Outsmarting our Genes for a Happier, Healthier Life

Scientific **"Slap-it-Silly"** Approaches to Preventing and Overcoming Serious Disease

Fear-Based "Medicine"

EPIGENETICS

- *"the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself."*

Controlling risk in BRAC1 gene variant carriers

- Studied supplemental selenium and its ability to reduce the number of chromosome breaks in carriers of BRAC1 gene variant
- Compared with control group, 49% increase in chromosome breakage among carriers

Increased Rates of Chromosome Breakage in BRCA1 Carriers Are Normalized by Oral Selenium Supplementation

Dosing in study: 690 mcg pure selenium(selenite) per ml of 70% ethanol solution - 0.2 ml given twice daily (138 mcg each) for a **daily total of 276 mcg**

RESULTS:

- **Among the *BRCA1* carriers** (*n* = 32), this level of supplementation resulted in an increase in the mean serum selenium from 56.7 ± 12.7 to 90.2 ± 17.6 ng/mL (*P* < 0.001)

- **Conclusion:** The mean level of chromosome breaks in carriers following supplementation was similar to that of the non-carrier controls (0.40 versus 0.39). Oral selenium is a good candidate for chemoprevention in women who carry a mutation in the *BRCA1* gene.

Cancer Epidemiol Biomarkers Prev May 2005 *14;* 1302

Selenium & Glutathione

Nutr Res. 2011 Feb;31(2):165-8. doi: 10.1016/j.nutres.2010.10.012. Epub 2011 Feb 12.

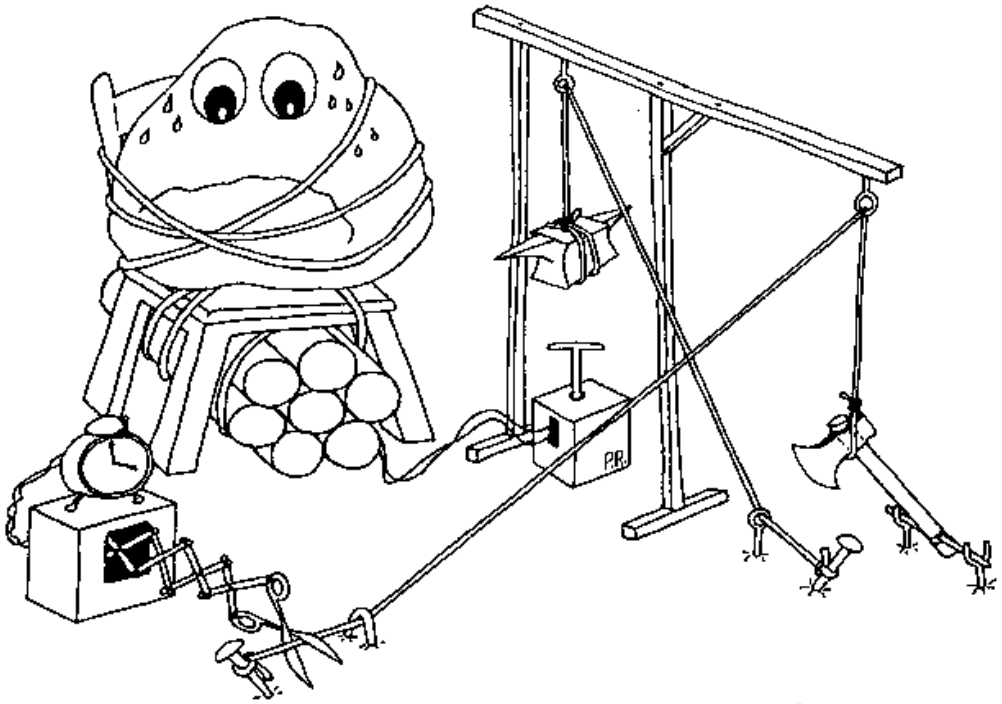
Selenium glycinate supplementation increases blood glutathione peroxidase activities and decreases prostate-specific antigen readings in middle-aged US men.

Zhang W[1], Joseph E, Hitchcock C, DiSilvestro RA.

ABSTRACT Prostate hypertrophy (enlargement) is more often benign than malignant. It is age related, increasing to over 80% in men over 80. Several factors are related to this condition, one being male hormones (androgens) and another being deficiencies in glutathione (GSH) enzymes, in particular GSH-S-transferases. It has been proposed that deficiency in this glutathione enzyme system increases the likelihood of developing both an enlarged prostate and prostate cancer (1). In addition to the traditional treatments (surgical removal, laser therapy, radiotherapy, chemotherapy and hormonal treatment) for prostate cancer, a number of alternative or complementary therapies are gaining acceptance. One is diet (low fat, high fiber) and another is the use of antioxidants including vitamin A, lycopene and selenium. A recent study by the National Cancer Institute showed that selenium supplementation dramatically reduced the incidence of prostate cancer (2) and others have confirmed that higher selenium levels in individuals correlated with a decreased risk of developing advanced prostate cancer (3). It is noteworthy that selenium is an integral part of GSH peroxidase, the enzyme that mediates antioxidation by glutathione. Androgens have been reported to stimulate free radical damage and deplete glutathione in human prostate cancer cells (4). Given the natural decline of glutathione levels with aging, it is suggested that androgens induce pro-oxidative stress which, unopposed by a weakened glutathione system, contributes to the development of prostate cancer.

