely credited for first awakening the public to its benefits. The six Colorado siblings developed a hemp extract low in delta-9-tetrahydrocannabinol (THC), the psychoactive component in marijuana, and high in cannabidiol (CBD), a phytocannabinoid that is not associated with the intoxicating effects of the plant. That hemp extract came to be known as Charlotte's Web after the parents of a little girl named Charlotte Figi convinced the brothers to provide their daughter with CBD-rich hemp oil.

Charlotte suffered from a severe type of medication-resistant epilepsy known as Dravet syndrome. She was having 300 seizures per week and her heart frequently stopped. After consuming three to four milligrams of the hemp oil per pound of body weight, Charlotte's seizures disappeared. The case received a lot of publicity in major media outlets such as CNN.

Since then the demand for hemp as a medicinal has skyrocketed and so too has the number of companies producing it and doctors prescribing it. Its benefits have been demonstrated both clinically and in the scientific literature. Based on that scientific research and clinical observations, I employ hemp oil in clinical practice to support the health of patients with epilepsy, anxiety, depression, post-traumatic stress disorder, schizophrenia, inflammation and pain among other applications. In this article, I will discuss a new cannabinoid certification program for both manufacturers and health care practitioners.

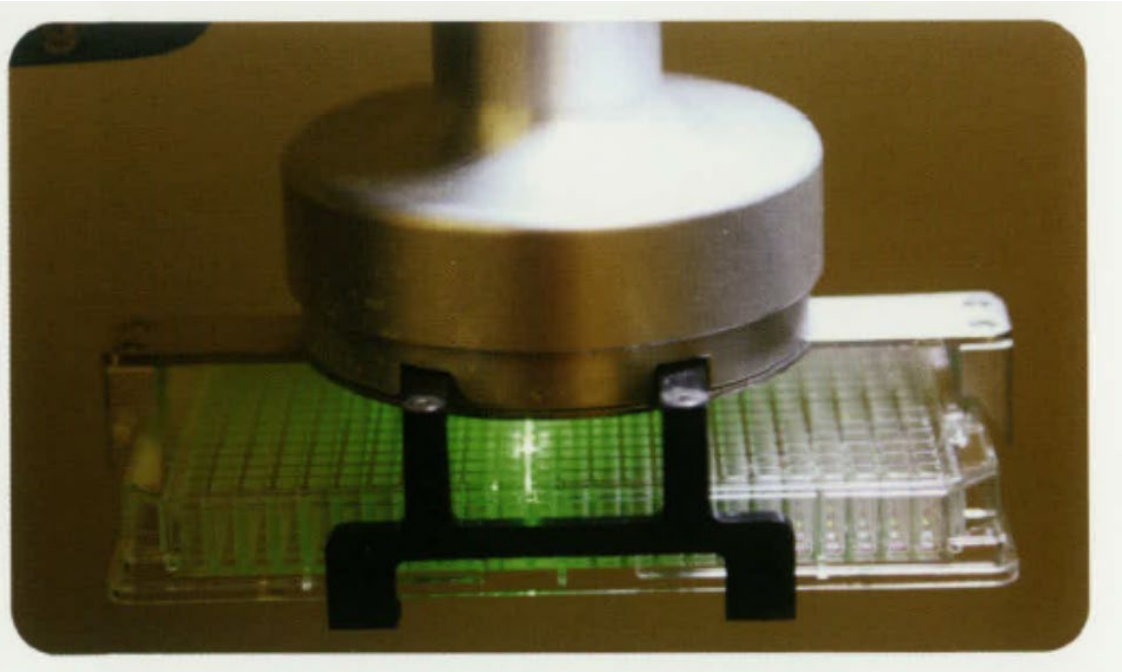
WHY CERTIFICATION IS IMPORTANT

Like the dietary supplement industry in its early years, the hemp oil marketplace is a Wild Wild West. Up until now, no entity was ensuring the consumer that optimal quantities of the beneficial cannabinoids found in hemp oil were actually contained in the purchased product.

As a manufacturer, in order to maintain a respectable reputation and avoid legal complications, it's important to ensure the hemp oil you're producing lives up to its label specifications.

A 2017 article in JAMA (The Journal of the American Medical Association) tested 84 CBD/hemp oil extracts purchased online and found that although CBD oil labeling had the highest degree of accuracy compared to other products tested, 55% were either under-labeled (more CBD was detected in the product than claimed on the label) or over-labeled (CBD content that was negligible or less than 1% of the amount on the label). In this study, the over-labeled CBD products contained insufficient levels similar to concentrations that resulted in the Food and Drug Administration (FDA) sending warning letters to 14 businesses in 2015-2016. Some of the products also contained more THC than noted on the label. In the United States, only hemp oil brands that contain less than 0.3% THC are legal. Therefore, certainty surrounding the THC

My Clinical Approach — “Testing Not Guessing”




Q&A