Minding Your Gray Matter:
Neurodegeneration and Hormone Optimization

Jay H. Mead, MD, FASCP
Medical Director
Labrix Clinical Services, Inc.
Learning objectives

• Identify pathophysiology of common neurodegenerative diseases.
• Discuss classification of hormones as neuro-protective or neurotoxic.
• Recognize how to optimize hormone levels to prevent and treat neurodegenerative disease.
• Examine gluten’s impact on the CNS diseases
Numbers

• In June 2008, CDC statistics reported that Alzheimer disease surpassed diabetes as the 6th leading cause of death in the US.

• Parkinson disease (PD) and Alzheimer disease (AD) are the two most common neurodegenerative disorders in American adults.

Incidence of Alzheimer’s
• general population = 1-2%
• individuals over 65 years old = 5-10%
• individuals over 80 years old = 20-30%

Rising per year relative to other causes of death

The 15 leading causes of death were as follows:

1. Diseases of heart
2. Malignant neoplasms
3. Chronic lower respiratory diseases
4. Cerebrovascular diseases
5. Accidents (unintentional injuries)
6. Alzheimer’s disease
7. Diabetes mellitus
8. Influenza and pneumonia
9. Nephritis, nephrotic syndrome and nephrosis
10. Intentional self-harm (suicide)
11. Septicemia
12. Chronic liver disease and cirrhosis
13. Essential hypertension and hypertensive renal disease
14. Parkinson’s disease
15. Pneumonitis due to solids and liquids

Washington, D.C., May 19, 2010 -- Total costs of care for individuals with Alzheimer’s disease by all payers will soar from $172 billion in 2010 to more than $1 trillion in 2050, with Medicare costs increasing more than 600 percent, from $88 billion today to $627 billion in 2050. During the same time period, Medicaid costs will soar 400 percent, from $34 billion to $178 billion. One factor driving the exploding costs by 2050 is that nearly half (48 percent) of the projected 13.5 million people with Alzheimer’s will be in the severe stage of the disease – when more expensive, intensive around-the-clock care is often necessary.
• In 2014, the 85-years-and-older population includes about 2 million people with Alzheimer’s disease, or 40 percent of all people with Alzheimer’s age 65 and older

• When the first wave of baby boomers reaches age 85 (in 2031), it is projected that more than 3 million people age 85 and older will have Alzheimer’s

• By 2050, there could be as many as 7 million people age 85 and older with Alzheimer’s disease, accounting for half (51 percent) of all people 65 and older with Alzheimer’s

• One third of all seniors who die in a given year have been diagnosed with Alzheimer's or another dementia
Prevalence of Alzheimer's disease
(by decades from 1900-2050)

Origins of Neurodegenerative Diseases

- Not well understood
- Genetic
- Environmental
- Genetic AND environmental
- Abnormal processing of proteins
  - Ineffective mechanisms for removal
  - Mistake in protein formation or folding
Alzheimer’s Disease = Type 3 Diabetes?

It has been demonstrated that insulin resistance occurs in the brains of people with AD.

Individuals with insulin resistance, particularly type 2 diabetes, have an estimated 50-65% increased risk of suffering from AD.

Insulin Resistance and Alzheimer’s disease

“IR in tissues outside the brain with or without hyperglycemia can potentially cause insulin resistance in the brain and thereby contribute to the onset of Alzheimer’s disease.”

- Impaired glucose tolerance (IGT) during the 6th decade of life doubles the risk of developing Alzheimer's later on.
- A Japanese study of 1,000 men and women over age 60 showed that those with diabetes were twice as likely to develop Alzheimer's within 15 years, and 1.75 times more likely to develop any form of dementia.

“Obesity and dementia: Adipokines interact with the brain.”

• Obesity has been associated with changes in brain structure, cognitive deficits, dementia and Alzheimer’s disease.

• Adipokines, defined as hormones, cytokines and peptides secreted by adipose tissue, may have more widespread influence and functionality in the brain than previously thought.

• Six adipokines, and their actions in the obese and non-obese conditions will be discussed. Included are: plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6), tumor necrosis factors alpha (TNF-α), angiotensinogen (AGT), adiponectin and leptin.

“Higher normal fasting plasma glucose is associated with hippocampal atrophy: The PATH Study.”

- Substantial evidence showing an association between type 2 diabetes (T2D) and cerebral atrophy, cognitive impairment, and dementia is accumulating.

- Association between plasma glucose levels and hippocampal and amygdalar atrophy in a sample of 266 cognitively healthy individuals free of T2D, aged 60-64 years, taking part in a longitudinal study of aging (2-4yrs).

- High plasma glucose levels within the normal range were associated with greater atrophy of structures relevant to aging and neurodegenerative processes, the hippocampus and amygdala.

Hormones and neurons

- Gonadal hormone function extends beyond reproductive system!
- De novo synthesis in the CNS allows for regulation of neural function including neurogenesis.
  - Small molecular weight
  - Ability to penetrate the blood brain barrier

Gonadal hormones play important role in physiology as well as anatomy of the brain.