Patricia A.L. Kongshavn, Ph.D *Former Professor: Department of Medicine, McGill University, Montreal, Canada*

Glutathione & Apoptosis



Rebecca Roentsch Montrone, BS

Glutathione & Apoptosis

"Glutathione also fights cancer. It selectively stimulates apoptosis (cell death) of malignant cells while leaving healthy cells unaffected.[6] It does this by regulating the tumor suppressor protein p53. Under normal conditions the p53 protein senses DNA damage in a cell and slows the rate of cell division, giving the cell time to repair itself. If the DNA cannot be repaired, p53 tells the cell to kill itself (apoptosis). Treatment with glutathione may reverse the cancer process. Various studies have shown glutathione reverses development of neuroblastoma, cervical carcinoma, leukemia, and other cancers.[7]"

http://www.denvernaturopathic.com/news/glutathione.html

Glutathione & DNA Supervision

Rebecca Roentsch Montrone, BS

Can oral glutathione beat IV therapy?(Report)

Townsend Letter: by Michael Ash, BSc, DO, ND, F.DipION, and by **Marty Jones, PharmD**

Reduced glutathione, also known as glutathione or GSH, is found in all living systems.(1) Lowered GSH tissue levels have been observed in several disease conditions.(2) The restoration of cell GSH levels in a number of these conditions has proved to be beneficial. Thus, strategies to boost cell glutathione levels are of marked therapeutic significance.

*"**THE CONCLUSION** at this stage is that an alternative to the current oral and IV options may be found in **the acetylated form of glutathione**, and if further analysis and clinical experiences continue to support this as a valid clinical strategy, there will be many patients very pleased to have access to such a simple strategy to enhance GSH levels where required."*

Glutathione/Cancer Paradox

A Clinical Study published in **Anticancer Research**, showed a nutraceutical supplement, while synthesizing GSH in healthy cells - selectively ***lowered cancer cells of their glutathione***, thus rendering them more vulnerable to radiation and chemotherapy. Paradoxically, the nutraceutical – while raising GSH levels in healthy cells – triggered the opposite reaction in cancer cells.

A research team from Saskatchewan gave toxic doses of chemotherapy to patients with *advanced progressive cancer* – plus raised their GSH levels. They hoped that raising GSH in normal cells only – and their results bear them out. ***More than half the patients*** showed either improvement or stabilization. These findings are collaborated with other studies showing cancer patients were more likely to respond to chemotherapy and radiation therapy – when their GSH levels were raised.

The Cancer Letter reports, Spanish researchers found that elevated GSH levels induced a swift and direct apoptosis mechanism in tumor cells, enhancing the efficiency of chemotherapy.

Far Fewer Side Effects

In addition, patients with higher GSH levels in normal cells, experience ***far fewer*** side effects from chemotherapy and radiation therapy.

Radiotherapists studying the protective role of GSH have linked patients who raised their GSH levels before undergoing treatment – with having been 'protected' from radiation burns and greater tolerance to therapy.

A large Scottish study of one hundred and fifty women with cancer, being treated with standard chemotherapy cisplatin, were supplemented to raise their GSH levels.

They were compared to a second group without raised GSH levels.

The first group, who raised their GSH, had statistically less:

- depression
- vomiting
- hair loss
- shortness of breath
- neurotoxicity
- wasting

In addition, their mental concentration and kidney function improved measurably, and there was a distinct trend toward a healthier outcome.

