

Fire on the Brain: A Functional Medicine Approach to Reversal of Cognitive Decline

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Monotherapeutic approach to Alzheimer's disease

need a programmatic approach

Similar to HIV: monotherapy did not work
Triple drug therapy works



Think of 36 holes in roof –not 2000 (maybe 70-80) factors to modulate
2 tacks on chair, remove one, not hurt half as much

Bapineuzumab

antibody against N-terminus of Amyloid Beta

- Prevents amyloid deposition in APO e4 carriers with mild to moderate AD
- No effect in noncarriers
- Failed to prevent cognitive and functional decline
- Side effect was vasogenic cerebral edema and microhemorrhage

Phase 3 clinical trials failed x 2

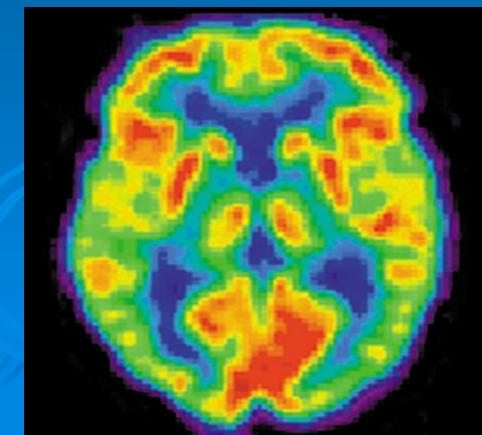
New model?

Multi-variable trials, with programs and drug candidates

Problems with clinical trials of monotherapies and pt selection:

- 25% of patients had minimal amyloid plaque on PET and Autopsy
- Variation based on status of APO e4
- 2 large Bapineuzumab clinical trials
36% of non-carriers did not meet PET amyloid
- Distinguishing between AD and non-AD dementia will become more important for therapy and for clinical trials

Do we need a better way???



Traditional evaluation for dementia

CBC

Chemistry

TSH

RPR (syphilis test)

B12

MRI

(newer FDG PET and amyloid PET)

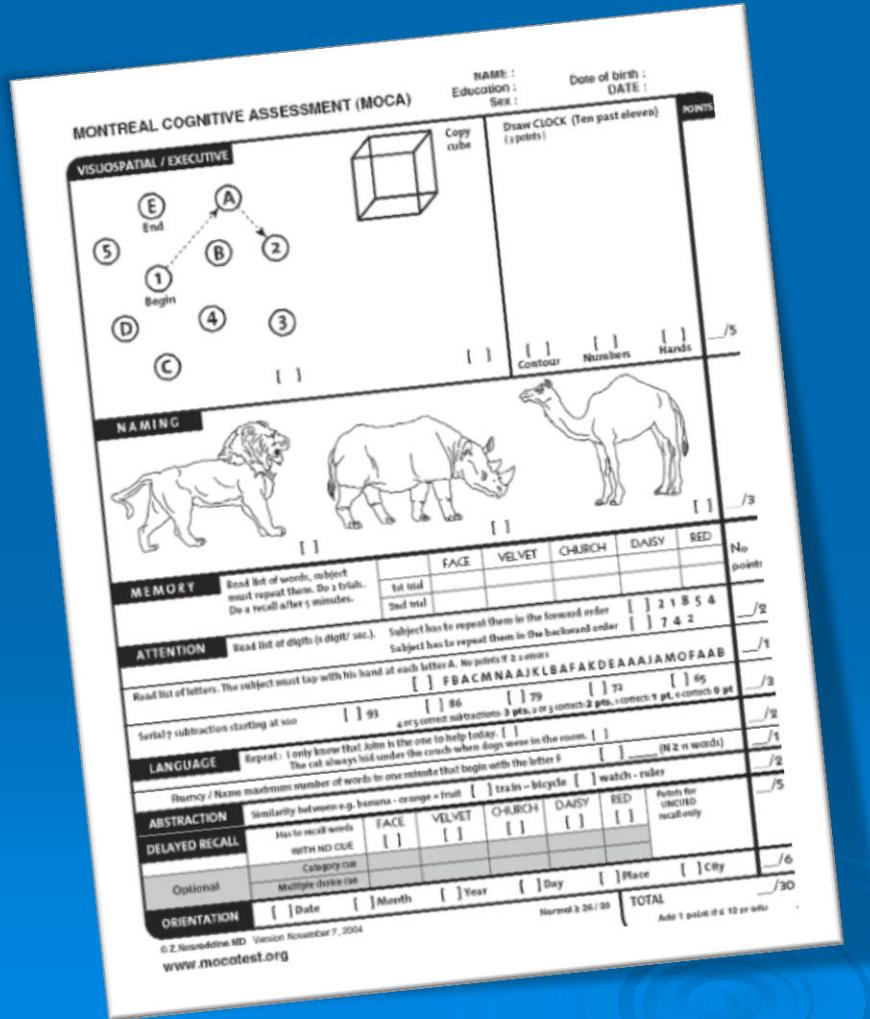
MMSE or MOCA (paper 15 min memory test)

DX: Alzheimer's

TX: Monotherapy-marginal benefit

Continued decline to nursing home or worse

Montreal Cognitive Assessment - MoCA



Features:

< 10 minutes

Proprietary (recently)

Best for MCI (<26/30)

Dementia: < 19/30

FUNCTIONAL MEDICINE APPROACH

Look at previous markers, BUT.....

LET'S TAKE A WHOLE SYSTEMS APPROACH
PERSONALIZED PRECISION INDIVIDUALIZED
EMPLOY A COLLABORATIVE TEAM

GENETICS

MICROBIOME

TOXICITY

NUTRIENT DEFICIENCIES/B12/folate/zinc/vit D

DIETARY CHANGES/OBESITY/INSULIN RESISTANCE

OXIDATIVE STRESS

HORMONE IMBALANCE/DEFICIENCIES

SLEEP/HYPOXIA/APNEA

EXERCISE

BRAIN STIMULATION/MEDITATION/REST

The 7 keys for Functional Medicine

Optimize nutrition

Balance hormones

Reduce inflammation

Fix digestion

Enhance detoxification

Boost energy metabolism

Calm the mind



Food, bugs, toxins, trauma



Getting Healthy is a
Team Sport

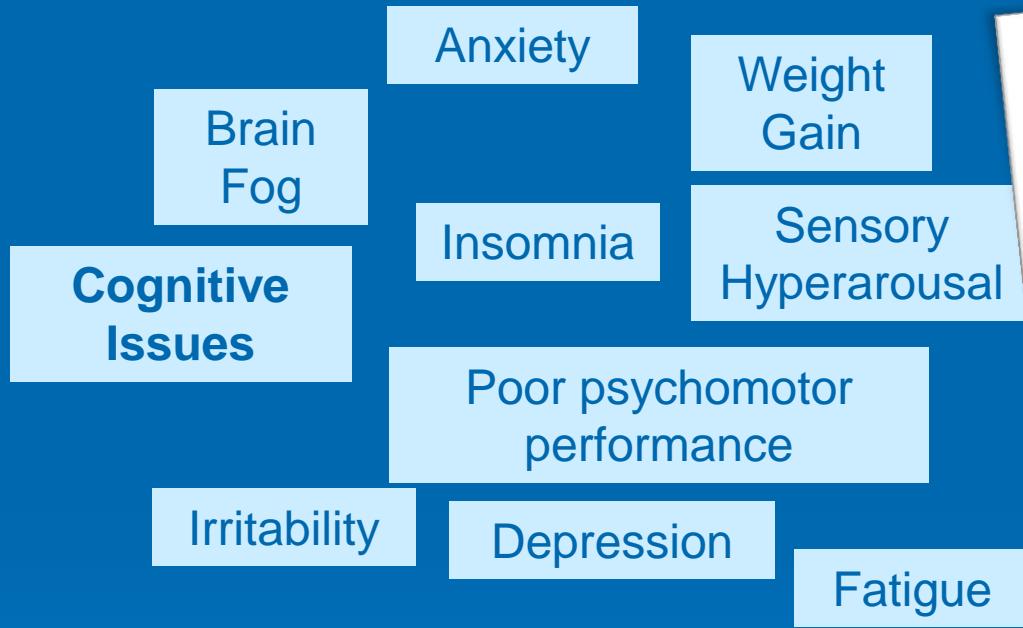
The Collaborative Care Team



Inflammation



Do these Symptoms look Familiar?



Chronic inflammation can result in these and other neuro/endo/metabolic manifestations



Emerging Risk Factors: Inflammation

TNF alpha

Rheumatoid Arthritis increased CV risk

Risk decreased with TNF inhibitors (?new statin)

IgG, IgA, IgE

Gluten/food sensitivities

Antigen Complexes

IL-1b, 4, 6, 10, 12, 17

Infectious Disease

Chlamydia, CMV, EBV, Mycoplasma, HSV

Fungal, mycotoxins, Lyme

David Perlmutter, MD:

- 90% of adults have HSV1

Why do only 30% get cold sores??
Epigenetics or Host factors?

- HSV1 may be related to Alzheimer's

-HSV affects same area of brain as AD; causes similar memory problems post infection

-Increased association with APOE ε4

- HSV 1 DNA located in amyloid plaques
- Apoe4 may be more susceptible to neuronal damage by HSV1
In Apoe4-70% of in plaque contain HSV DNA

Cognitive Impairment and Celiac Disease

William T. Hu, MD, PhD et al

Arch Neurol. 2006;63(10):1440-1446.

“association exists between progressive cognitive impairment and celiac disease”

Emerging Risk Factors

Insulin Resistance/Metabolic Syndrome/Hyperglycemia

APOE ε4

Apo B / Apo A1

Fibrinogen

hs-CRP/Myeloperoxidase/PLAC-2/TMAO

Methylation

Lp(a)

Low HDL2b

Small Dense LDL

Increased PA11

Vitamin D deficiency

Increased Factor VII

Increased Factor X

IL-1, TNF alpha, IL-6

SNPs

Hormone deficiencies

Other Risk Factors

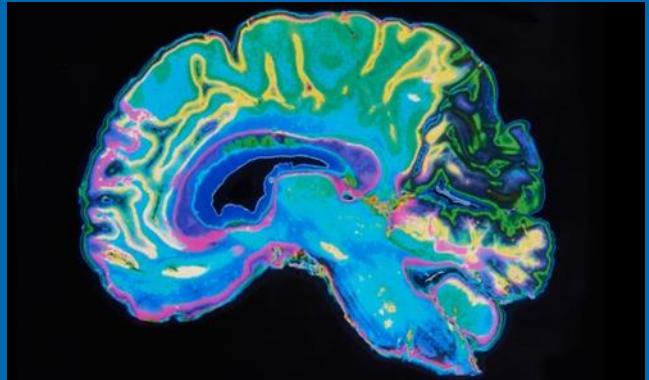
Central Obesity

Sedentary Lifestyle

Stress

Social Isolation

Lack of Love, Social Support, Purpose in Life



Toxins

Caregiver Role

Depression

Anger & Hostility

Adverse childhood events

DIETARY RISK FACTORS

Overall caloric intake

Low nutrient density

High caloric density

Gluten/Casein

Food Additives/Dyes

Glyphosate

Increased Na⁺/K⁺ ratio

Acid load/alkaline

Hydrogenated fats

High glycemic load

Fructose

Low ORAC value

Cholesterol and fat(?)



Remember hearing how the

“fight-or-flight” response

was what helped save the species

from things like saber-tooth tigers?



Throw some....

- hormone imbalance*
- nutrition imbalance*
- toxic environment*
- depression/anxiety*
- altered microbiome*

.....into the mix.

No wonder patients AND caregivers
have inflammation/heart/brain dx
And are Sick and Tired of Being Sick and Tired...



SPRAYING MALATHION INSECTICIDE.....

VIEWPOINT

Personomics

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.

Sir William Osler

Roy C. Ziegelstein,
MD, MACP

Department of
Medicine, Johns
Hopkins University
School of Medicine,
Baltimore, Maryland.

When Francis S. Collins, MD, PhD, director of the US National Institutes of Health, and Harold Varmus, MD, director of the US National Cancer Institute, recently commented on President Barack Obama's new Precision Medicine Initiative,¹ they highlighted the improvements in human health that could result from real-time measurements of blood glucose, blood pressure, and heart rhythm; from defining each individual's unique genotypes, gut microbes, and peripheral blood immune cells; and from detecting circulating tumor cells or tumor DNA. There can be no doubt that if genomics, proteomics, pharmacogenomics, metabolomics, and epigenomics can be used to identify treatments that are uniquely tailored to the individual, the possibilities are almost unimaginable. However, an important element

fluence human health and disease are often not integrated with the biological sciences in the preclinical curriculum. This can send a message to students that psychosocial and societal issues are less important to patient care than the basic sciences. Yet the importance of understanding each patient as a person is as critical to teach young physicians as anything else in medical school or residency training. It is not simply that it improves patient satisfaction or contributes to the joy of medical practice, it actually contributes importantly to identifying the correct diagnosis and optimal treatment for the individual patient. Teaching medical students and residents the skills involved in patient-centered care and communication and enhancing the behavioral and social science content of a medical school's curriculum are just as important as teaching the molecular and genetic basis of health and illness.

The suffix "-ome" or "-omics" is often added to an area of human biology, conveying the impression that

Current thinking??

In genetically susceptible persons with the right environmental & epigenetic cues:

homocysteine:
impairs DNA repair in neurons

sensitizes them to oxidative damage
induced by amyloid



Epigenetics

How environmental factors
can change the way our genes function

Epigenome:

The software that tells our DNA how to function

Tell patients: It's about how food and lifestyle choices bathe over your genes.

*YOU CAN turn on good ones or
turn off bad ones.*

“You are not your genetic destiny”

Test	Genes	Tendencies
Oxidative Stress	SOD1, SOD2, SOD3, GPx1, CAT	Heart disease, Aging, Diabetes, Alzheimer's
Vitamin D	VDR, CYP27B1, GC	Bone loss, MS, Heart disease, Inflammation
Neurotransmitter Synthesis/ Folate Methylation	COMT, MTHFR	Fibromyalgia, Fatigue, ADD, Autism, Depression, Anxiety
Celiac Disease	HLA-DQ2.5, HLA-DQ8	Gluten sensitivity, brain fog, GI distress
Metal Detoxification	GSTM1	Chronic fatigue syndrome, Detox issues, Fibromyalgia,
Multiple Drug Resistance	MDR1	Altered response to drugs, Detox issues

Functional Genetics

Canto



Owen



Rhesus monkeys are almost the same biological age. Guess which one has been on a long-term calorie-restricted diet?