• In human adults, the preoptic nucleus of the hypothalamus can be up to twice as large as in males.

• There is a greater percentage of gray matter in females and greater percentage of white in males.

Hormone therapy (HT) is protective against Parkinson’s disease, Alzheimer’s disease, stroke and cardiovascular disease

Neurodegeneration and Hormones

- Hormone deficiencies are associated with disease status and cognitive behavior
- Decreases in neuroprotective hormone levels may result in reduced protection against environmental and genetic agents promoting neurodegeneration

Estrogen

• The link between estradiol and cognitive function is well known, as many menopausal women experience depression, loss of cognitive and motor skills and mood changes.


Estradiol

• Neuroprotective activity
  • Against toxicities, oxidative stress, amyloid B peptide-induced toxicity and glutamate-induced excito-toxicity
  • Against pathologic events of cerebral ischemia

Estrogen

• Estradiol reduces cognitive decline and improves symptoms in women who have undergone surgical menopause

Estrogen receptor-β regulates human tryptophan hydroxylase-2 through an estrogen response element in the 5' untranslated region.

• In the dorsal raphe nucleus, 17β-estradiol (E2) increases the expression of the brain-specific, rate-limiting enzyme for serotonin biosynthesis, tryptophan hydroxylase-2 (Tph2).

• We illustrate a direct regulation of the TPH2 transcription by estradiol and ERβ via a newly identified ERE half-site within the TPH2 promoter: Estradiol- or an ERβ agonist-induced TPH2 transcription was blocked by an ER antagonist, while membrane impermeable form of estradiol did not induce transcription. Deletion or mutation of the ERE half-site abolished ligand-induced TPH2 transcription.

Progesterone

- Essential for maintaining a healthy brain
- Decreases risk of age-associated brain dysfunction including Alzheimer’s disease

Progesterone, not MPA

• Progestins are not equal to progesterone when it comes to neuroprotection.

• Medroxyprogesterone acetate, one of the primary progestins, appears to be ineffective as a neuroprotectant.

Not Just for Girls

Though progesterone levels are generally higher in females, the level of progesterone during the follicular phase of the menstrual cycle has been demonstrated to be similar to the levels seen in men.

Progesterone

• Progesterone can increase brain-derived neurotrophic factor (BDNF) when bound to the progesterone receptor.

• Even without a progesterone receptor, progesterone increases phosphorylation of extracellular signal-related kinase, which is neuroprotective.

Many Mechanisms

• Progesterone reduces injury resulting from glutamate and glucose deprivation.
• Progesterone protects against amyloid B-peptide toxicity.
• Progesterone reduces cell death following global ischemia.

Its production in the brain, by oligodendrocytes and other cell types, provides clues to its critical role in neural homeostasis. Indeed, the 10-fold increase of progesterone during fetal growth is thought by some experts to be primarily for neuronal development.

...progesterone suppresses synthesis of proinflammatory cytokines such as TNF-α, IL-1, and IL-6, limiting inflammation, microglial activation, and further neuronal injury.

Nonetheless, patients in the progesterone group demonstrated a 50% reduction in 30-day mortality compared with the controls. There were no serious adverse events attributed to progesterone exposure.
One of the most studied hormones:

There are 260+ citations in PubMed related to progesterone and brain injury.
Myelin

Progesterone administration in rat studies has increased expression of myelin proteins in damaged sciatic nerves, indicating that there may be benefit in demyelinating diseases such as multiple sclerosis.

Very Early Administration of Progesterone for Acute Traumatic Brain Injury

- Double bind placebo controlled trial 882 pts with moderate to severe TBI
- There was no significant difference between the progesterone group and the placebo group in the proportion of patients with a favorable outcome (relative benefit of progesterone, 0.95; 95% confidence interval [CI], 0.85 to 1.06; P=0.35).
- The trial was stopped for futility with respect to the primary outcome.

Metabolites

• One of progesterone’s primary metabolites, allopregnanolone, can bind to GABA receptors and result in chloride conductance.

• Allopregnanolone may also reduce potential apoptotic events in the mitochondria during injury.

Catamenial Epilepsy

• Definition: Catamenial (from the Greek kata, by; men, month) epilepsy refers to seizure exacerbation in relation to the menstrual cycle.

• Catamenial epilepsy affects up to 70% of women with epilepsy. Catamenial seizures are common among women with focal or generalized epilepsy, which affects an estimated 1 million women in the United States.

• The progesterone metabolite allopregnanolone has been identified as a key endogenous neurosteroid with powerful anti-seizure activity. Allopregnanolone is a potent, positive allosteric modulator of GABA(A) receptors.

Progesterone and low-dose vitamin D hormone treatment enhances sparing of memory following traumatic brain injury.

- Progesterone’s (Pg) benefit is reduced with vitamin D deficiency
- Post TBI vitamin D deficient rats given Pg (16mg/kg) and low dose vitamin D3 (5µg/kg) demonstrated better preservation of spatial memory and performance acquisition, and reduced neuronal loss, than the Pg only group
- This correlated with increased GRAP (glial fibrillary acidic protein) production

Effect of low doses of progesterone in the expression of the GABA(A) receptor α4 subunit and procaspase-3 in the hypothalamus of female rats.