Randy Jirtle/Duke University

Hypo-methylated



Yellow Mouse

- High risk cancer, diabetes, obesity
- Reduced lifespan

Hyper-methylated



Agouti Mouse

- Lower risk of cancer, diabetes, obesity
- Prolonged life

Maternal
Supplements
with
zinc
methionine
choline
folate
B12



Homocysteine

Folate, Vitamin B12, and Serum Total Homocysteine Levels in Confirmed Alzheimer Disease

Robert Clarke, MD; A. David Smith, DPhil; Kim A. Jobst, DM; Helga Refsum, MD; Lesley Sutton, BSc

Homocysteine

- An amino acid that occurs as an intermediate in the metabolism of methionine and cysteine

Independent Risk Factor for
Heart Disease and Alzheimer's Disease

*Tell patients it is a “toxic protein”
to the heart and to the brain*

The Progression of Cognitive Impairment

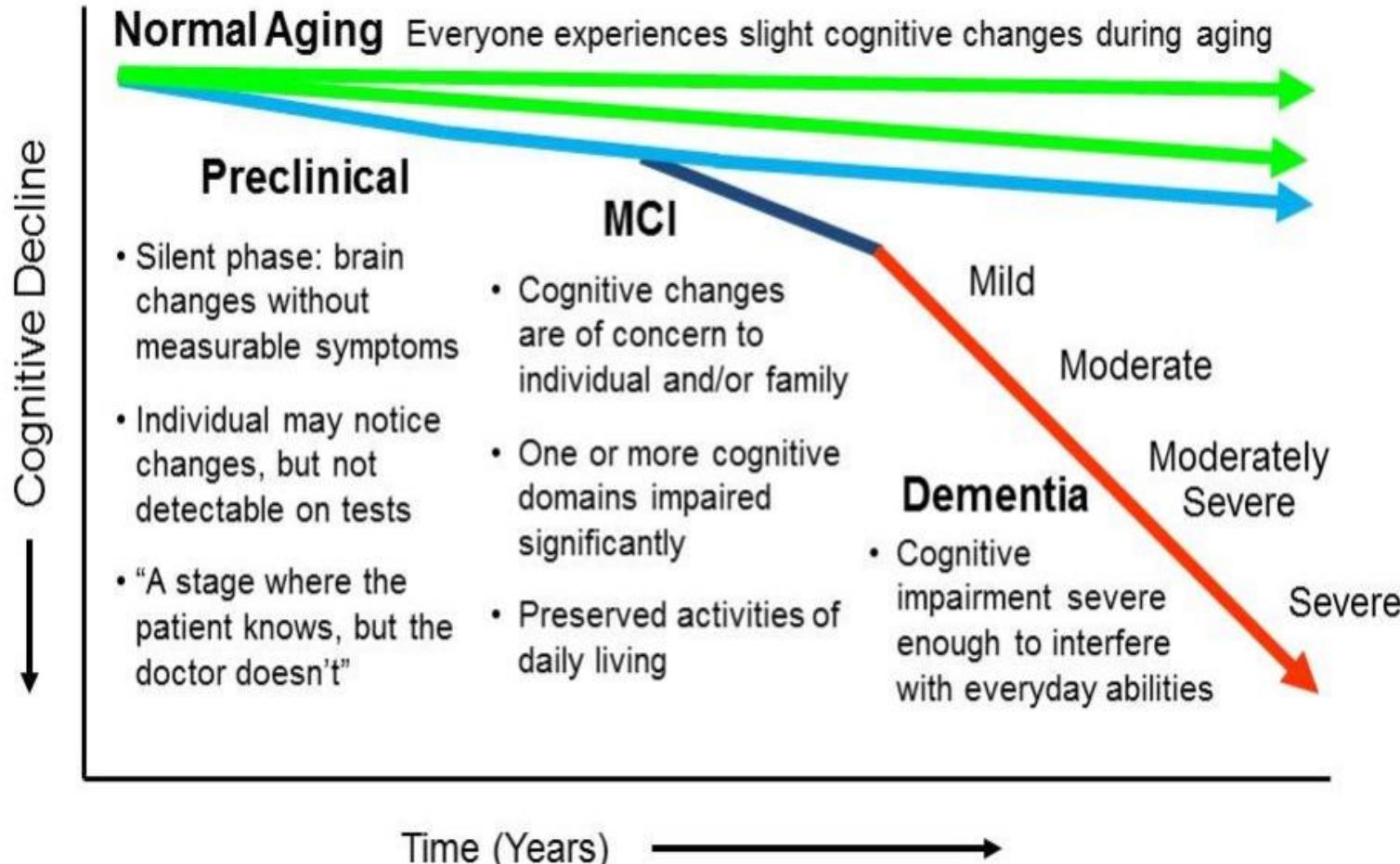


table 1 Types of Dementia and Their Typical Characteristics*

Type of Dementia	Characteristics
Alzheimer's disease	<p>Most common type of dementia; accounts for an estimated 60 percent to 80 percent of cases. About half of these cases involve solely Alzheimer's pathology; many have evidence of pathologic changes related to other dementias. This is called mixed dementia (see mixed dementia in this table).</p> <p>Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavior changes and, ultimately, difficulty speaking, swallowing and walking.</p> <p>Revised criteria and guidelines for diagnosing Alzheimer's were proposed and published in 2011 (see pages 12-13). They recommend that Alzheimer's be considered a slowly progressive brain disease that begins well before clinical symptoms emerge.</p> <p>The hallmark pathologies of Alzheimer's are the progressive accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes are eventually accompanied by the damage and death of neurons.</p>
Vascular dementia	<p>Previously known as multi-infarct or post-stroke dementia, vascular dementia is less common as a sole cause of dementia than Alzheimer's, accounting for about 10 percent of dementia cases. However, it is very common in older individuals with dementia, with about 50 percent having pathologic evidence of vascular dementia (infarcts). In most cases, the infarcts coexist with Alzheimer's pathology.¹⁰</p> <p>Impaired judgment or the ability to make decisions, plan or organize are more likely to be initial symptoms, as opposed to the memory loss often associated with the initial symptoms of Alzheimer's.</p> <p>Vascular dementia occurs most commonly from blood vessel blockage or damage leading to infarcts (strokes) or bleeding in the brain. The location, number and size of the brain injuries determine whether dementia will result and how the individual's thinking and physical functioning will be affected.</p> <p>In the past, evidence of vascular dementia was used to exclude a diagnosis of Alzheimer's (and vice versa). That practice is no longer considered consistent with the pathological evidence, which shows that the brain changes of both types of dementia commonly coexist. When two or more types of dementia are present at the same time, the individual is considered to have mixed dementia (see mixed dementia in this table).</p>
Dementia with Lewy bodies (DLB)	<p>People with DLB have some of the symptoms common in Alzheimer's, but are more likely to have initial or early symptoms of sleep disturbances, well-formed visual hallucinations and slowness, gait imbalance or other parkinsonian movement features. These features, as well as early visuospatial impairment, may occur in the absence of significant memory impairment.</p> <p>Lewy bodies are abnormal aggregations (or clumps) of the protein alpha-synuclein that accumulate in neurons. When they develop in a part of the brain called the cortex, dementia can result. Alpha-synuclein also aggregates in the brains of people with Parkinson's disease (PD), in which it is accompanied by severe neuronal loss in a part of the brain called the substantia nigra. While people with DLB and PD both have Lewy bodies, the onset of the disease is marked by motor impairment in PD and cognitive impairment in DLB.</p> <p>The brain changes of DLB alone can cause dementia. But very commonly brains with DLB have coexisting Alzheimer's pathology. In people with both DLB and Alzheimer's pathology, symptoms of both diseases may emerge and lead to some confusion in diagnosis. Vascular dementia can also coexist and contribute to the dementia. When evidence of more than one dementia is present, the individual is said to have mixed dementia (see mixed dementia in this table).</p>

table 1 (cont.)

Types of Dementia and Their Typical Characteristics*

Type of Dementia	Characteristics
Frontotemporal lobar degeneration (FTLD)	<p>Includes dementias such as behavioral-variant FTLD, primary progressive aphasia, Pick's disease, corticobasal degeneration and progressive supranuclear palsy.</p> <p>Typical early symptoms include marked changes in personality and behavior and difficulty with producing or comprehending language. Unlike Alzheimer's, memory is typically spared in the early stages of disease.</p> <p>Nerve cells in the front (frontal lobe) and side regions (temporal lobes) of the brain are especially affected, and these regions become markedly atrophied (shrunken). In addition, the upper layers of the cortex typically become soft and spongy and have protein inclusions (usually tau protein or the transactive response DNA-binding protein).</p> <p>The brain changes of behavioral-variant FTLD may occur in those age 65 years and older, similar to Alzheimer's disease, but most people with this form of dementia develop symptoms at a younger age (at about age 60). In this younger age group, FTLD is the second most common degenerative dementia.</p>
Mixed dementia	<p>Characterized by the hallmark abnormalities of more than one type of dementia — most commonly Alzheimer's combined with vascular dementia, followed by Alzheimer's with DLB, and Alzheimer's with vascular dementia and DLB. Vascular dementia with DLB is much less common.³⁴</p> <p>Recent studies suggest that mixed dementia is more common than previously recognized, with about half of those with dementia having mixed pathologies.³⁴</p>
Parkinson's disease (PD) dementia	<p>Problems with movement (slowness, rigidity, tremor and changes in gait) are common symptoms of PD.</p> <p>In PD, alpha-synuclein aggregates appear in an area deep in the brain called the substantia nigra. The aggregates are thought to cause degeneration of the nerve cells that produce dopamine.</p> <p>The incidence of PD is about one-tenth that of Alzheimer's.</p> <p>As PD progresses, it often results in dementia secondary to the accumulation of Lewy bodies in the cortex (similar to DLB) or the accumulation of beta-amyloid clumps and tau tangles (similar to Alzheimer's disease).</p>
Creutzfeldt-Jakob disease	<p>This very rare and rapidly fatal disorder impairs memory and coordination and causes behavior changes.</p> <p>Results from a misfolded protein (prion) that causes other proteins throughout the brain to misfold and malfunction.</p> <p>May be hereditary (caused by a gene that runs in one's family), sporadic (unknown cause) or caused by a known prion infection.</p> <p>A specific form called variant Creutzfeldt-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease.</p>
Normal pressure hydrocephalus	<p>Symptoms include difficulty walking, memory loss and inability to control urination.</p> <p>Caused by impaired reabsorption of cerebrospinal fluid and the consequent build-up of fluid in the brain, increasing pressure in the brain.</p> <p>People with a history of brain hemorrhage (particularly subarachnoid hemorrhage) and meningitis are at increased risk.</p> <p>Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid.</p>



2 Types of AD

Early Onset (also known as Familial):

- Has strong hereditary component
- Accounts for only 5% of all cases
- Starts earlier-50's and progresses faster
- Chromosome 14=abnormal presenilin 1
- Chromosome 1=abnormal presenilin 2

Late Onset AD *related to APOE*

APOE gene (located on chromosome 19)

APOE ε2, *APOE ε3*, and *APOE ε4*.

The 5 common genotypes are 2/3, 3/3, 2/4, 3/4, and 4/4

APOE ε2 - common and may provide protection

APOE ε3 - the most common-neutral role

APOE ε4 - present in about 30% increased risk

Double Variant *APOE ε4* - 40-90% increased risk

Evolution protection of *APOE4* for innate immune system

Alzheimer's disease triples healthcare costs for Americans aged 65 or older



5.3
million people
have Alzheimer's

9.9
million unpaid
caregivers

6th
leading cause
of death

Alzheimer's Prevalence

1 in 9 older Americans has Alzheimer's
2/3 are women!

1 in 3 elderly that die in a given year
have been diagnosed with Alzheimers
or other forms of dementia

In 2017, dementia resulted in
18 billion hrs of unpaid care
\$230 billion cost
By 15 million caregivers (2/3 are women)

CARING FOR COGNITIVE DECLINE CAUSES COGNITIVE DECLINE!!!

Caregivers vs Non Caregivers

-more stress

-more depression and anxiety symptoms/higher scores

-higher cortisol if acute

STAGE 1-2 ADRENAL DYSREGULATION

-lower cortisol if prolonged

STAGE 2-3 ADRENAL DYSREGULATION

-lower BDNF levels

-significantly **worse** performances
on **attention**, working **memory** and **executive function** tests

-all cognitive tests showed impaired performance

The Collaborative Care Team



Links Between Inflammation and Disease

“Inflammation is the body's response to environmental stimuli that normally eliminates the aggressor agent(s) and restores tissue physiology”

When chronic, it can cause:

Cardiovascular

Diabetes

Autoimmune diseases

Cancer

Alzheimer's disease

Identical Twins Different Use of NSAIDS Different Outcomes



McGeer PL, McGeer E, Rogers J, Sibley J.
Anti-inflammatory drugs and Alzheimer disease.
Lancet. 1990;335:1037

Ibuprofen Suppresses Plaque Pathology and Inflammation in a Mouse Model for Alzheimer's Disease

G. P. Lim^{1,3}, F. Yang^{1,3}, T. Chu^{1,3}, P. Chen^{1,3}, W. Beech^{1,3}, B. Teter^{1,3}, T. Tran^{1,3}, O. Ubeda^{1,3}, K. Hsiao Ashe⁵,
S. A. Frautschy^{1,2,3,4}, and G. M. Cole^{1,2,3,4}

+ Show Affiliations

The Journal of Neuroscience, 1 August 2000, 20(15): 5709-5714;

Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms.

Halliday G¹, Robinson SR, Shepherd C, Kril J.

⊕ Author information

Abstract

1. Of the neurodegenerative diseases that cause dementia, Alzheimer's disease (AD) is the most common. Three major pathologies characterize the disease: senile plaques, neurofibrillary tangles and inflammation. We review the literature on events contributing to the inflammation and the treatments thought to target this pathology. 2. The senile plaques of AD consist primarily of complexes of the beta-amyloid protein. This protein is central to the pathogenesis of the disease. 3. Inflammatory microglia are consistently associated with senile plaques in AD, although the classic inflammatory response (immunoglobulin and leucocyte infiltration) is absent. beta-Amyloid fragments appear to mediate such inflammatory mechanisms by activating the complement pathway in a similar fashion to immunoglobulin. 4. Epidemiological studies have identified a reduced risk of AD in patients with arthritis and in leprosy patients treated with anti-inflammatory drugs. Longitudinal studies have shown that the consumption of anti-inflammatory medications reduces the risk of AD only in younger patients (< 75 years). 5. There is a considerable body of in vitro evidence indicating that the inflammatory response of microglial cells is reduced by non-steroidal anti-inflammatory drugs (NSAID). However, no published data are available concerning the effects of these medications on brain pathology in AD. 6. Cyclooxygenase 2 enzyme is constitutively expressed in neurons and is up-regulated in degenerative brain regions in AD. Non-steroidal anti-inflammatory drugs may reduce this expression. 7. Platelets are a source of beta-amyloid and increased platelet activation and increased circulating beta-amyloid have been identified in AD. Anti-platelet medication (including NSAID) would prevent such activation and its potentially harmful consequences. 8. Increased levels of luminal beta-amyloid permeabilizes the blood-brain barrier (BBB) and increases vasoconstriction of arterial vessels, paralleling the alterations observed with infection and inflammation. Cerebral amyloidosis is highly prevalent in AD, compromising the BBB and vasoactivity. Anti-inflammatory medications may alleviate these problems.

Inflammation, anti-inflammatory agents and Alzheimer disease: The last 12 years

Article Type: Research Article

Authors: McGeer , Patrick L. | Rogers , Joseph | McGeer , Edith G.

Affiliations: Kinsmen Laboratory of Neurological Research , University of British Columbia, Vancouver BC, CanadaSun Health Research Institute, Sun City, Arizona, USA

Abstract: Two basic discoveries have spurred research into inflammation as a driving force in the pathology of Alzheimer disease (AD). The first was the identification of activated microglia in association with the lesions. The second was the finding that rheumatoid arthritics were relatively spared from the disease. These findings spurred the first pilot trial of a classical NSAID in the treatment of AD. This trial showed promise for indomethacin as a useful therapeutic agent but appropriate follow up trials have not been done. However, more than 20 epidemiological studies have since been conducted showing a sparing effect for antiinflammatories in AD, including four which specifically addressed the use of classical NSAIDs. Other key findings linking inflammation to AD pathology are the identification of activated complement fragments, including the membrane attack complex, as well as inflammatory cytokines in association with the lesions. In vitro, activated microglia release factors which are toxic to neurons, and these can be partially blocked by NSAIDs. Future directions should include a search for other inflammatory mediators in AD and exploitation of current knowledge to improve available treatments.

Keywords: NSAID indomethacin complement membrane attack complex immunohistochemistry reactive microglia

Journal: Journal of Alzheimer's Disease, vol. 9, no. 3 Supplement, pp. 271-276, 2006

27 July 2006 | Accepted 27 July 2006 | Published 2006

Aging Cell, 2004 Aug;3(4):169-76.

How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes.

Blasko I¹, Stampfer-Kountchev M, Robatscher P, Veerhuis R, Eikelenboom P, Grubeck-Loebenstein B.

⊕ Author information

Abstract

A huge amount of evidence has implicated amyloid beta (A beta) peptides and other derivatives of the amyloid precursor protein (beta APP) as central to the pathogenesis of Alzheimer's disease (AD). It is also widely recognized that age is the most important risk factor for AD and that the innate immune system plays a role in the development of neurodegeneration. Little is known, however, about the molecular mechanisms that underlie age-related changes of innate immunity and how they affect brain pathology. Aging is characteristically accompanied by a shift within innate immunity towards a pro-inflammatory status. Pro-inflammatory mediators such as tumour necrosis factor-alpha or interleukin-1 beta can then in combination with interferon-gamma be toxic on neurons and affect the metabolism of beta APP such that increased concentrations of amyloidogenic peptides are produced by neuronal cells as well as by astrocytes. A disturbed balance between the production and the degradation of A beta can trigger chronic inflammatory processes in microglial cells and astrocytes and thus initiate a vicious circle. This leads to a perpetuation of the disease.

Int J Biochem Cell Biol. 2005 Feb;37(2):289-305.

The role of inflammation in Alzheimer's disease.

Tuppo EE¹, Arias HR.

Author information

Abstract

Considerable evidence gained over the past decade has supported the conclusion that neuroinflammation is associated with Alzheimer's disease (AD) pathology. Inflammatory components related to AD neuroinflammation include brain cells such as microglia and astrocytes, the classic and alternate pathways of the complement system, the pentraxin acute-phase proteins, neuronal-type nicotinic acetylcholine receptors (AChRs), peroxisomal proliferators-activated receptors (PPARs), as well as cytokines and chemokines. Both the microglia and astrocytes have been shown to generate beta-amyloid protein (Abeta), one of the main pathologic features of AD. Abeta itself has been shown to act as a pro-inflammatory agent causing the activation of many of the inflammatory components. Further substantiation for the role of neuroinflammation in AD has come from studies that demonstrate patients who took non-steroidal anti-inflammatory drugs had a lower risk of AD than those who did not. These same results have led to increased interest in pursuing anti-inflammatory therapy for AD but with poor results. On the other hand, increasing amount of data suggest that AChRs and PPARs are involved in AD-induced neuroinflammation and in this regard, future therapy may focus on their specific targeting in the AD brain.

PPAR gamma -Glitazones (diabetes); also activated by NSAIDs

Characterization of Inflammatory Biomarkers and Candidates for Diagnosis of Alzheimer's Disease

Eva Bagyinszky¹, Young Chul Youn², Seong Soo A. An^{1,*} & SangYun Kim³

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Inflammation in Alzheimer Disease—A Brief Review of the Basic Science and Clinical Literature

Tony Wyss-Coray^{1,2} and Joseph Rogers³

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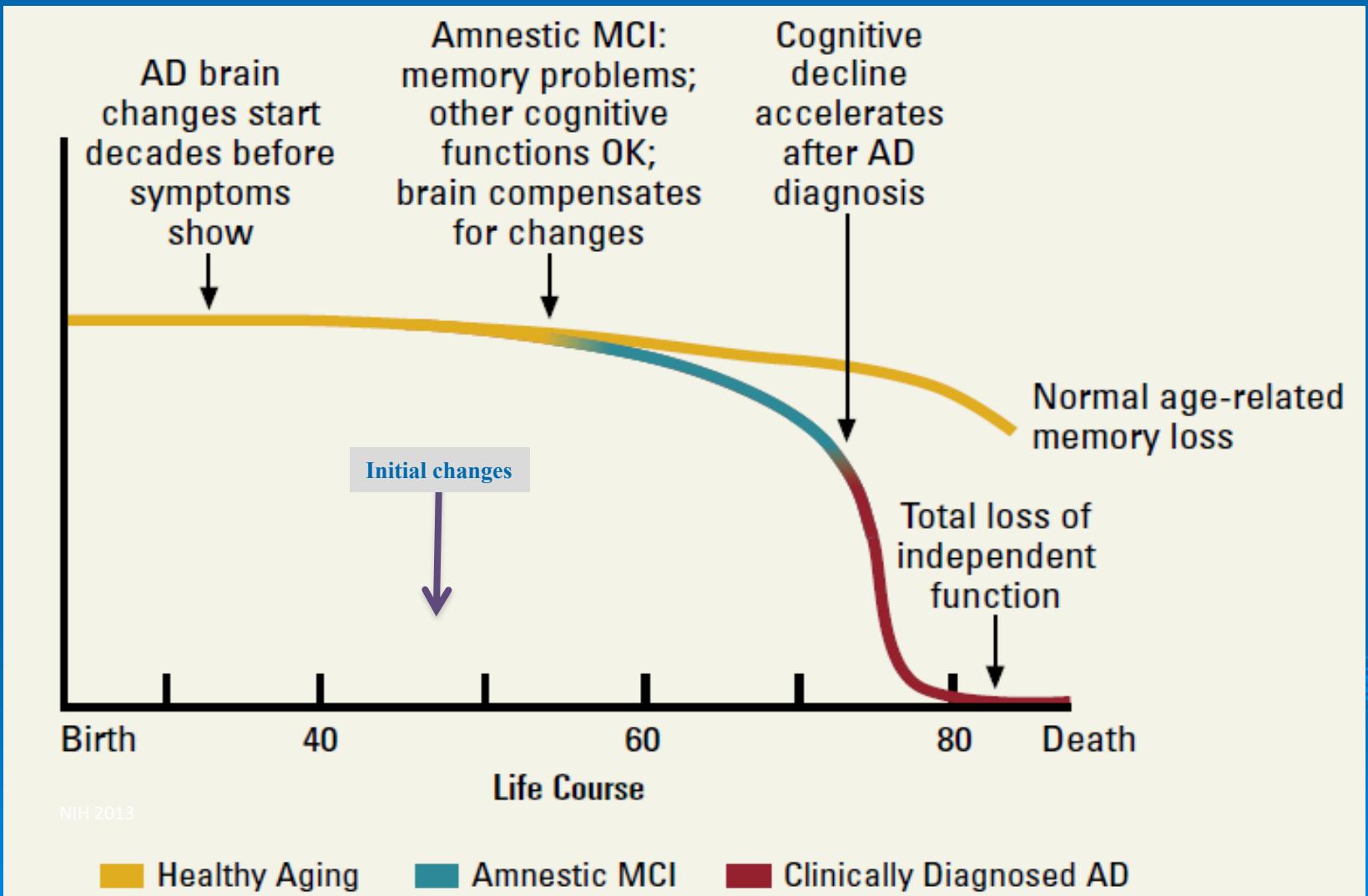
This article has been [cited by other articles in PMC](#).

Abstract

Go to:

Biochemical and neuropathological studies of brains from individuals with Alzheimer disease (AD) provide clear evidence for an activation of inflammatory pathways, and long-term use of anti-inflammatory drugs is linked with reduced risk to develop the disease. As cause and effect relationships between inflammation and AD are being worked out, there is a realization that some components of this complex molecular and cellular machinery are most likely promoting pathological processes leading to AD, whereas other components serve to do the opposite. The challenge will be to find ways of fine tuning inflammation to delay, prevent, or treat AD.

Intervening prior to MCI optimal!



Reversal of cognitive decline: A novel therapeutic program

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Aging, Vol 6 No. 9, Sept 2014

<u>Patient</u>	<u>History, evaluation</u>	<u>Diagnosis</u>	<u>Status</u>
67F 3/3	2yr memory ?; FH+	aMCI	Normal x 2.5 yrs; working
69M 4/3	12yr memory ↓; FDG-PET+, NPsych+	Early AD	"Clearly improved;" working
70M 4/3	4yr memory ↓; NPsych+, failed MemTrax	AD	Improved; MemTrax passed
75M 3/3	1yr memory ↓	SCI	Improved; working
75F C677T	1yr memory ↓	aMCI/early AD	Improved
55F 3/3	4yr memory ↓	aMCI/early AD	Normal; working
72M 3/3	7yr memory ↓	aMCI	Improved; working
55M 4/3	2yr memory ↓	SCI	Normal; working
63F 4/3	FH dementia, mild memory ↓	SCI	Normal, negative amyloid PET; working
60F 4/3	4yr rapid decline; MoCA 6, amyloid PET+	Late AD	Decline

F, female; M, male; 3/3, ApoE 3/3; 4/3, ApoE 4/3; C677T, the C677T mutation in methylene tetrahydrofolate reductase (MTHFR); FH, family history; aMCI, amnestic mild cognitive impairment; SCI, subjective cognitive impairment; FDG-PET+, fluorodeoxyglucose positron emission tomography interpreted as typical of Alzheimer's disease; amyloid PET+, amyloid PET scan read as abnormal, indicative of amyloid accumulation; NPsych+, quantitative neuropsychology tests showing abnormalities typical of AD; MoCA, Montreal Cognitive Assessment; MemTrax, an iPhone application that quantitates memory.

Metabolic profiling distinguishes three subtypes of Alzheimer's disease

Dale E. Bredesen^{1,2}

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² Buck Institute for Research on Aging, Novato, CA 94945, USA

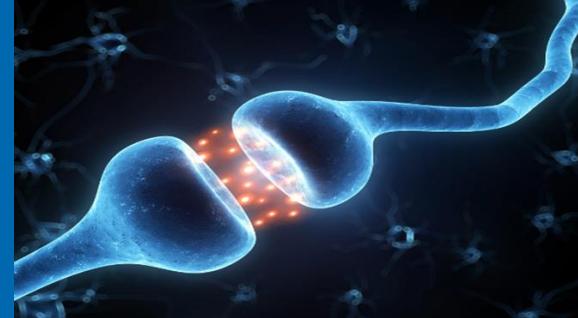
Key words: inflammation, neurodegeneration, cognition, insulin resistance, biomarkers, dementia, dyscalculia

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SUBTYPES

1. Inflammatory “hot”
2. Non inflammatory/atrophy “cold”
combo most common
3. Toxic-heavy metal, biotoxin
4. Vascular-multi infarct dementia
5. Traumatic –TBI or CTE

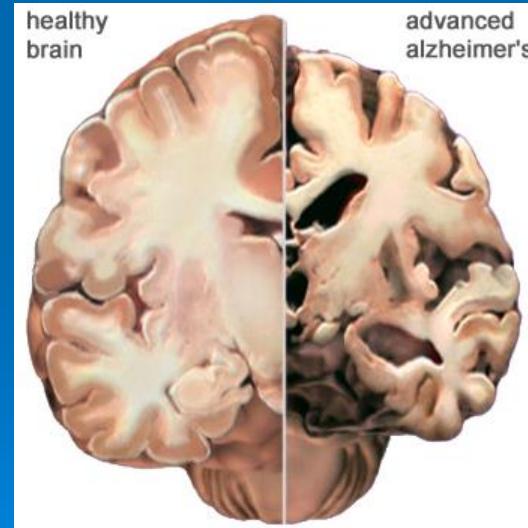


SUBTYPES

Inflammatory “hot”
Type 1



Non inflammatory/Atrophy “cold”
Type 2



combo 1.5 “inflammatrophic”



Subtype 3: Toxic

These patients represent a group that is uniquely different

Dyscalculia, aphasia, executive dysfunction
distinct from typical amnestic

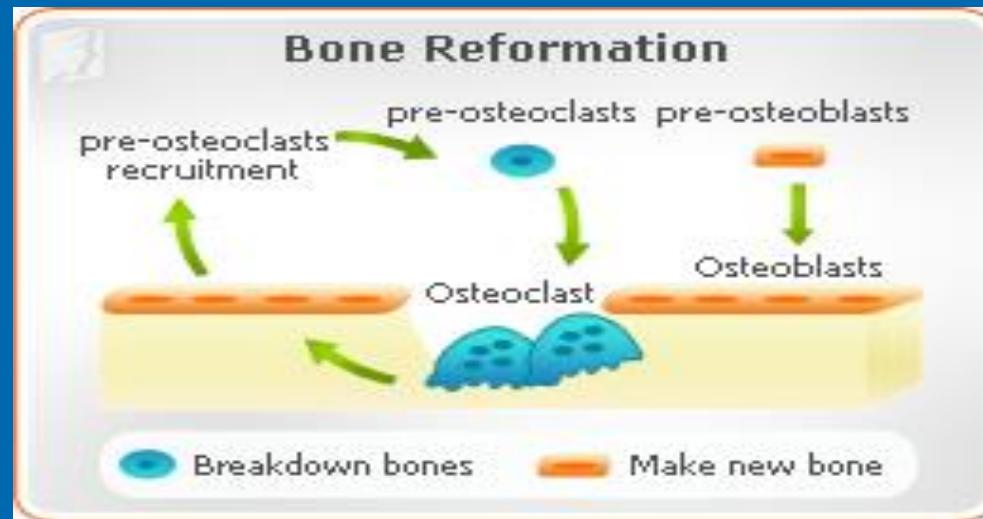
- (1) early symptom onset, typically in the 5th-6th decades
- (2) lack of family history
- (3) ApoE4-negative in the majority
- (4) MRI showing general cortical rather than hippocampal atrophy

Features of the Common Subtypes

	FAMILY HISTORY COMMON?	USUAL AGE AT ONSET	AMNESTIC INITIAL PRESENTATION	APO E4 COMMON?	HIPPOCAMPAL ATROPHY ON IMAGING
TYPE 1 “HOT”	YES	6-7 th decade	YES	YES	COMMON
TYPE 2 “COLD”	YES	7-8 th decade	YES	YES	COMMON
<u>COMBO</u>	YES	7-8 th decade	YES	YES	COMMON
TYPE 3 “TOXIC”	NO	5,6 th decade	Depression Math Organization Sx inc. w/stress	NO	CORTICAL

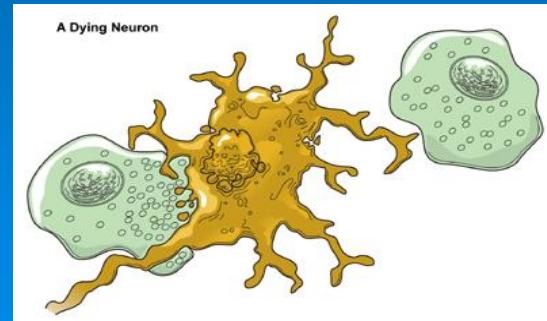
Alzheimer's as a signaling imbalance

Osteoporosis:



Alzheimer's:

Synaptoclastic



Synaptoblastic

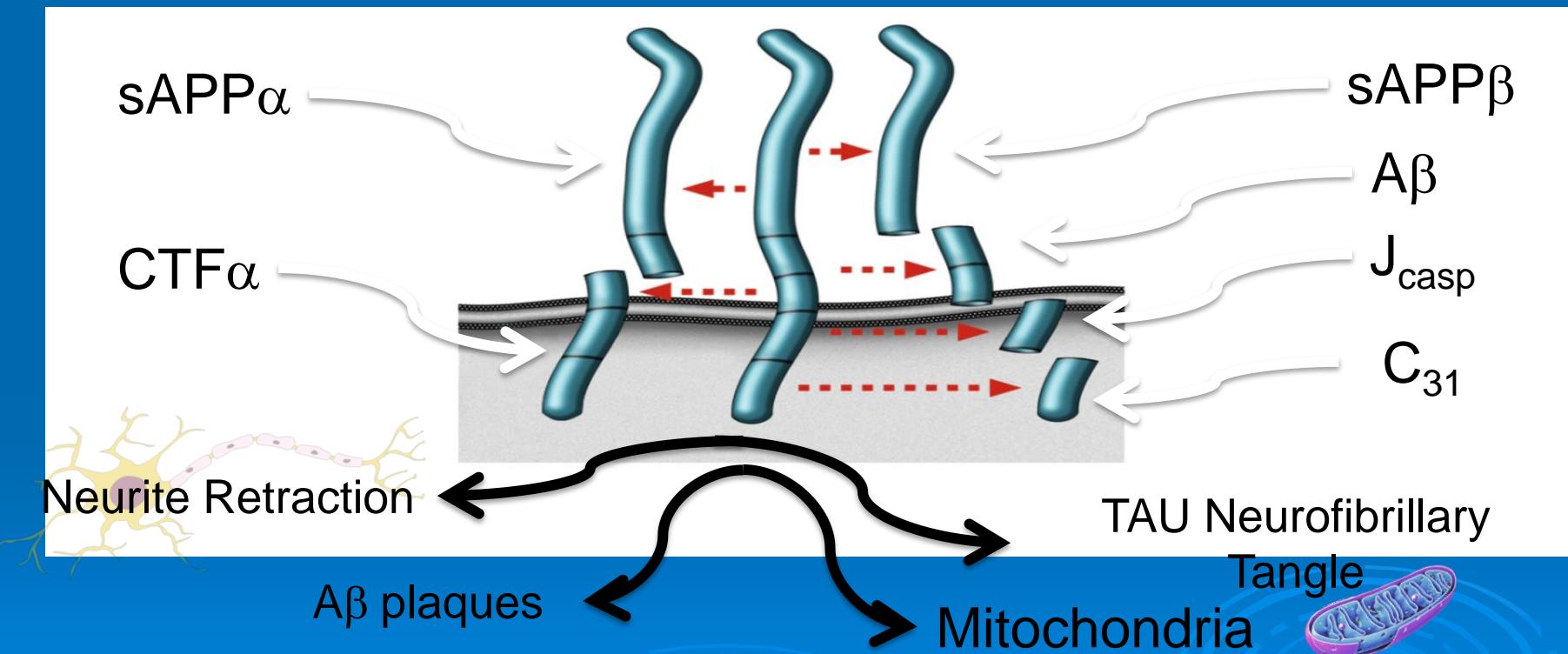


Blastic = good

Trophic,
Anti-AD

Clastic = bad

Anti-trophic,
Pro-AD



Goal	Approach	Rationale and References
Optimize diet: minimize simple CHO, minimize inflammation.	Patients given choice of several low glycemic, low inflammatory, low grain diets.	Minimize inflammation, minimize insulin resistance.
Enhance autophagy, ketogenesis	Fast 12 hr each night, including 3 hr prior to bedtime.	Reduce insulin levels, reduce Aβ.
Reduce stress	Personalized—yoga or meditation or music, etc.	Reduction of cortisol, CRF, stress axis.
Optimize sleep	8 hr sleep per night; melatonin 0.5mg po qhs; Trp 500mg po 3x/wk if awakening. Exclude sleep apnea.	[36]
Exercise	30-60' per day, 4-6 days/wk	[37, 38]
Brain stimulation	Posit or related	[39]
Homocysteine <7	Me-B12, MTHF, P5P; TMG if necessary	[40]
Serum B12 >500	Me-B12	[41]
CRP <1.0; A/G >1.5	Anti-inflammatory diet; curcumin; DHA/EPA; optimize hygiene	Critical role of inflammation in AD
Fasting insulin <7; HgbA1c <5.5	Diet as above	Type II diabetes-AD relationship
Hormone balance	Optimize fT3, fT4, E2, T, progesterone, pregnenolone, cortisol	[5, 42]
GI health	Repair if needed; prebiotics and probiotics	Avoid inflammation, autoimmunity
Reduction of Aβ	Curcumin, Ashwagandha	[43-45]
Cognitive enhancement	Bacopa monniera, MgT	[46, 47]
25OH-D3 = 50-100ng/ml	Vitamins D3, K2	[48]
Increase NGF	H. erinaceus or ALCAR	[49, 50]
Provide synaptic structural components	Citicoline, DHA	[51].
Optimize antioxidants	Mixed tocopherols and tocotrienols, Se, blueberries, NAC, ascorbate, α-lipoic acid	[52]
Optimize Zn:fCu ratio	Depends on values obtained	[53]
Ensure nocturnal oxygenation	Exclude or treat sleep apnea	[54]
Optimize mitochondrial function	CoQ or ubiquinol, α-lipoic acid, PQQ, NAC, ALCAR, Se, Zn, resveratrol, ascorbate, thiamine	[55]
Increase focus	Pantothenic acid	Acetylcholine synthesis requirement
Increase SirT1 function	Resveratrol	[32]
Exclude heavy metal toxicity	Evaluate Hg, Pb, Cd; chelate if indicated	CNS effects of heavy metals
MCT effects	Coconut oil or Axona	[56]

CHO, carbohydrates; Hg, mercury; Pb, lead; Cd, cadmium; MCT, medium chain triglycerides; PQQ, polyquinoine quinone; NAC, N-acetyl cysteine; CoQ, coenzyme Q; ALCAR, acetyl-L-carnitine; DHA, docosahexaenoic acid; MgT, magnesium threonate; fT3, free triiodothyronine; fT4, free thyroxine; E2, estradiol; T, testosterone; Me-B12, methylcobalamin; MTHF, methyltetrahydrofolate; P5P, pyridoxal-5-phosphate; TMG, trimethylglycine; Trp, tryptophan

The perfect Alzheimer's drug would:

Reduce APP β -cleavage, reduce γ -cleavage, increase α -cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of A β , increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase Sirt1, reduce NFkB, increase telomere length, reduce glial scarring, enhance repair, etc.

The perfect Alzheimer's drug would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of A_β, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransm increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFkB, increase telomere length, reduce glial scarring, enhance repair, etc.

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Supplements

Huperzine

Vinpocetine

Bacopa

Gingko

Phoshatidyl Serine

Acetyl-L Carnitine

Theanine

5HTP

Prebiotic/Probiotic

Saccromyces boulardii

Zinc

Milk thistle/Silmaryin

Selenium/iodine

Fish oil

Potassium

Magnesium

Calcium

Vitamin C, A

Methyl-B12/methyl folate

Multi-vitamin

CoQ10

Vitamin D3 w/ K2

Adrenal

Ashwaganda

Rhodiola

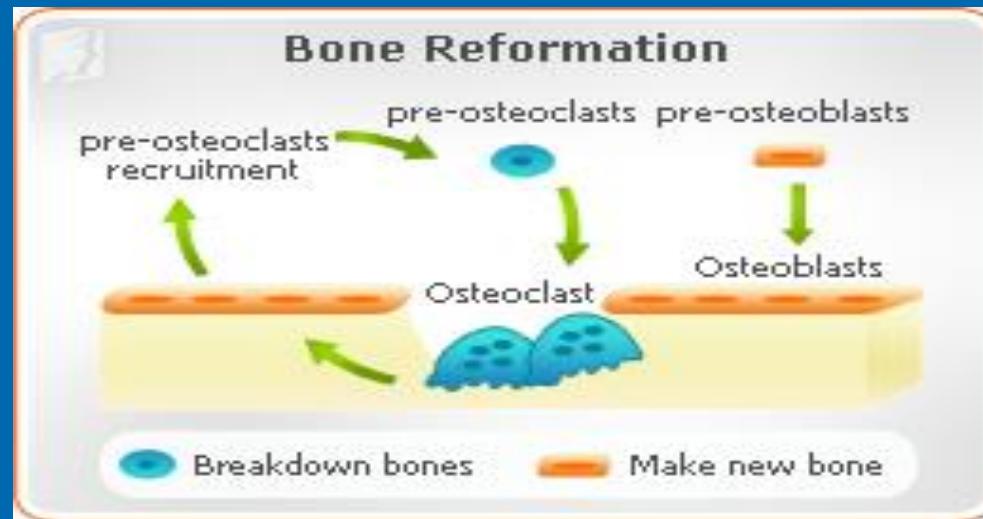
Glandulars

DHEA/pregnenolone

Cat's claw

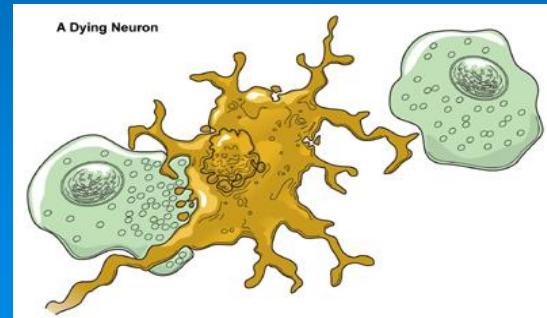
Alzheimer's as a signaling imbalance

Osteoporosis:



Alzheimer's:

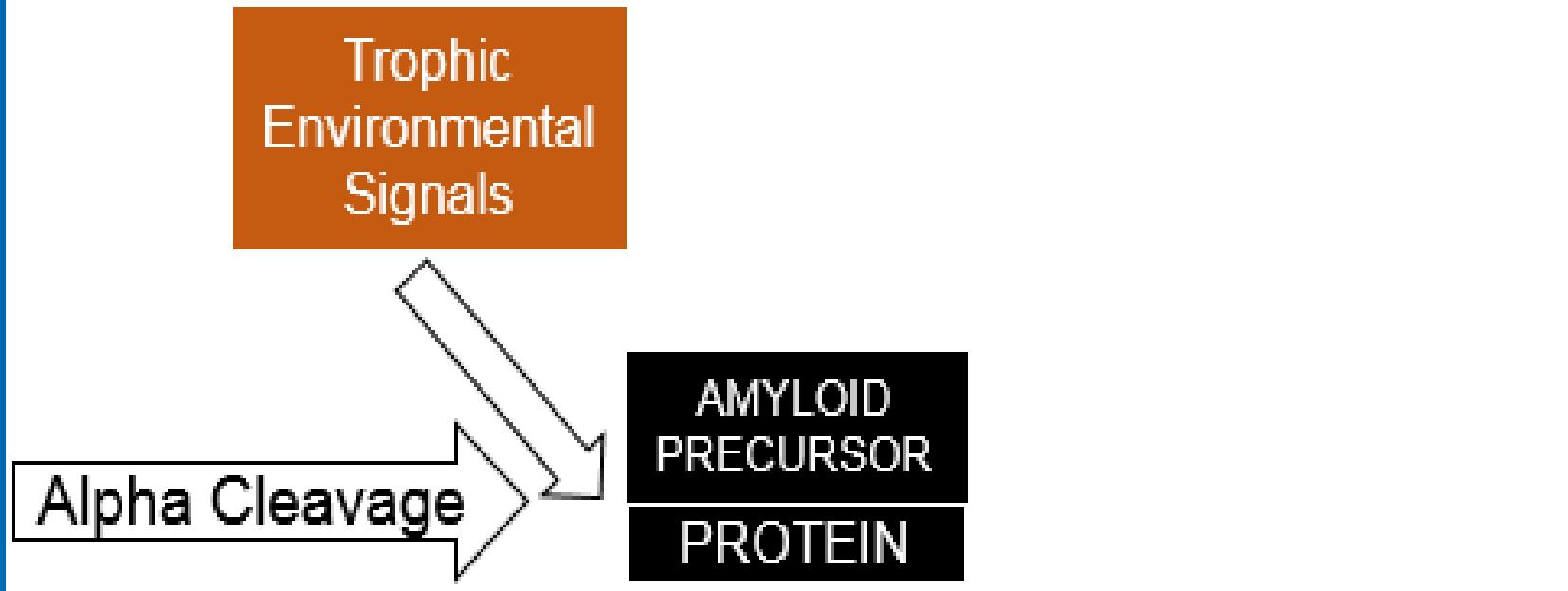
Synaptoclastic



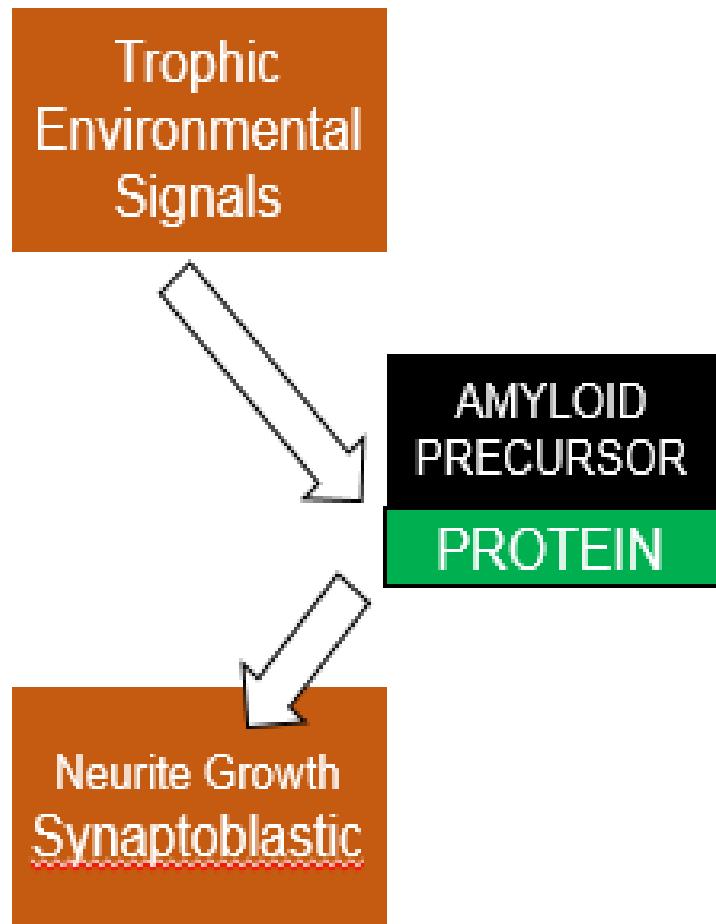
Synaptoblastic



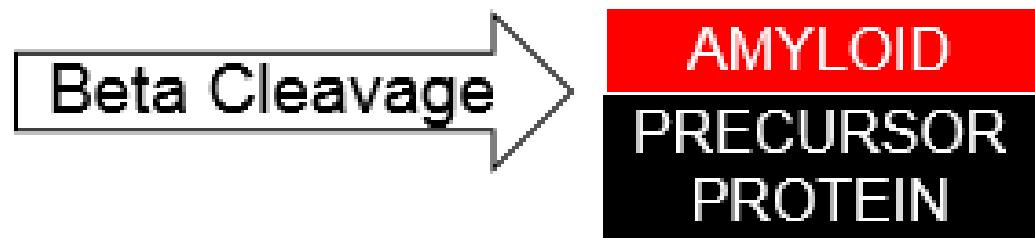
Trophic or “Favorable” Signals Cleave at the APP Alpha Site



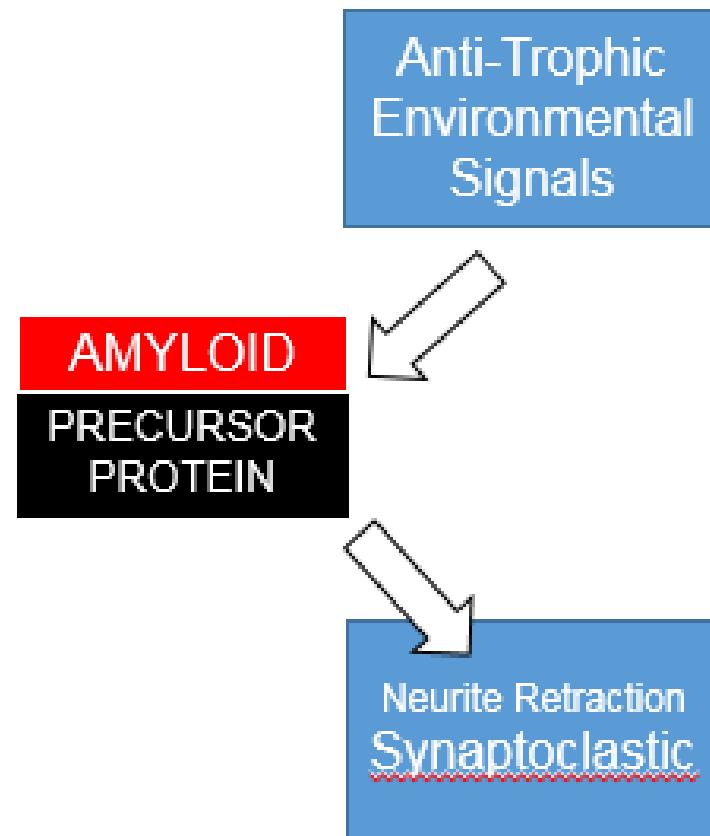
Alpha Cleavage Products Promote Neurite Growth and Synaptoblastic Activity