• Progesterone is a steroid which regulates neural function, thereby modulating neurotransmission, cell survival, and behavior. Previous studies by our group have shown that chronic administration of low doses of progesterone in diestrus II female rats has an antidepressant-like effect in the forced swimming test (FST).

• Progesterone increased the expression of GABA(A) receptor α4 subunit but did not change the expression of SERT.

• Such effects may be involved in the antidepressant-like effect of progesterone in female rats exposed to the FST.

The Effects of Vitamin D on Brain Development and Adult Brain Function

- Vitamin D is a neuro active steroid involved in brain development, neurochemistry and adult brain function.
- Deficiencies are associated with schizophrenia, Parkinson’s disease, Alzheimer’s disease, depression and cognitive decline.

1α,25-Dihydroxyvitamin D3 enhances cerebral clearance of human amyloid-β peptide(1-40) from mouse brain across the blood-brain barrier.

• Low levels of vitamin D3 (<20-30ng/dl) increase risk of AD
• AD is associated with BBB dysfunction
• Active form of 1,25DiOH vitamin D3 increase CNS elimination of amyloid-β peptide by 1.3 times
• Vitamin D receptor mRNA increased (genomic)
• Stimulated forskolin a clearing protein (non-genomic)

Vitamin D, Cognitive Dysfunction and Dementia in Older Adults

• Low levels of vitamin D (1,25DiOH) are associated with all forms of dementia
  • Elderly Italians’ cognitive decline 60% higher with 25(OH)D <25nmol (sufficiency >75nmol)
  • Elderly US male cognitive decline 41% higher if 25(OH)D in lowest quartile (<49.7nmol) compared to the highest quartile (>74.4nmol)

Vitamin D in the Healthy and Inflamed Central Nervous System

- High dose vitamin D protects against development and progression of MS
- Vitamin D binding protein, VDR, and enzymes needed for metabolism (CYP27B1) are present in neurons, glial cells and invading lymphocytes
- Vitamin D modulates inflammation, demyelization, axonal damage and remyelination in MS

Estriol (E3)

• Down regulates the immune system and quells autoimmunity – in males too
• Is neuroprotective autoimmunity – in males too
• Reverses active plaque formation (8 mg/day PO)
• Phase II clinical trials

Further characterization indicated that estriol inhibited nuclear transcription factor kappa B (NF-kappa B), which controls a variety of immune-related genes.

Source

Multiple Sclerosis Research Unit, Baylor-Methodist Multiple Sclerosis Center and Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA.

Abstract

The protective role of pregnancy in autoimmune disease has been hypothesized to be associated with immune suppression by estriol. This study was undertaken to examine the regulatory effects of estriol on T cell migration, including transmigration and the cytokine production profile. Estriol significantly inhibited T cell transmigration at a concentration range typical of pregnancy, which correlated with decreased T cell expression of matrix metalloproteinase-9. Estriol was also found to alter the cytokine profile of T cells toward Th2 phenotype by up-regulating the production of IL-10 and inhibiting TNFalpha secretion of T cells. However, the inhibitory effects of estriol on T cells were not antigen-dependent. Further characterization indicated that estriol inhibited nuclear transcription factor kappa B (NF-kappa B), which controls a variety of immune-related genes. This study provides new evidence that estriol is a potent regulator for the T cell functions potentially through its interaction with the NF-kappa B signaling pathway.
We treated non-pregnant female multiple sclerosis patients with the pregnancy hormone estriol in an attempt to recapitulate the beneficial effect of pregnancy.

Treatment of multiple sclerosis with the pregnancy hormone estriol.

Sicotte NL, Liva SM, Klutch R, Pfeiffer B, Pascual S, Ophoff R, Wu TC, Yolken RR

Source

Department of Neurology, Reed Neurosciences Institute, University of California, Los Angeles, Los Angeles, CA 90095, USA.

Abstract

Multiple sclerosis patients who become pregnant experience a significant decrease in relapses that may be mediated by a shift in immune responses from T helper 1 to T helper 2. Animal models of multiple sclerosis have shown that the pregnancy hormone, estriol, can ameliorate disease and can cause an immune shift. **We treated nonpregnant female multiple sclerosis patients with the pregnancy hormone estriol in an attempt to recapitulate the beneficial effect of pregnancy.** As compared with pretreatment baseline, relapsing remitting patients treated with oral estriol (8 mg/day) demonstrated significant decreases in delayed type hypersensitivity responses to tetanus, interferon-gamma levels in peripheral blood mononuclear cells, and gadolinium enhancing lesion numbers and volumes on monthly cerebral magnetic resonance images. When estriol treatment was stopped, enhancing lesions increased to pretreatment levels. **When estriol treatment was re instituted, enhancing lesions again were significantly decreased.** Based on these results, a larger, placebo-controlled trial of estriol is warranted in women with relapsing remitting multiple sclerosis. This novel treatment strategy of using pregnancy doses of estriol in multiple sclerosis has relevance to other autoimmune diseases that also improve during pregnancy.