Anti-trophic or “Unfavorable” Signals Cleave at the APP Beta Site



Beta Cleavage Products Promote Neurite Retraction and Synaptoclastic Activity



EPIGENETIC
EFFECT OF
ApoE4



Inflammatory
Molecules
and
Biomarkers

AMYLOID
PRECURSOR
PROTEIN

Neurite Retraction
Synaptoclastic

Predictors of Success

Predictors of Failure

Presymptomatic
7 million E4/E4 - 75 million E4/--

SCI / PCI
Subjective / Preclinical Cognitive Impairment

MCI
Especially if amnestic;
identifiable contributors

Early AD
Especially if not already on AD meds

Individuals with cognitive changes who are otherwise healthy

Non-type 3
SCI, PCI, MCI, or early AD

Atrophy limited to hippocampus

Age < 75

Advanced Alzheimer's

Long term progressive symptoms

On multiple medications, especially donepezil and memantine

Poorly compliant patient, family, caretaker, MD, or care team

Type 3
Especially when beyond early MCI

Those who are slow, with diffuse synaptic loss

Age > 75

Clinical: Threshold effect

Keep treating until improvement begins

Working on years of pathophysiology

Usually first signs in 3-6 months

The first positive sign is that progression stops or slight improvement are both great signs

Continued decline means that something has been missed—cognitive decline does not occur without reason

The most common reasons for failure:

compliance

collaborative care team

missing key inputs

Type 1 systemic inflammation

high hs-CRP (high-sensitivity C-reactive protein)

High cytokines - interleukin-1 and interleukin-6

Balance between NF κ B and the sirtuin SirT1
-altered in favor of inflammation (reduced SirT1)

,

Unlike other neuro-inflammatory diseases
-inflammation in AD involves primarily the innate immune system

-pathology of AD includes inflammatory microglia/activated astroglia

- phagocytosis of amyloid- β peptide is reduced by inflammation in patients with AD

Inflammatory microenvironments
'cytokine storms'

Modulation of innate immunity of patients with Alzheimer's disease by omega-3 fatty acids

Innate immune system of patients with Alzheimer's disease and mild cognitive impairment (MCI) is dysregulated

Current immune therapies target single mechanisms in the adaptive immune system but not innate immunity

Defective macrophages from Alzheimer's patients

recover phagocytic function with Omega 3



Diabetes and Inflammation on the Attack
Glycosylation= Caramelize our Cells

Type 3 diabetes is sporadic Alzheimer's disease

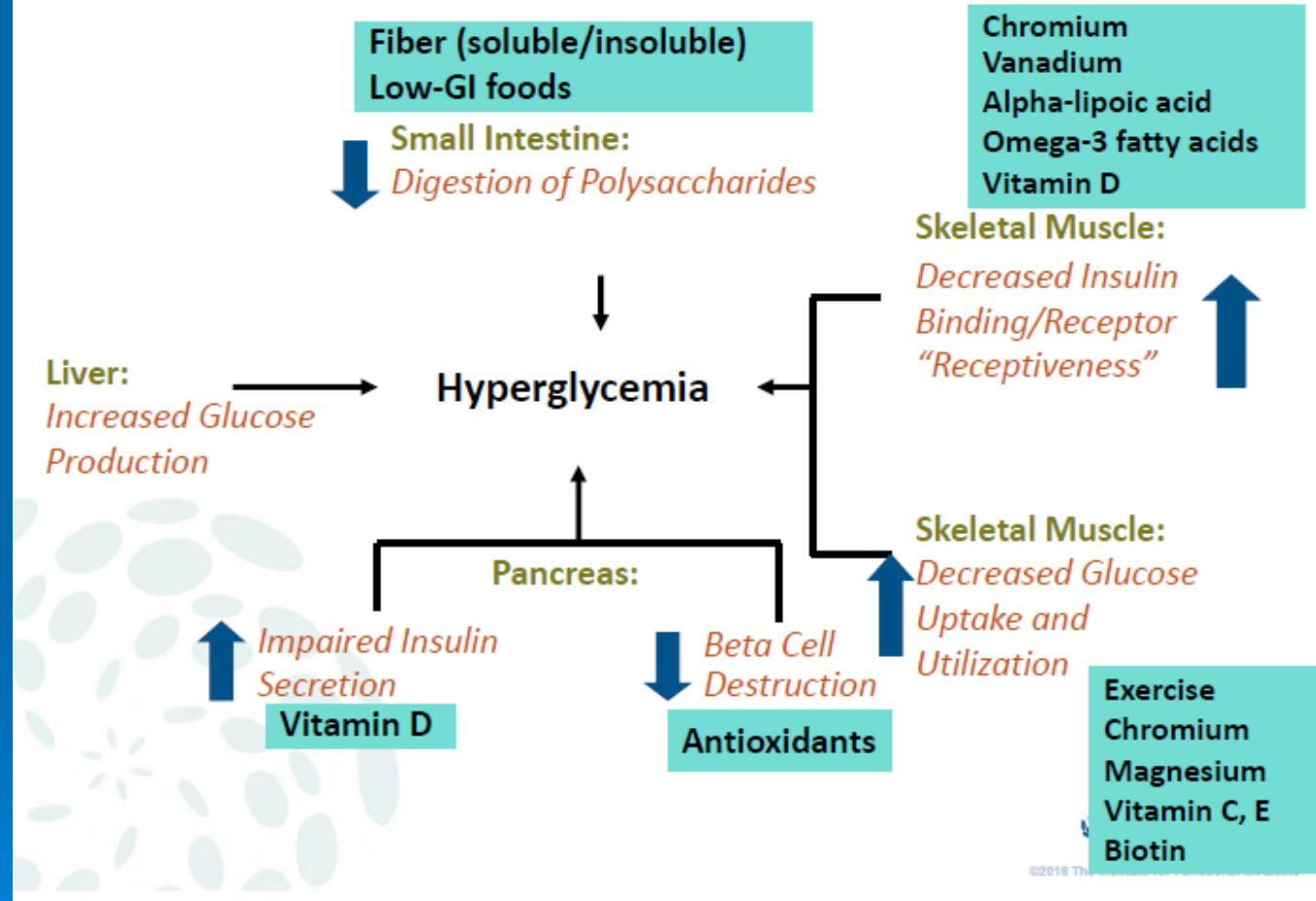
Evidence supports that AD is a metabolic disease mediated by impairments in brain insulin responsiveness, glucose utilization, and energy metabolism

- lead to oxidative stress, inflammation

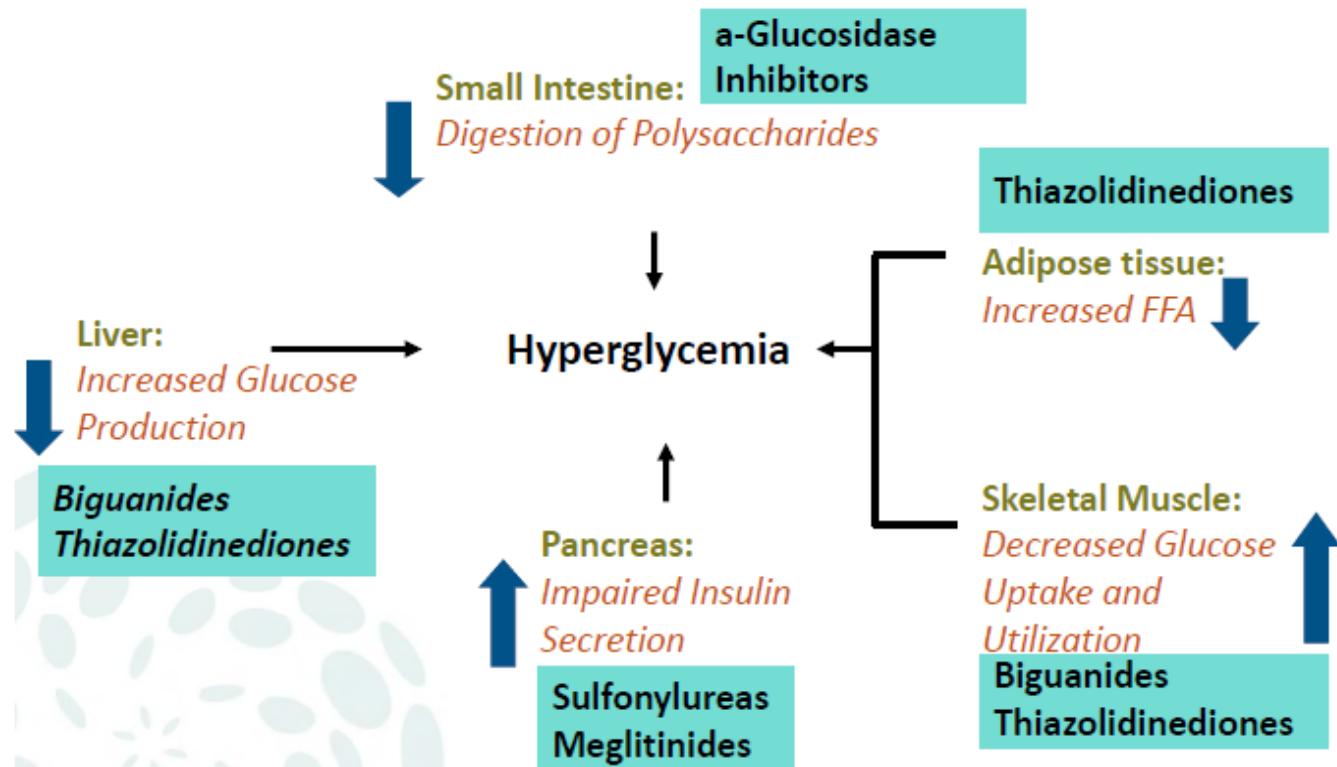
Directly contribute to the structural, functional, molecular, and biochemical abnormalities that characterize AD

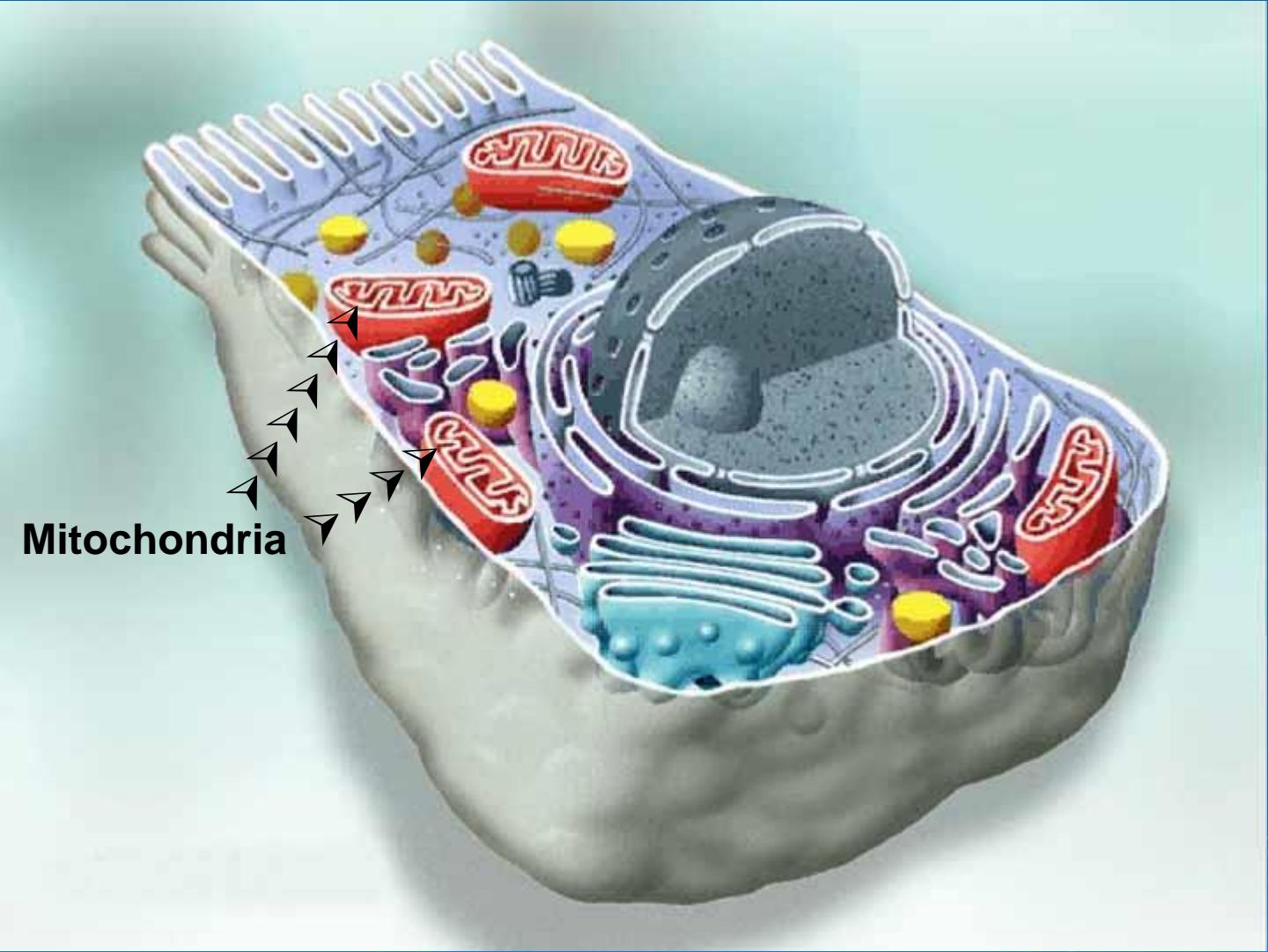
- neuronal loss
- synaptic disconnection
- tau hyperphosphorylation
- amyloid-beta accumulation

Pathophysiology of Hyperglycemia



Pathophysiology of Hyperglycemia

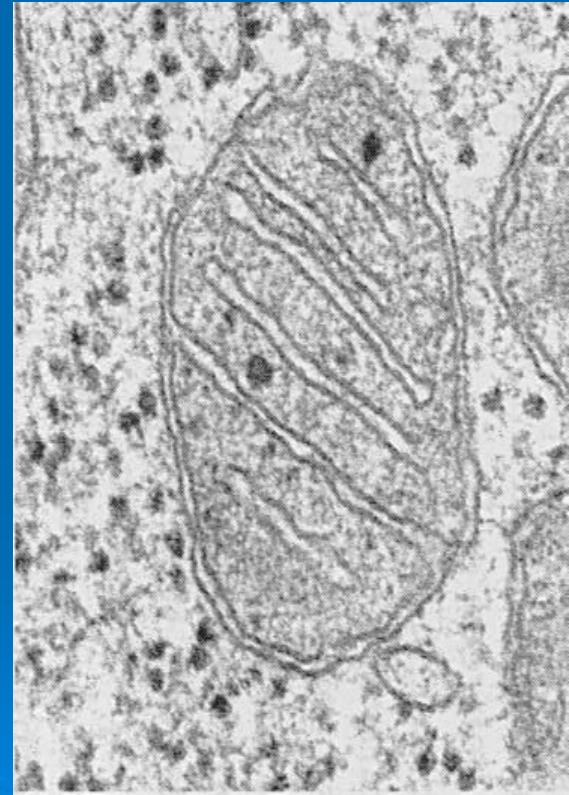




Mitochondrial Dysfunction And Diabetes

“..., it has been elucidated that some environmental factors, pollutants, and mitochondrial toxins are involved in the pathogenesis of type 2 diabetes.

Taken together, we suggest that mitochondrial dysfunction plays a role in the pathophysiology of insulin insensitivity....”



Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease

“In addition to their epidemiologic and clinical association, mounting recent evidence indicates shared mechanisms of pathogenesis between metabolic disorders and AD. We discuss the concept that peripheral and central nervous system inflammation link the pathogenesis of AD and metabolic diseases.”

Oxidative Stress Evaluation

Damaged Fats

Lipid Peroxides, oxidized LDL, Isoprostan F2

Damaged Sugars

HgbA1c, AGEs

Damaged Proteins

3-Nitrotyrosine

Damaged DNA

8-OH Deoxyguanosine

8-Hydroxy-deoxyGuanosine (8-OH-dG)

- Results from damaged DNA, marker of mitochondrial damage
- Markedly increased by cigarette smoking and environmental toxin (PAH) exposure
- Increases with total calorie and/or carbohydrate intake
- Increases with PUFA intake; lowered with MUFA
- Elevated in Parkinson's disease & lung cancer
- Reduced by physical exercise

Dietary ketosis enhances memory in MCI

23 subjects

6 week intervention



High Carb vs Low Carb diet (Ketogenic)

Ketone levels positively correlated with memory performance

(no effect on depressive symptoms)

Ketogenic Diet Approach

reduces inflammation (NF κ B)

enhances mitochondrial biogenesis

enhances ATP production

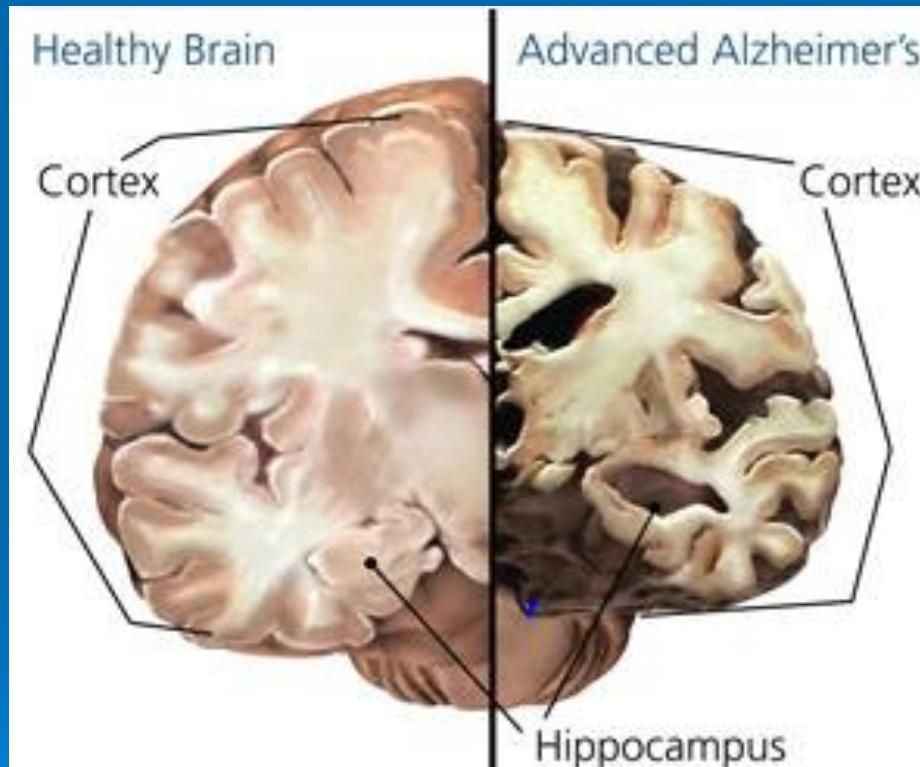
reduces ROS production

reduces apoptosis

increases insulin sensitivity

increases leptin sensitivity

SUBTYPE 2



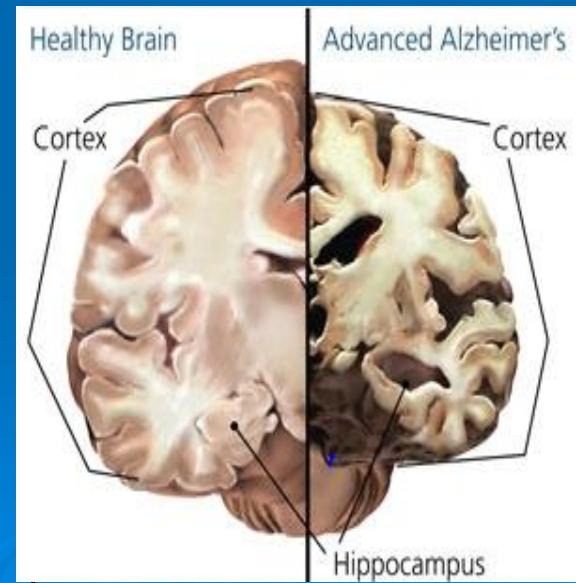
Non inflammatory/Atrophic “cold”

Type 2
characterized by an atrophic profile

Reduced trophic support
from hormones and vitamin D

Increased homocysteine

Insulin resistance

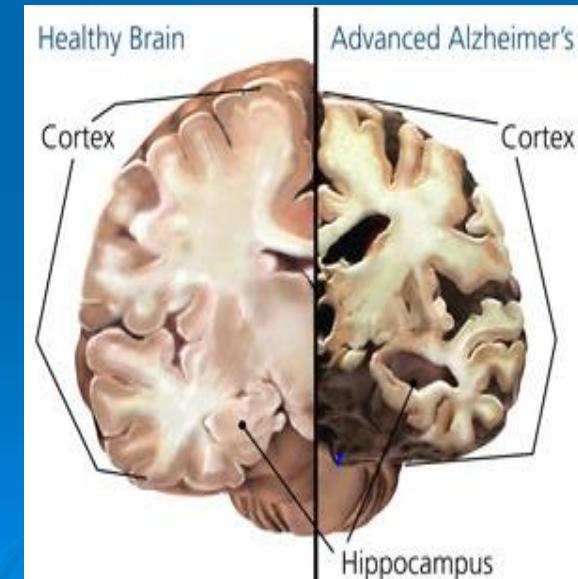


Subtype 2 Non-inflammatory

How much does each risk factor vs contributes directly?

Homocysteine- exerts multiple effects on cognitive decline

- increasing tau phosphorylation
- glutamate receptor dysfunction
- neuronal apoptosis induction
- endoplasmic reticulum stress
- DNA methylation
- mitochondrial dysfunction
- vascular damage
- oxidative stress



Vitamin D deficiency



70% to 90% of older adults with AD are affected

Low vitamin D associated with global cognitive impairment

Vitamin D

Increases the amount of acetylcholine in the brain

Provides neuronal protection against AD

- anti-inflammatory action

- antioxidant effect

Regulates concentration of intracellular calcium
in hippocampal neurons

= anti-trophic effect

Combination of memantine plus vitamin D on cognition in AD

Patients with AD who took memantine plus vitamin D for 6 months (300 pts)

4-point gain in MMSE score

vitamin D alone

memantine alone

had no change



Case Control Study

Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes

Blanca Murillo Ortiz, Joel Ramírez Emiliano, Edna Ramos-Rodríguez, Sandra Martínez-Garza, Hilda Macías-Cervantes, Sergio Solorio-Meza, Texar Alfonso Pereyra-Nobara

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Author contributions: All the authors contributed to the paper.

Institutional review board statement: This protocol was approved by the local bioethics committee (R-2014-1001-88).

Informed consent statement: The informed consent was obtained from each volunteer.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Data sharing statement: No data were created no data are available.

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Manuscript source: Invited manuscript

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Trophic Factors

Low levels of BDNF are associated with cognitive impairment in patients with DM2

The decrease of BDNF occurs early and progressively in patients in AD

What Disrupts Hormonal Balance?

Nutritional Insufficiencies

Inflammation

Chronic Stress

Adiposity

Altered
Biotransformation

Toxins

Infections

Genetic Propensity

Food/Diet

Smoking

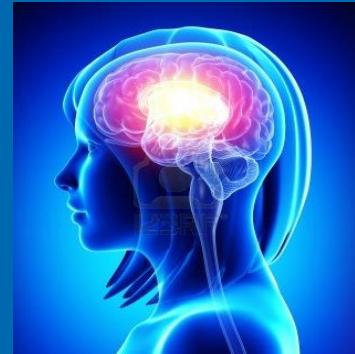
Food allergy
& intolerances

Hormonal
Dysfunction



Signs and Symptoms

What are the questions for women?



Who needs hormone replacement?

What is the right target level for hormone replacement?

Should you measure hormone levels? Which ones? And how?

Is there a critical window after which you should not give hormones?

Should we be treating asymptomatic women?

Is bioidentical estrogen/progesterone safe/safer/not safe?

Should women be given testosterone? What kind? How much?

What are the questions for women?

Does Estradiol improve cognition in women?

When is optimal time to start?

When is diminishing return with increased risk?

Does Progesterone matter?

Equine estrogen vs bioidentical?

Medroxyprogesterone/progestin vs bioidentical?

Role of testosterone, DHEA, pregnenolone?

Who to strongly consider for Bioidentical Hormone Replacement Therapy

Who to strongly avoid Hormone Replacement Therapy?



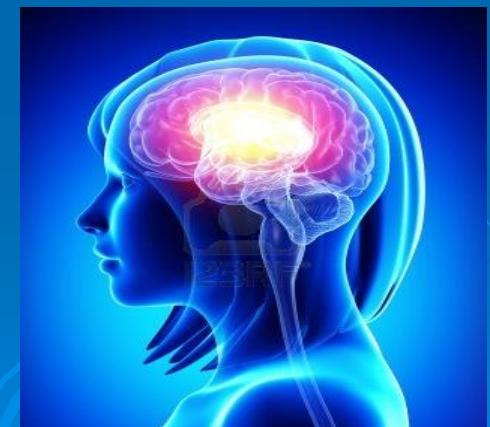
Why not just give hormones?

A general rule in systems biology is that since and unpr makes shou system to respond, unless we intend a catastrophic change with a quick removal of the stimulus (emergency medicine).
Translation from conventional medicine:
Give the smallest amount of hormone for the shortest period of time

WOMEN'S HEALTH INITIATIVE WHIMS 2 CEE/MP MEMORY

200% increase in dementia with CEE .625
and medroxyprogesterone 2.5 mg per day

49% increase in dementia taking CEE .625
alone



Shumaker SA et al; JAMA. 2003 May 28;289(20):2651-62.

International Menopause Society

“The **excessive conservatism** engendered by the presentation to the media of the first results of the WHI in 2002 has disadvantaged a decade of women who may have missed the potential therapeutic window to reduce their future cardiovascular, fracture and dementia risk.”

D.W. Sturdee, A. Pines, IMS Writing Group, et al. (2011). Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 14 302–320.

Prevention of Alzheimer's disease, cerebrovascular disease and dementia in women: The case for menopause hormone therapy.

Bilateral oophorectomy before the natural menopause is associated with an increased incidence of dementia



Increased risk is significantly reduced by estrogen therapy

Recent advances in menopause hormone therapy including transdermal estrogen therapy have favorably influenced the balance of benefits and risks.

“A case can be made for menopause hormone therapy in healthy postmenopausal women for 5-10 years starting during the menopausal transition
(the 'window of opportunity')

To delay or prevent the development of dementia in later life.”

Hormone exposure/risk of cognitive impairment in Swedish twins

6000 women

65–84 years old

Longer reproductive years linked with decreased risk of cognitive impairment
($p < .01$)

LATER MENOPAUSE =
LOWER RISK OF COGNITIVE DECLINE

Oophorectomy, estrogen, and dementia: A 2014 update

Three studies have compared women with oophorectomy before menopause consistently show increased cognitive decline/dementia

Case control and cohort studies show neuroprotective effects in women who received estrogen treatment in the early postmenopausal ages 50–60 years

Suggests a neuroprotective effect of estrogen

Conclusion:

Women who undergo oophorectomy before menopause or women with premature menopause should be considered for hormonal treatment for cognitive protection

Hormone exposure/risk of cognitive impairment in Swedish twins

Hormone Tx

-40% decline in the risk of cognitive impairment

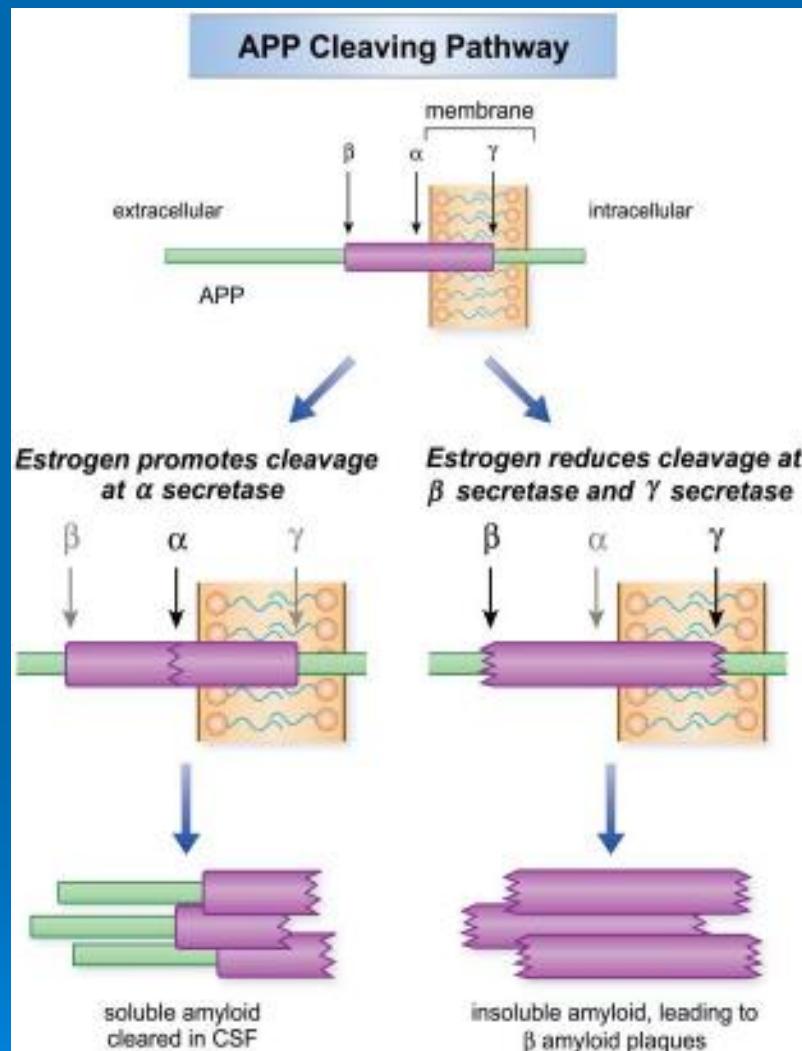
Conclusion:

Later menopause

Hormone replacement therapy with estrogen
(alone or with progesterone)

= Decreased the risk of cognitive impairment

Estradiol and Amyloid Precursor Protein Pathway



Estradiol is SYNAPTOBLASTIC

- Reduces Beta amyloid toxicity
- Reduces Beta amyloid levels
- Increases clearance of Beta amyloid from CSF
- Reduces inflammatory response to Beta amyloid
- Increases the density of hippocampal neurons
- Increases synaptic plasticity via E2 receptors
- Increases synaptic density via E2 induced BDNF

How to assess patient as hormone candidate and monitoring:

Full Functional Medicine evaluation with female pelvic exam

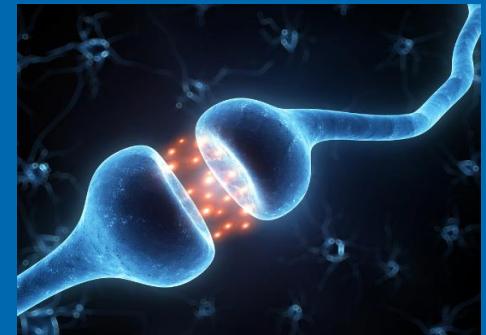
Labs:

- E2, E1, Progesterone, Testosterone total, DHEA-S, SHBG, Estrogen 2/4/16 metabolites
- CBC, chemistry w/ glu/insulin/HgbA1c, CRP, B12, Ferritin, vitamin D
- Lipid panel, Lp(a), homocysteine, fibrinogen, PLAC-2, EKG; ?IL-6, TNF-a
- Fractionated lipid particle panel if needed
- ?CIMT/EBCT/Stress Echo if personal/family hx or concerns
- Factor V Leiden, Prothrombin mutation for coagulation genetic risk
- Dexa, Mammo yearly/biannual, breast ultrasound yearly/biannual, MRI ?thermogram benefit-when coupled with above not solo evaluation

Protective Nutritional Support

To Do:

- Eat more organic vegetables
- Support GI health
- Improve detox mechanisms
- Support adrenal balance
- Sleep
- Enjoyable exercise
- Use bioidentical hormones when needed

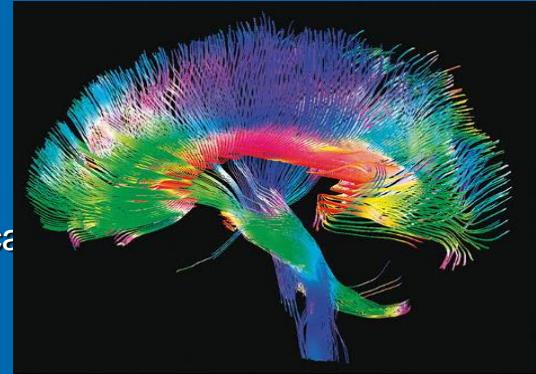


Avoid:

- Sugar, caffeine, alcohol and junk food
- Toxic chemicals and xenoestrogens
- Hormone imbalance
- Stress
- Avoid unnecessary drugs or artificial hormones

Progesterone

If on estradiol and has a uterus MUST be on progesterone
-protect uterine lining hyperplasia-may lead to endometrial ca



Pre-menopause
Cycled dosing

100-200 mg day 14 to start of cycle, stop then restart day 14 etc.