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[PubMed - indexed for MEDLINE]
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Here, the immunomodulatory effects of oral estriol therapy were assessed. PBMCs collected longitudinally during the trial were stimulated with mitogens, recall Ags, and glatiramer acetate.

Abstract

The protective effect of pregnancy on putative Th1-mediated autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, is associated with a Th1 to Th2 immune shift during pregnancy. The hormone estriol increases during pregnancy and has been shown to ameliorate experimental autoimmune encephalomyelitis and collagen-induced arthritis. In addition, estrogens induce cytokine changes consistent with a Th1 to Th2 shift when administered in vitro to human immune cells and in vivo to mice. In a pilot trial, oral estriol treatment of relapsing remitting multiple sclerosis patients caused significant decreases in enhancing lesions on brain magnetic resonance imaging. Here, the immunomodulatory effects of oral estriol therapy were assessed. PBMCs collected longitudinally during the trial were stimulated with mitogens, recall Ags, and glatiramer acetate. Cytokine profiles of stimulated PBMCs were determined by intracellular cytokine staining (IL-5, IL-10, IL-12 p40, TNF-alpha, and IFN-gamma) and cytomertic bead array (IL-2, IL-4, IL-5, IL-10, TNF-alpha, and IFN-gamma). Significantly increased levels of IL-5 and IL-10 and decreased TNF-alpha were observed in stimulated PBMC isolated during estriol treatment. These changes in cytokines correlated with reductions of enhancing lesions on magnetic resonance imaging in relapsing remitting multiple sclerosis. The increase in IL-5 was primarily due to an increase in CD4(+) and CD8(+) T cells, the increase in IL-10 was primarily due to an increase in CD64(+) monocyes/macrophages with some effect in T cells, while the decrease in TNF-alpha was primarily due to a decrease in CD8(+) T cells. Further study of oral estriol therapy is warranted in Th1-mediated autoimmune diseases with known improvement during pregnancy.

PMID:
14634144
[PubMed - indexed for MEDLINE]
Significantly increased levels of IL-5 and IL-10 and decreased TNF-alpha were observed in stimulated PBMC isolated during estriol treatment.

These changes in cytokines correlated with reductions of enhancing lesions on magnetic resonance imaging in relapsing remitting multiple sclerosis.
Estrogen receptor (ER) expressions, ERalpha and ERbeta, were found to be equivalent in both genders.

Encephalomyelitis: implications for multiple sclerosis.

Palaszynski KM, Liu H, Loo KK, Voskuhl RR.

Source

Department of Neurology, Reed Neurology, School of Medicine, 750 Westwood Plaza, Los Angeles, CA 90024.

Abstract

Estrogen treatment has been found to be protective in experimental autoimmune encephalomyelitis (EAE) and possibly multiple sclerosis (MS). We investigated whether the effect of estrogen treatment is gender-specific. Estrogen receptor (ER) expressions, ERalpha and ERbeta, were found to be equivalent in both genders. EAE disease severity in both females and males was decreased with estriol treatment as compared to placebo. Finally, proinflammatory cytokine production during autoantigen-specific immune responses was decreased with estriol treatment in both females and males. These data support a potential role for estriol treatment for men in addition to women with MS.

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Mechanisms of action include both immunomodulatory and directly neuroprotective pathways.

In vivo studies have shown that estrogen treatment can be neuroprotective in animal models of Parkinson’s disease, cerebellar ataxia, late onset leukodystrophy, stroke and spinal cord injury, often by reducing apoptosis [49-55].

Thus, while it is controversial if the risk: benefit ratio of estrogen therapy is acceptable for preventative treatment of healthy individuals, its safety profile clearly compares favorably with available drugs for therapy of patients with MS.

Although long thought to act primarily on T cells, recent evidence demonstrated that myeloid cells, such as dendritic cells (DCs), are essential in mediating estrogen’s protective effects.

Abstract

Chronic inflammation contributes to numerous diseases, and regulation of inflammation is crucial for disease control and resolution. Sex hormones have potent immunoregulatory abilities. Specifically, estrogen influences immune cells and inflammation, which contributes to the sexual dimorphism of autoimmunity and protection against disease seen during pregnancy in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). Although long thought to act primarily on T cells, recent evidence demonstrated that myeloid cells, such as dendritic cells (DCs), are essential in mediating estrogen’s protective effects.

Estriol (E3), a pregnancy-specific estrogen, has therapeutic efficacy in MS and EAE, and we evaluated whether E3 could act exclusively through DCs to protect against the inflammatory autoimmune disease EAE. Levels of activation markers (CD80 and CD86) and inhibitory costimulatory markers (PD-L1, PD-L2, B7-H3, and B7-H4) were increased in E3 DCs. E3 DCs had decreased proinflammatory IL-12, IL-23, and IL-6 mRNA expression, increased immunoregulatory IL-10 and TGF-β mRNA expression, and a decreased ratio of IL-12/IL-10 protein production. Importantly, transfer of E3 DCs to mice prior to active induction of EAE protected them from developing EAE through immune deviation to a Th2 response. This protection was apparent, even in the face of in vitro and in vivo inflammatory challenge. In summary, our results showed that E3 generates tolerogenic DCs, which protect against the inflammatory autoimmune disease EAE. Targeted generation of tolerogenic DCs with immunomodulatory therapeutics, such as E3, has potential applications in the treatment of numerous autoimmune and chronic inflammatory diseases.
Estriol generates tolerogenic dendritic cells in vivo.