Menopause
100-200 mg continuous but monitor levels (fat soluble can get too high levels)
-affect downstream hormones synthesis-cortisol, androgens, estrogen

Dosages
Oral micronized progesterone commercially (peanut oil) available doses 100/200 mg
Can be compounded without peanut oil or in SR (sustained release for sleep)
in any dose –typically min 60 mg needed up to 200 mg

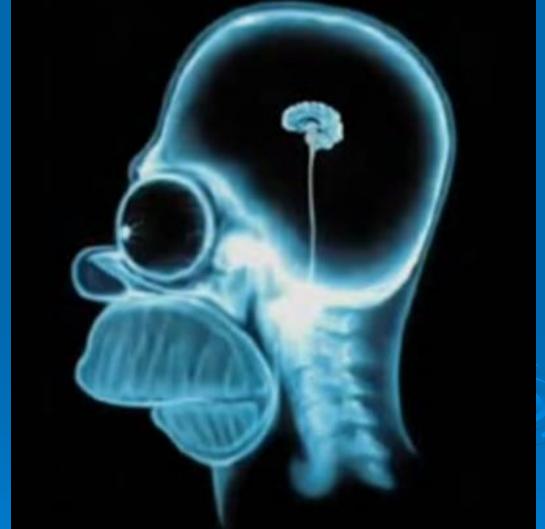
Oral, compounded cream (with other hormones too), troche, vaginal suppository

Progesterone

- associated with changes in regional brain activation patterns during a visual memory task
- greater activation in left prefrontal cortex/right hippocampus
- increase in number of words remembered following the verbal task performed during the fMRI scanning session
- associated with improved neuropsychological measures of verbal working memory compared to placebo.

WHAT ARE THE QUESTIONS FOR MEN?

- What about men and testosterone?
- When, for how long, what levels, how to monitor?
- What about men and DHEA, pregnenolone?



Role of testosterone in the early development of AD

Baltimore Longitudinal Study of Aging

- 574 men without AD were followed for a mean of 19.1 years

For every 10-unit (nmol/nmol) **increase** in the free testosterone index risk of developing AD was found to be **reduced** by 26%

- **low testosterone levels predict:**
development of AD 10 years in advance



Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM & Resnick SM. Neurology 2004 62 188–193.

Effects of testosterone replacement on activity in different regions of the brain

1. 18FDG PET mental rotation task in hypogonadal men before and after 10 weeks treatment with testosterone replacement

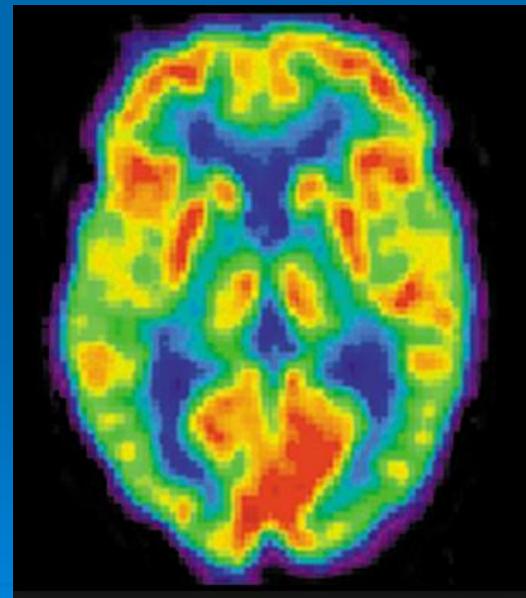
-improved visuospatial performance with enhanced cerebral glucose metabolism

2. SPECT showed that cerebral perfusion

increased in midbrain, superior frontal gyrus, midcingulate gyrus
after testosterone replacement

3. fMRI regional brain activation in hypogonadal men

-**low activation of cerebral cortices**
was restored following testosterone replacement



Zitzmann M, Weckesser M, Schober O & Nieschlag E. Experimental and Clinical Endocrinology and Diabetes 2001 109 302–304.
Azad N, Pitale S, Barnes WE & Friedman N. Journal of Clinical Endocrinology and Metabolism 2003 88 3064–3068.
CrossRefMedlineWeb of Science
Park K, Seo JJ, Kang HK, Ryu SB, Kim HJ & Jeong GW. International Journal of Impotence Research 2001 13 73–81.

Testosterone:

- Inhibits β -amyloid found in plaques
- Inhibits hyper-phosphorylated tau in neurofibrillary tangles
- Reduce β -amyloid secretion in rat cortical neurons
- Alters processing of amyloid precursor protein
- Reduce β -amyloid-induced neurotoxicity



Gouras GK, Xu H, Gross RS, Greenfield JP, Hai B, Wang R & Greengard. PNAS 2000 97 1202–1205.

Abstract/FREE Full Text

↵ Pike CJ. Brain Research 2001 919 160–165.

P

Production

Production/synthesis and secretion of the hormone

T

Transport

Transport/conversion/distribution/ interaction with other hormones

S

Sensitivity

Cellular sensitivity to the hormone signal

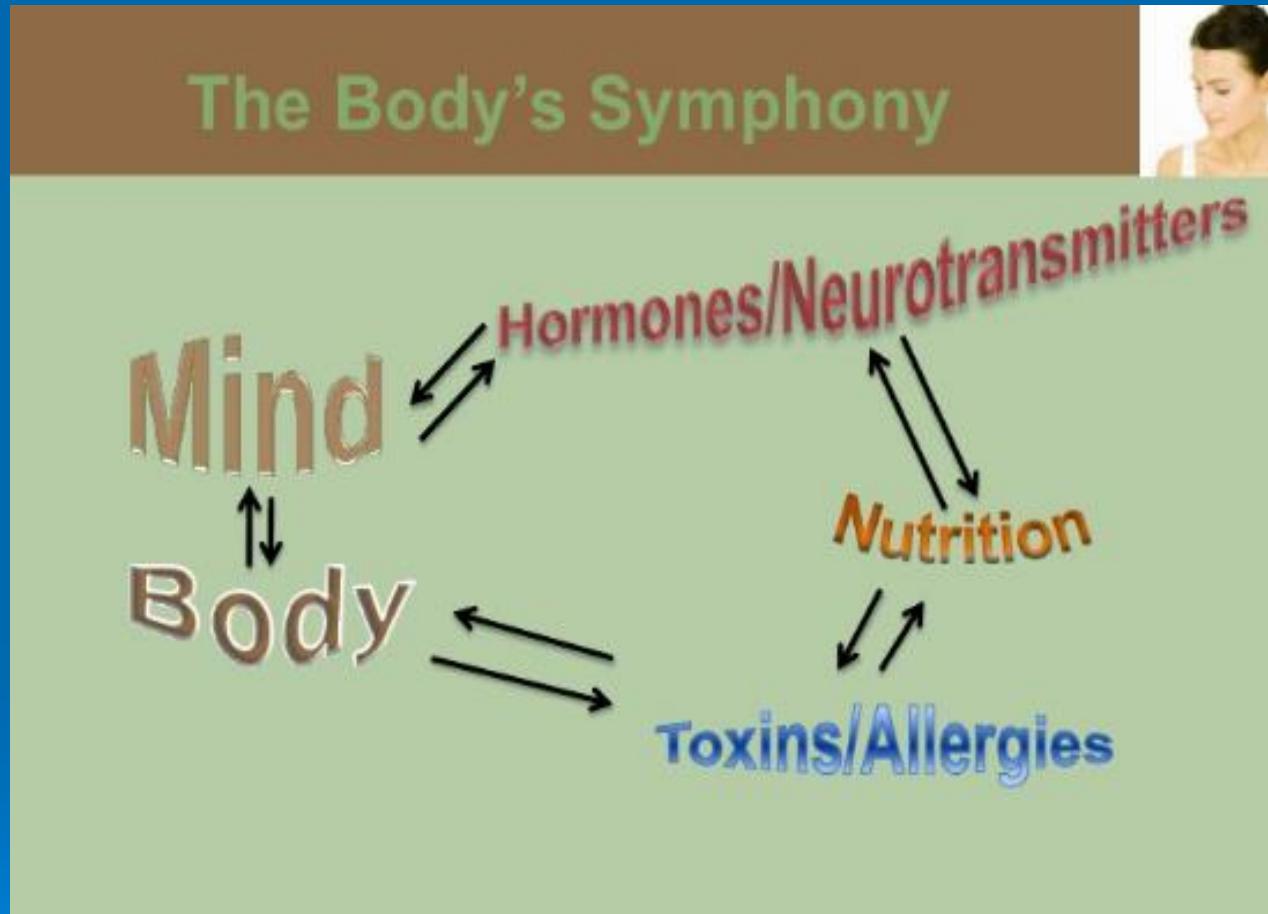
D

Detoxification

Detoxification/excretion of the hormone



H-P-T-A-G-G axis



Hypothalamic

Pituitary

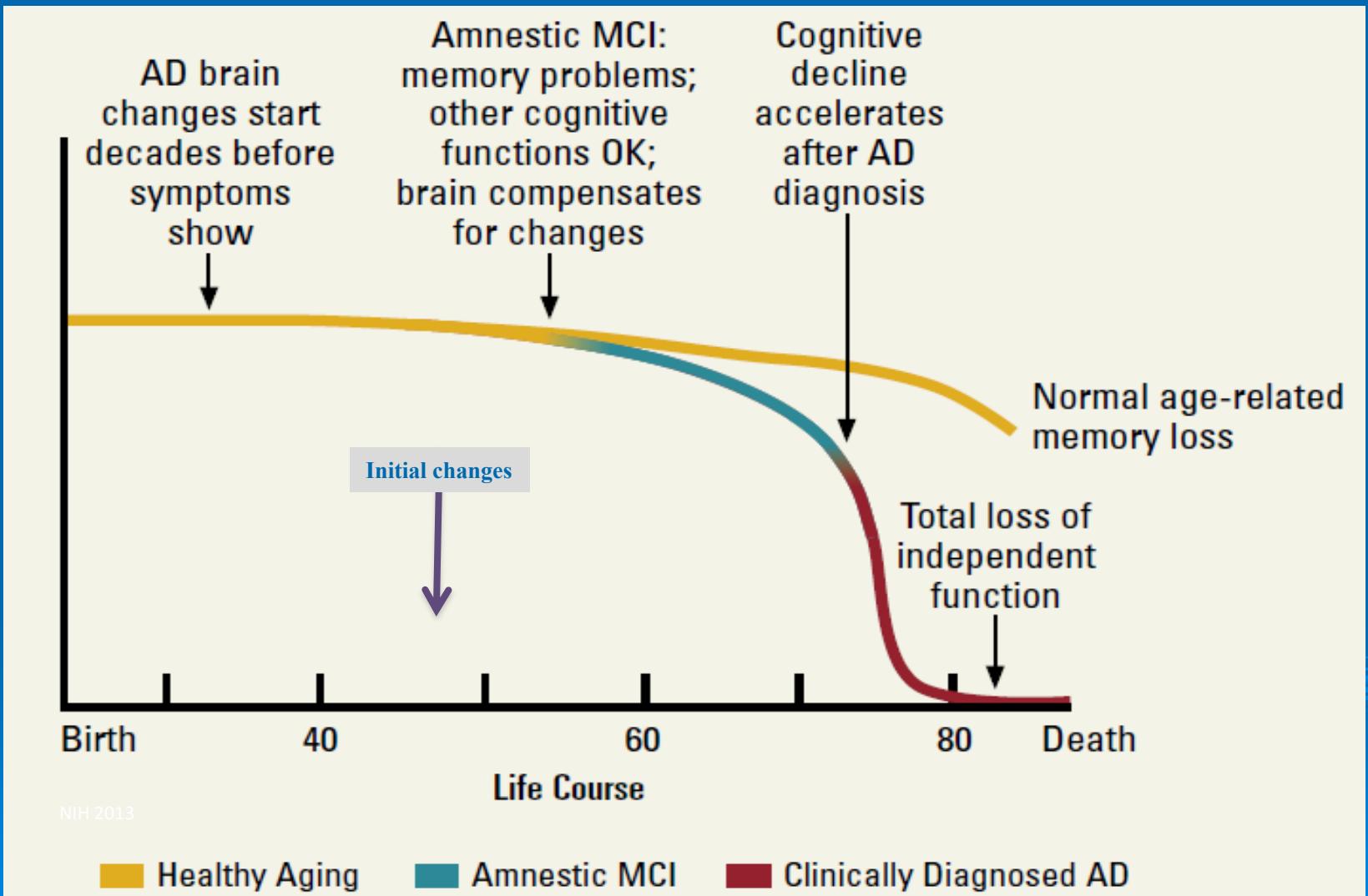
Thyroid

Adrenal

Gonadal

Gut

Intervening prior to MCI optimal!





THANK YOU!!

A Tale of Two Patients

The power of the collaborative team

Jayne: one not successful....

Mary: a successful care plan/team!

Jayne 66 year old female publisher

Lived in Salt Lake City

Husband and daughter came with patient
(step father to daughter)

daughter in nursing school
“ this is all her idea....”

Tacrine mild benefit for 2 years still progressive decline
stopped driving, homebound

Primary Care MD thought was waste of money on all the testing
and waste of time and should try Tacrine again....

No change essentially in labs or scores or functional status at
3 month, 6 month, 9 month

at 12 month follow up, no change, family decided to quit the program

“I told her this wasn’t going to help, nothing can”
father to daughter

1 week later daughter calls
“supplements all in a box in the garage, not doing the nutrition/ketogenic, not taking any meds except for Multi vitamin rec by original doctor”

Mary 67 year old female author

Same labs and history essentially as Jayne

Tacrine mild benefit, stopped driving,
homebound

Husband and primary care MD very supportive

Implemented treatment plan

Mary

Lived in a small town 50 miles away
very well known and loved

Neighbor – nutritionist

2 granddaughters - yoga instructors

Everyone was ‘all in’ on the program
after house call

Mary

Within one month, husband and
granddaughters
noticed improvement

-memory, mood and energy

6 months marked improvement in MOCA

12 months essentially normal with better
energy, mood, activities

18 months later driving exam DMV passed

Case Study

A 67 year old married woman, former professional author

Hx rheumatic fever as child, birth a crash C section

Had 4-5 yr hx of memory problems

- leaving stove on several times
- had a small fire in the kitchen

She had progressive memory loss then sudden decline after a food poisoning illness

MRI with age = atrophy

Usual labs within normal range (TSH, B12, RPR)

Case Study, cont.

“Treatment”:

- Told “take the single medication” and that there was nothing else to do
- Stopped driving, reduced social activities, homebound
- Doctor told the husband:
 - “Look at placement for her soon as she will likely not be able to stay at home.”

Case Study, cont.

History, cont.:

- She was moderately obese
 - Total BF 34%
 - Visceral Fat score 21 (10 normal) by BIA
- ‘Pre-diabetic’ for over 10 yrs
- ‘Sensitive stomach’ whole life
 - constant bloating
- Told she had ‘thyroid issues’
 - never treated
- Chronic vaginal discharge
 - negative GYN eval

Case Study, cont.

History, cont.:

- Recurrent UTI treated with antibiotics
 - Usually needed Diflucan after for fungal infections
 - GYN and UROLOGY workup negative
- Uneventful Menopause age 50
- Death of Mother caused mild depression
 - 7 years prior-medicated with sweets

Case Study, cont.

History, cont.:

- Mild sleep apnea
 - Wakes with headache
- Nocturnal hypoxia overnight on room air home study
- Placed on nocturnal oxygen: 2L nc with resolution

Case Study, cont.

Labs:

- Vitamin D: 14
- B12: normal 233 (220-1220)
- Folate: normal 4.2 (3.0-14)
- hs-CRP: elevated 7.9 ideal <1.0
- IL-6: Elevated
- Homocysteine: elevated 16 labs says ok <15 (goal <8)
- Positive for gluten sensitivity: +TTG IgG, - IgA
 - Low serum IgA....
- High IgG food panel casein/whey/gluten

Case Study, cont.

Labs, cont.:

- TSH: 4.5 with the lab range up to 5.0
- TPO antibody: 430 = Hashimoto's (<20)
- E2, E1, Progesterone: 'menopausal' level=very low
- Cortisol circadian saliva test: low in am and high in evening
- DHEA, testosterone, pregnenolone low normal

Case Study, cont.

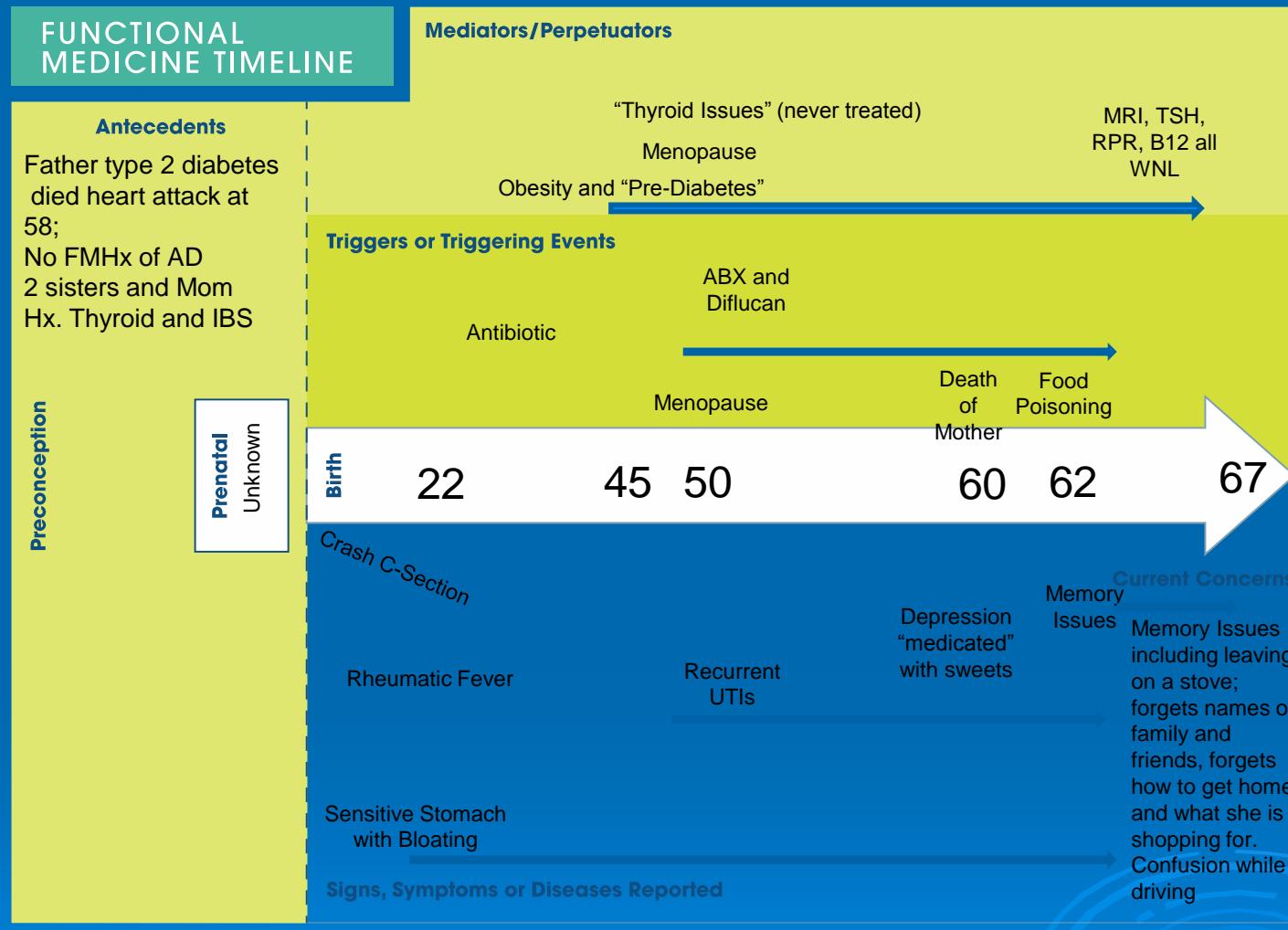
Labs, continued:

- HgbA1c 5.9
- Fasting glucose 98
- Insulin elevated at 26 lab range under 24 (goal <10)
- Glucose Tolerance Test
 - glucose 165
 - but insulin 124!
- ApoE 3/4
- Heterozygous MTHFR 677
- MMSE 22/30
- MOCA 20/30
- +FDG PET
- +Neuropsych eval by University MD

Stool analysis

- High fecal fats
- Low secretory IgA
- 2 different candida species on stool analysis
- No protective lactobacillus/bifidobacter

Build the Timeline First



The Lifestyle Factors May be the Most Important! (Highly recommend health coaches!)

FUNCTIONAL MEDICINE MATRIX
Retelling the Patient's Story

Antecedents

Triggering Events

Mediators/Perpetuators

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation Defense & Repair

Structural Integrity Energy

Mental Emotional

Spiritual

Communication Biotransformation & Elimination

Reversing Cognitive Decline

Modifiable Personal Lifestyle Factors

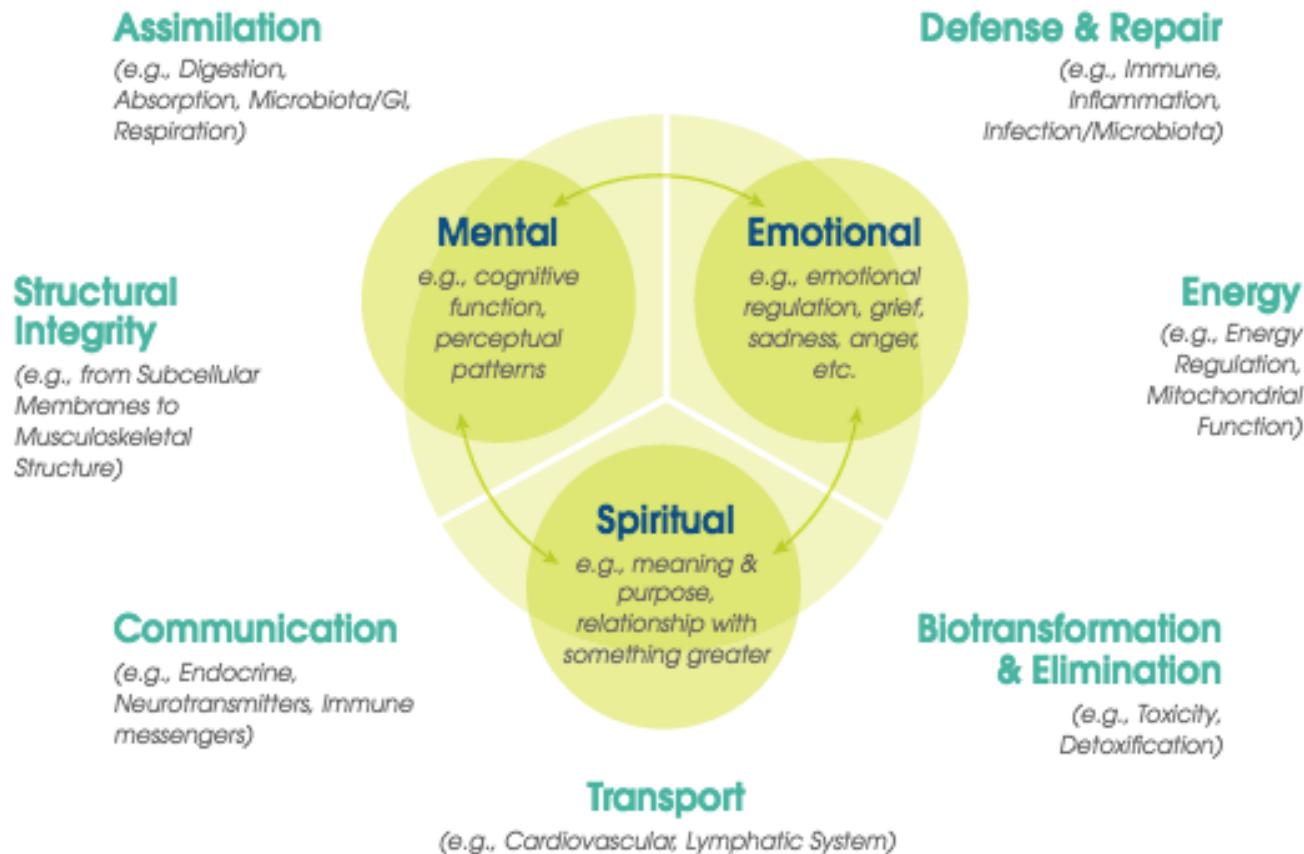
Sleep & Relaxation Exercise & Movement Nutrition Stress Relationships

Name: _____ Date: _____ CC: _____

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Then map the bioterrain on the Functional Medicine Matrix

Physiology and Function: Organizing the Patient's Clinical Imbalances



FUNCTIONAL MEDICINE MATRIX

Retelling the Patient's Story

Antecedents

ApoE 3 4 Father type 2 diabetes died heart attack at 58;
Heterozygous No FMhx of AD
MTHFR 2 sisters and Mom Hx Thyroid and IBS

Triggering Events

Menopause
ABX and Diflucan
Death of mother
Food Poisoning

Mediators/Perpetuators

Menopause
Thyroid Dysfunction
Obesity and Pre-Diabetes

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation

High fecal fats
Dysbiosis
Candida
Low secretory IgA

Structural Integrity

Low Serum IgA



Defense & Repair

hs-CRP 7.9, elev IL-6
+for gluten TTG IgG
Low Serum IgA
Hi IgG casein/whey/gluten

Energy

Hypothyroid?
Hypoxia

Communication

Menopause levels of female hormones
TSH 4.5 (5.00)
TPO AB 430
Cortisol 4 diurnal rhythm high in evening

Biotransformation & Elimination

Transport
HgbA1c 5.9
fasting glucose 98
Insulin 26
GTT
glucose 165 /insulin 124
Low globulin

IBS
Dysbiosis
Fatty liver

Modifiable Personal Lifestyle Factors

Sleep & Relaxation

Difficulty falling asleep
Wakes with HA
Nocturnal Hypoxia

Exercise & Movement

Very little exercise
No aerobic

Nutrition

Carb cravings in evening
SAD diet

Stress

Death of mother

Relationships

Husband/grand-daughter support

Visit by Visit

Prep for first visit

- Living Matrix timeline prior to visit filled out by patient and family

First Visit (99204/99205)

- Timeline/Matrix, Physical Exam, Lab testing plans

Office visit f/u for labs/initial nutrition/coaching plans

- Nurse only – 99211
- 99212 if MD there for 5-10 min

Handouts/info

Coaching/nutrition weekly

Follow up 2,3,4... (99213, 99214, 99215)

- Lab follow up, program follow up

Case Study, cont.

Care plan:

MD, Nurse and Nutritionist in office, Virtual Health Coach

Small town 50 miles away, offered house call to follow up on the labs and establish care plan

Collaborative care team

Husband-all in

- Nutritionist neighbor
 - Cardiometabolic Food Plan
- 2 of her grandchildren yoga teachers
 - yoga and exercise with meditation/imagery/HRV

Visit by Visit: Case example - RCD

- Prep for first visit
- First Visit (99204/99205)
 - MRI, full labs:
- CBC
- iron
- Ferritin
- Chem 14
- Insulin
- Cortisol
- Vit B12/C/D
- TSH
- RBC Mg
- ?organic acids, IgG/IgA food panel, Stool/GI eval
- hsCRP
- Homocysteine
- HSV
- Celiac panel
- CoQ10
- Omega-3 index
- Zinc/copper
- Mercury/arsenic/lead

Visit by Visit: Case example - RCD

➤ Office visit #2 – Follow-up

- Labs, initial nutrition/coaching plans
 - Intro health coach visit 1
 - Nurse only – 99211
 - 99212 if MD there for 5-10 min
- Epworth - sleep study needed?/nocturnal oximetry?
- MOCA/MMSE
- MSQ
- Diet questionnaire, Toxicity questionnaire
- Med review/supplement review

Visit by Visit: Case example - RCD

➤ Office visit #3 – follow-up

- Review labs and pursue further workup
- Discuss patient's care team and other ways to support
- Answer questions, plan for next visit

Visit by Visit: Case example - RCD

- Office visit #4 – Follow-up
 - Review treatment program
 - Personalize plan further to individual needs
 - Review collaborative care team needs/success
- Further f/u visits every 4-8 weeks to support program for 6-12 months
 - Repeat MRI for volumetric change?
 - Repeat labs for progress
 - Repeat MOCA/MMSE
 - Review collaborate care team

Case Study, cont.

- Remove gluten/dairy from diet; Medical smoothie (next slide)
- Nystatin 500,000 iu bid x 30 days
- Saccharomyes Boulardii, probiotics, digestive enzyme, glutamine
- Sublingual vitamin D3 5,000 IU/day
(to a blood level of 80)
- 1 mg methyl B12 injections IM weekly for 6 weeks, then 1 mg sublingual daily.

Case Study, cont.

Supplements:

- D ribose: 5 g/day
- Coenzyme Q10: 200 mg/day
- Carnitine: 500 mg/day
- Glutathione: 200 mg/day
- Zinc: 30 mg/selenium: 200 mcg/day
- Sublingual vitamin D3 with K2
- Methyl B12 sublingual: 1 mg/day
- Medium chain triglycerides: 1 tbsp/day
- Omega 3 DHA/EPA: 750 mg BID
- Resveratrol: 500 mg/day

Other Treatment:

- Removed gluten/dairy from her diet-Medical Shake Protein Smoothie
- Nystatin and *Saccharomyces Boulardii* for yeast
- Probiotics/glutamine/digestive enzymes

Hormones 'menopausal' level
bioidentical hormones? YES
Biest 80/20 0.5 mg, Prog 45 mg, Test 0.5 mg

Assessed family history, personal history
Genetics (Factor V/Factor II, MTHFR, APOe)
Estrogen metabolism
CV risk stratification (CIMT, Stress Echo)

Compounded T4/T3 thyroid 65 mcg per day
TSH maintained at 1.0

- Free T4 and free T3 upper 1/3 of normal range
- Normalized RT3
- Thyroid antibodies dropped still positive (TPO 62).

The Collaborative Care Team



GROUP VISITS



Provider-patient encounter where patient and caregiver receive education for improved chronic disease management

Expands visit time for partnership btw provider, caregiver, patient

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Our Coaches:

Passionate. Inspired. Dedicated.

READY TO WORK WITH A STUDENT HEALTH COACH?

The 7 keys for Functional Medicine

Optimize nutrition

Balance hormones

Reduce inflammation

Fix digestion

Enhance detoxification

Boost energy metabolism

Calm the mind



Food, bugs, toxins, trauma



THANK YOU!!

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