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During pregnancy, it is evolutionarily advantageous for inflammatory immune responses that might lead to fetal rejection to be reduced and anti-inflammatory responses that promote transfer of maternal antibodies to the fetus to be increased. Estrogens, including estradiol and estriol, progesterone, and glucocorticoids increase over the course of pregnancy and affect transcriptional signaling of inflammatory immune responses at the maternal-fetal interface and systemically.
During pregnancy, the reduced activity of natural killer cells, inflammatory macrophages, and helper T cell type 1 (Th1) cells and production of inflammatory cytokines, combined with the higher activity of regulatory T cells and production of anti-inflammatory cytokines, affects disease pathogenesis. The severity of diseases caused by inflammatory responses (e.g., multiple sclerosis) is reduced and the severity of diseases that are mitigated by inflammatory responses (e.g., influenza and malaria) is increased during pregnancy.
The bidirectional interactions between hormones and the immune system contribute to both the outcome of pregnancy and female susceptibility to disease.
Estriol; the ‘Good’ Estrogen Advances and Updates in its Clinical Uses

Erin Lommen, ND
Jay H Mead, MD

ABSTRACT

Estriol, coined the “weaker” of the three endogenous estrogens, has significant therapeutic effects, some of which are little known to clinicians. Estriol provides numerous clinical benefits, commanding the attention of researchers dating as far back as 1966 and continues to garner substantial consideration as a valuable and viable therapeutic agent. Some of the most common and effective treatments that employ estriol include: hot flashes, insomnia, skin enhancement, vaginal atrophy and reduced frequency of urinary tract infections. Most recently, estriol has shown the potential to treat individuals with Th1-mediated autoimmune illnesses, including multiple sclerosis and rheumatoid arthritis. This review article will update the clinical effects and benefits of estriol and further clarify the documented advances which support the substantial therapeutic benefits of estriol for autoimmune conditions. The availability of compounded estriol preparations will also be addressed.

Keywords: Cytokines; Dendritic cells; Estriol; Menopause; Multiple sclerosis; Rheumatoid arthritis; Th1 autoimmunity
Testosterone

- Down regulates the immune system and quells autoimmunity
- Neuroprotective
- Both males and females

Testosterone and Aggressive Behavior in Man

• Aggressive behavior arises in the brain through interplay between subcortical structures in the amygdala and the hypothalamus in which emotions are born and the prefrontal cognitive centers where emotions are perceived and controlled.

• Neuroimaging techniques in adult males have shown that testosterone activates the amygdala enhancing its emotional activity and its resistance to prefrontal restraining control.

“Low testosterone and the risk of dementia in elderly men: Impact of age and education.”

• Within the population based Three-City study, including 3650 men age 65 years and older, a case-cohort design was set up after 4-years of follow-up. Baseline plasma levels of total 17-β estradiol (Total-E2), total testosterone (total-T) and bioavailable testosterone (bio-T) were measured for all cases of incident dementia (n = 105) and for a random sample of the cohort (n = 413).

• Risk for dementia associated with low bio-T was greater in older men (80 years or older) than in younger men (younger than 80 years; HR, 3.11; P = .011 vs. HR, 1.07, P = .715, respectively) and in men with high level of education compared with those with low level of education (HR, 2.32; P = .0002 vs. HR, 0.95; P = .790, respectively). No significant association was found between Total-E2 and dementia.

• CONCLUSIONS: Low levels of testosterone are associated with a risk for dementia in elderly men. The association between low bio-T and dementia may be more relevant to men 80 years or older and men with a high level of education.

In the beginning...

Stress and glucocorticoids during prenatal development can cause dysfunction of the HPA axis negative feedback and lead to anxiety, hyperactivity and learning impairments.

Subjective memory complaints are associated with diurnal measures of salivary cortisol in cognitively intact older adults.

• In multivariate logistic regression analyses with SMC as outcome, averaged postpeak cortisol, the cortisol awakening response, and depressive symptoms were significant predictors, whereas gender, memory performance, anxiety, and APOE-e4 status were not.

• Significant associations between SMC and diurnal measures of cortisol in cognitively intact elderly suggest that hypothalamic-pituitary-adrenal axis dysfunction may contribute to early neuropathologic changes in older adults who complain of memory decline undetected on neuropsychological testing.

The current study compared salivary cortisol levels and memory performance in young and older adults tested in environments manipulated to be stressful (unfavorable condition) or not stressful (favorable condition) for each age group.
In older adults only, we found significantly high cortisol levels and low memory performance in the condition favoring young adults. In contrast, cortisol levels were lower and memory performance was better when older adults were tested in conditions favoring them. There was no effect of testing condition in young adults.
The results demonstrate that older adults' memory performance is highly sensitive to the testing environment. These findings have important implications for both research and clinical settings in which older adults are tested for memory performance.
Disruption in GSH homeostasis and modification of the enzymes that are dependent on GSH as a substrate have been linked to initiation and progression of the neurodegenerative diseases.

Conclusions
Over the past several decades the role of intracellular GSH has been studied intensively. Such research continues to provide evidence for the importance of GSH in the regulation of cellular dysfunctions of the neurodegenerative diseases, including Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and Friedreich’s ataxia. Disruption in GSH homeostasis and modification of the enzymes that are dependent on GSH as a substrate have been linked to initiation and progression of the neurodegenerative diseases. The dysregulation of GSH and GSH-dependent enzymes induces a variety of cellular problems that can lead to mitochondrial dysfunction, accumulation of ROS/RNS damage, disruption of signaling pathways, protein aggregation, and ultimately cell death. It is certain that more research is needed not only to define more accurately how disruption of the network of GSH-dependent reactions leads to nerve cell damage, but also to discover new ways to prevent and/or reverse that damage and thereby develop more effective therapies for the neurodegenerative diseases.
Growth factors decrease in subjects with mild to moderate Alzheimer's disease (AD): potential correction with dehydroepiandrosterone-sulphate (DHEAS).

These data suggested that DHEAS is able to increase the immuno-endocrine production of neuroprotective growth factors, which is reduced in AD subjects, so suggesting a new approach in the treatment of dementia.

Resveratrol

- Neuro-regenerative and neuro-protective qualities
  - Beneficial for: Alzheimer’s Dz, stroke, Parkinson’s Dz, Huntington’s Dz and epilepsy
  - Study found individuals with the habit of daily moderate wine consumption (9drinks/wk women; 12-14drinks/wk men) enjoy significant reductions in cardiovascular and neurodegenerative mortality when compared with individuals who abstain.

“Clinical investigation of the protective effects of palm vitamin e tocotrienols on brain white matter.”

• A 121 volunteers aged ≥35 years with cardiovascular risk factors and MRI-confirmed white matter lesions (WMLs) were randomized to receive 200 mg mixed tocotrienols or placebo twice a day for 2 years.

• The mean WML volume change between the 2 groups was not significantly different (P=0.150) at the end of 1 year but was significant at the end of 2 years for both per-protocol and intention-to-treat analyses (P=0.019 and P=0.018). No significant difference was observed in the blood chemistry parameters between the 2 groups.

• CONCLUSION: “Mixed tocotrienols* were found to attenuate the progression of WMLs”.

• *Note: typical dosing is 200mg bid

“Impact of Mindfulness-Based Stress Reduction training on intrinsic brain connectivity.”

- 32 Healthy women randomized to participate in an 8-week Mindfulness-Based Stress Reduction (MBSR) training course or an 8-week waiting period.

- Relative to the control group, MBSR subjects showed (1) increased functional connectivity within auditory and visual networks, (2) increased functional connectivity between auditory cortex and areas associated with attentional and self-referential processes, (3) stronger anticorrelation between auditory and visual cortex, and (4) stronger anticorrelation between visual cortex and areas associated with attentional and self-referential processes.

- CONCLUSION: “These findings suggest that 8 weeks of mindfulness meditation training alters intrinsic functional connectivity in ways that may reflect a more consistent attentional focus, enhanced sensory processing, and reflective awareness of sensory experience.”

“Relaxation response affects gene activity, from Harvard’s Stress Management Special Health Report”

• The study compared the activity of genes in 19 healthy adults who were long-term users of relaxation techniques and in 19 healthy adults who hadn’t used relaxation techniques.

• Those who used relaxation techniques used a variety of methods—such as meditation, yoga, breath focus, or repetitive prayer.

• The researchers found that the activity of certain genes differed between these two groups.

• The genes were involved with controlling how the body handles free radicals, inflammation processes, and cell death.

• In order for the genetic changes to persist, relaxation response techniques have to be done regularly.

Theories of Extinction

We can’t be certain what killed the dinosaurs, but they definitely should have cut back on the gluten.
“Demonstration of high opioid-like activity in isolated peptides from wheat gluten hydrolysates.”

• “Because of a possible relationship between schizophrenia and celiac disease, a condition in some individuals who are sensitive to wheat gluten proteins in the diet, there has been interest in observations that peptides derived from wheat gluten proteins exhibit opioid-like activity in in vitro tests”.

• Fractionated peptides were tested for opioid-like activity by competitive binding to opioid receptor sites in rat brain tissue in the presence of tritium-labeled dihydromorphine.

• Peptides showed considerable differences in activity; while some peptides exhibited no activity, 0.5 mg of the most active peptides were equivalent to 1 nM of morphine in the binding assay.

• “The most active peptides were derived from the gliadin fraction of the gluten complex”.

“Prevalence of resistant occipital lobe epilepsy associated with celiac disease in children.”

• None of the 100 healthy children in the control group was positive in terms of the tTG antibody test used to scan CD.

• In the group with epileptic activity in the occipital lobe, two patients out of 90 were tTG antibody positive. The seroprevalence was 1/45 (2.22 %) in this group (CD based on the endoscopic duodenal biopsy).

• 1 in 10 newly-diagnosed men had inadequate thiamin, folate, magnesium, calcium and zinc intakes.

• “Therefore, screening for CD is recommended in children with resistant epileptic activity in the occipital lobe.”

“Coeliac disease and infertility: making the connection and achieving a successful pregnancy.”

Undiagnosed coeliac disease is not uncommon in adults in the UK and can be a cause of unexplained infertility in women. Studies suggest that dietary treatment of women with coeliac disease may result in successful conception.

“Prolactin May Be Increased in Newly Diagnosed Celiac Children and Adolescents and Decreases after 6 Months of Gluten-Free Diet.”

- Prolactin exerts its role on the breast gland but also plays a modulatory role in autoimmune mechanisms.
- 67 patients and 39 healthy controls.
- In patients with hyperprolactinemia at diagnosis, PRL decreased after 6 months of GFD.
- Changes in the levels of inflammatory cytokines in CD may account for changes in PRL levels.

“Early-life vitamin D deficiency and childhood-onset coeliac disease.”

• Spring birth is a novel risk factor for CD in children.
• The association between season of birth and CD is due to seasonal differences in sunlight exposure and subsequent vitamin D status.
• Concomitant with global increases in CD prevalence, vitamin D deficiency also is increasingly recognized in children worldwide.
• “We propose a hypothesis model of early-life vitamin D deficiency in the pathogenesis of childhood-onset CD”.

“A migraine as initial presentation of celiac disease.”

• Migraine is a rare complication of CD.
• A case report of CD revealed by a migraine.

“A case of celiac disease mimicking amyotrophic lateral sclerosis.”

• A 44-year-old male presented to a general neurology clinic with a 6-month history of progressive right-sided spastic hemiparesis without sensory symptoms or signs. The thigh muscle in the affected leg showed signs of wasting. The patient had a remote family history of celiac disease.

• Neurological examination, neurophysiological studies, brain MRI scan, routine blood tests, duodenal biopsy, cerebrospinal fluid analysis including polymerase chain reaction test for JC virus DNA, serological testing for HIV and for the presence of serum antibodies to endomysium, gliadin and tissue transglutaminase.

• DIAGNOSIS: Celiac disease with neurological involvement, mimicking amyotrophic lateral sclerosis.

• MANAGEMENT: Strict gluten-free diet.

“Recurrent ischemic strokes in a young celiac woman with MTHFR gene mutation.”

• A 26-year-old woman affected by CD with secondary amenorrhea, carrier of a homozygous 5,10-methylenetetrahydrofolate reductase mutation with hyperhomocysteinemia, was affected by two occipital ischemic strokes within a period of 5 mo.

• At the time of the second stroke, while she was being treated with folic acid, acetylsalicylic acid and a gluten-free diet, she had left hemianopsia, left hemiparesthesias, and gait imbalance.

• The most probable cause for the recurrent stroke in this young woman remained CD, although the mechanisms involved are still unknown.

• The two main hypotheses concern malabsorption (with consequent deficiency of vitamins known to exert neurotrophic and neuroprotective effects) and immune-mediated mechanisms.

“Celiac disease diagnosed in the elderly.”

• A retrospective chart review was performed in cases of CD diagnosed after the age of 60.
• 7 patients with CD diagnosed after the age of 60 were identified. The most common presenting findings were weight loss, iron deficiency anemia, and diarrhea.
• Two with Alzheimer dementia, one peripheral neuropathy.
• Gluten free diet treatment led to complete resolution of symptoms in most cases and a significant weight gain (median 7.75 kg, range 5 to 11).
• Median lag in diagnosis was 8 years. CD is underdiagnosed in elderly patients.

“Gluten-free diet may alleviate depressive and behavioral symptoms in adolescents with coeliac disease: a prospective follow-up case-series study.”

• Coeliac disease in adolescents has been associated with an increased prevalence of depressive and disruptive behavioral disorders.

• Adolescent coeliac disease patients with depression had significantly lower pre-diet tryptophan/competing amino-acid (CAA) ratios and free tryptophan concentrations.

• Also significantly higher biopsy morning prolactin levels compared to those without depression.

• A significant decrease in psychiatric symptoms was found at 3 months on a gluten-free diet coinciding with significantly decreased coeliac disease activity and prolactin levels and with a significant increase in serum concentrations of CAAs.

“Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease.”

- Seven-day prospective food intake: N=105.
- Of macronutrients, only starch intake fell over 12 months (26% to 23%, P = 0.04).
- 1 in 10 of both newly-diagnosed and experienced women had inadequate thiamin, folate, vitamin A, magnesium, calcium and iron intakes.
- 1 in 10 newly-diagnosed men had inadequate thiamin, folate, magnesium, calcium and zinc intakes.
- CONCLUSIONS: Dietary intake patterns at 12 months on a GFD are similar to longer-term intake. Dietary inadequacies are common and may relate to habitual poor food choices in addition to inherent deficiencies in the GFD. Dietary education should also address the achievement of adequate micronutrient intake. Fortification of GF foods also needs to be considered.

“The interplay between iron accumulation, mitochondrial dysfunction, and inflammation during the execution step of neurodegenerative disorders.”

• Mitochondrial dysfunction, iron accumulation, oxidative damage and chronic inflammation are associated with a number of neurodegenerative diseases that includes Alzheimer's disease, Huntington disease, amyotrophic lateral sclerosis, Friedrich's ataxia and Parkinson's disease.

• Mitochondrial respiratory chain is the source of reactive oxygen species (ROS) derived from leaks in the electron transport chain. The coexistence of both iron and ROS makes this organelle particularly prone to hydroxyl radical-mediated damage.

• Inflammatory cytokines like TNF-alpha and IL-6 induce the synthesis of the divalent metal transporter 1 and promote iron accumulation in neurons and microglia.

• Hypothesis: mitochondrial dysfunction, iron accumulation and inflammation are part of a synergistic self-feeding cycle that ends in apoptotic cell death, once the antioxidant cellular defense systems are finally overwhelmed.

Urrutia PJ, Mena NP, Núñez MT. The interplay between iron accumulation, mitochondrial dysfunction, and inflammation during the execution step of neurodegenerative disorders. Front Pharmacol. 2014 Mar 10; 5: 38.
“Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity.”

• More recently the understanding and knowledge of gluten sensitivity (GS), has emerged as an illness distinct from celiac disease with an estimated prevalence 6 times that of CD. Gluten sensitive people do not have villous atrophy or antibodies that are present in celiac disease, but rather they can test positive for antibodies to gliadin.

• Both CD and GS may present with a variety of neurologic and psychiatric co-morbidities, however, extraintestinal symptoms may be the prime presentation in those with GS.
  • Neurological manifestations: gluten ataxia, seizure disorders, peripheral neuropathies, headache, myelopathies, gluten encephalopathy and white matter abnormalities
  • Psychiatric complications: anxiety disorders, depression and mood disorders, ADHD, autism spectrum disorders and schizophrenia

“No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates.”

• Patients with non-celiac gluten sensitivity (NCGS) do not have celiac disease but their symptoms improve when they are placed on gluten-free diets.

• Double-blind cross-over trial of 37 subjects (aged 24-61 y, 6 men) with NCGS and irritable bowel syndrome (based on Rome III criteria), but not celiac disease.

• Participants were randomly assigned to groups given a 2-week diet of reduced FODMAPs, and were then placed on high-gluten (16 g gluten/d), low-gluten (2 g gluten/d and 14 g whey protein/d), or control (16 g whey protein/d) diets for 1 week, followed by a washout period of at least 2 weeks.

• Twenty-two participants then crossed over to groups given gluten (16 g/d), whey (16 g/d), or control (no additional protein) diets for 3 days.

• In a placebo-controlled, cross-over rechallenge study, we found no evidence of specific or dose-dependent effects of gluten in patients with NCGS placed diets low in FODMAPs.

“Antibody response against gastrointestinal antigens in demyelinating diseases of the central nervous system.”

• Antibodies against gliadin, tTG, IF, PC and ASCA screened in 45 patients with AQP4-seropositive neuromyelitis optica (NMO) and NMO spectrum diseases (NMO/NMO-SD), 17 patients with AQP4-seronegative NMO, 85 patients with clinically definite multiple sclerosis (MS), and 48 healthy controls (HC).

• Thirty-seven percentage of patients with AQP4-seropositive NMO/NMO-SD and 28% of patients with MS had at least one particular antibody in contrast to 8% of HC (P < 0.01, respectively).

• Conclusion: Antibody responses against gastrointestinal antigens are common in MS and AQP4-seropositive NMO/NMO-SD, especially in longitudinally extensive myelitis.

“Reversal of cognitive decline: A novel therapeutic program.”

- 10 patients with memory loss associated with Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI).
- Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure (late stage AD).
- Six of the patients returned to work or continue working with improved performance. Improvements sustained, longest patient follow-up 2 1/2 years with sustained and marked improvement.
- The results also suggest cognitive decline may be driven in large part by metabolic processes.

Summary

• Steroid hormone decline is associated with neuro-degeneration
  • Includes: estradiol, progesterone, testosterone, DHEA and vitamin D
  • Supplementation has been shown to arrest and even reverse heretofore considered chronic unrelenting conditions
  • Pregnancy doses of estriol reverse MS injury
Summary

• Celiac disease and gluten sensitivity
  • Appears causative for neurological and psychiatric diseases
  • Gluten-free diet shows major benefits
  • Restricted FODMAP diet warrants further research
• Insulin resistance plays a major role in neuro-degenerative conditions
  • Low carbohydrate, high protein and healthy fat diet shows remarkable benefits.