Jimmy Gutman, MD – *American Healthcare Foundation*

Iodine Helps Prevent & Treat Breast Cancer

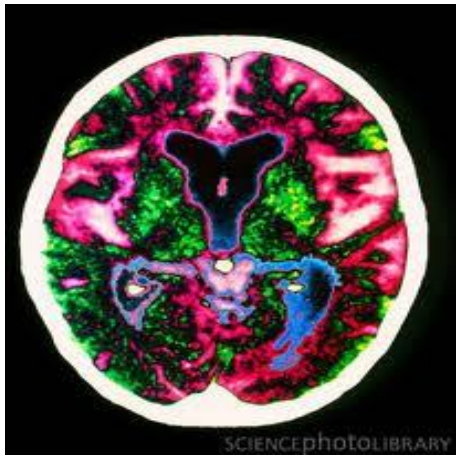
- Through the P450 system can change the body's estrogen into a form which inhibits cellular proliferation.
- This means that iodine/iodide can change the body's estrogen into a form which inhibits abnormal cellular reproduction
- Diminishes the effect that estrogen has in estrogen-receptor positive cells
- Helps increase BRCA1, which is tumor suppressive
- Helps keep cells sensitive to treatments such as Tamoxifen
- Jake Psenka, ND http://cancernd.blogspot.com/2009/01/iodine-helps-prevent-and-treat-breast.html

Slap it Silly!

Among other things to consider…

- Immune system support
- Turning off energy supply
- Interfering with cancer's odd glucose metabolism – effects on pH, etc.
- Nutrients and botanicals that directly kill cancer cells

Alzheimer's Disease



Rebecca Roentsch Montrone, BS

Genetics & Alzheimer's

Rebecca Roentsch Montrone, BS

MTHFR & Alzheimer's

Clin Neurol Neurosurg. 2013 Sep;115(9):1693-6. doi: 10.1016/j.clineuro.2013.03.015. Epub 2013 May 6.

Association of methylenetetrahydrofolate reductase polymorphisms with susceptibility to Alzheimer's disease.

Mansouri L[1], Fekih-Mrissa N, Klai S, Mansour M, Gritli N, Mrissa R.

Author information

Abstract

BACKGROUND:

Genetic risk factors play an important role in the pathogenesis of Alzheimer's disease (AD). In this case-control study, we examined the C677T and A1298C polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene and their correlation with this pathology.

OBJECTIVE:

To verify the association between MTHFR C677T and A1298C polymorphisms and Alzheimer's disease.

METHOD:

This work was conducted as a case-control study. Cases consisted of thirty-eight patients and 100 individuals without dementia constituted the control group. Genotyping of MTHFR polymorphisms was performed on patients and controls.

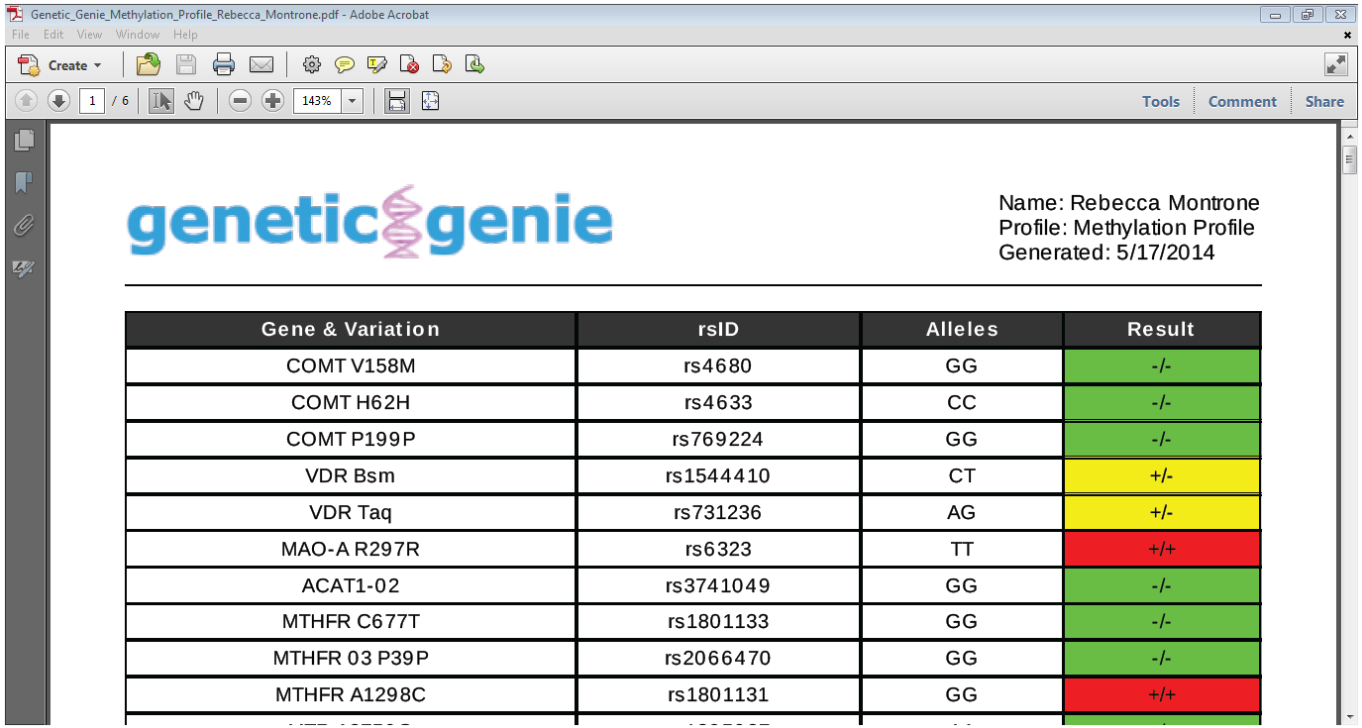
RESULT:

Genetic analyses did not indicate a significant association between the MTHFR C677T mutation and AD (C/T: 63.15% versus 39%, p=0.087). However, the genotype prevalence of the missense variant MTHFR A1298C was significantly different between patients and controls (A/C: 55% versus 7%, p<10(-3)). Our data suggest an association between the MTHFR A1298C mutation and AD; however, the MTHFR C677T mutation did not contribute to susceptibility for AD.

CONCLUSION:

The MTHFR A1298C polymorphism is a possible risk factor for Alzheimer's disease.

Becky's MTHFR Defect



Gene & Variation	rsID	Alleles	Result
COMT V158M	rs4680	GG	-/-
COMT H62H	rs4633	CC	-/-
COMT P199P	rs769224	GG	-/-
VDR Bsm	rs1544410	CT	+/-
VDR Taq	rs731236	AG	+/-
MAO-A R297R	rs6323	TT	+/+
ACAT1-02	rs3741049	GG	-/-
MTHFR C677T	rs1801133	GG	-/-
MTHFR 03 P39P	rs2066470	GG	-/-
MTHFR A1298C	rs1801131	GG	+/+

Rebecca Roentsch Montrone, BS

Epigenetic changes in Alzheimer's disease: Decrements in DNA methylation

Diego Mastroeni, Andrew Grover, Elaine Delvaux, Charisse Whiteside, Paul D. Coleman, Joseph Rogers Neurobiology of Aging Volume 31, Issue 12, December 2010, Pages 2025–2037

Abstract

DNA methylation is a vital component of the epigenetic machinery that orchestrates changes in multiple genes and helps regulate gene expression in all known vertebrates. We evaluated immunoreactivity for two markers of DNA methylation and eight methylation maintenance factors in entorhinal cortex layer II, a region exhibiting substantial Alzheimer's disease (AD) pathology in which expression changes have been reported for a wide variety of genes. We show, for the first time, neuronal immunoreactivity for all 10 of the epigenetic markers and factors, with highly significant decrements in AD cases. These decrements were particularly marked in PHF1/PS396 immunoreactive, neurofibrillary tangle-bearing neurons. In addition, two of the DNA methylation maintenance factors, DNMT1 and MBD2, have been reported also to interact with ribosomal RNAs and ribosome synthesis. Consistent with these findings, DNMT1 and MBD2, as well as p66a, exhibited punctate cytoplasmic immunoreactivity that co-localized with the ribosome markers RPL26 and 5.8 s rRNA in ND neurons. By contrast, AD neurons generally lacked such staining, and there was a qualitative decrease in RPL26 and 5.8 s rRNA immunoreactivity. Collectively, these findings suggest epigenetic dysfunction in AD-vulnerable neurons.

SUPPORTING METHYLATION

- Clean up the diet and environment to reduce demand for methyl groups
- Improve bowel performance before beginning detox
- Address any presence of yeast overgrowth
- Eliminate or at least reduce ingestion of folic acid
- Use nutrients to assist in achieving successful methylation
  - Methyl folate
  - Methylcobalamin, adenosylcobalamin, or hydroxocobalamin B12
  - Possibly methyl donors such as TMG or SAM-e
  - Acetyl-glutathione
  - Trace mineral support
  - Vitamins B2, B6
  - If high histamine is a problem a low-histamine diet and nutrients that help break down histamine

APOE4 & Alzheimer's

Apolipoprotein E, ε4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19q13.2 chromosomal region

- We observed a significant increased frequency of the APOE ε4 allele in late-onset and early-onset AD with ages at onset less than 60 and less than 65. The adjusted odds ratio (OR) of the bearers of at least one APOE ε4 allele was 4.10 ([1.84; 9.16]) when estimated in both populations with a logistic regression model.
- Hum. Mol. Genet. (1994) 3 (4):569-574.doi: 10.1093/hmg/3.4.569

Study offers an explanation for why the APOE4 gene enhances Alzheimer's risk

The gene variant disrupts lipid metabolism, but in cell experiments the effects were reversed by choline supplements. "The researchers also found that growing APOE4 yeast cells on a very nutrient-rich growth medium helped them to survive better than APOE4 yeast cells grown on the typical growth medium. Further experiments revealed that the nutrient that helped APOE4 cells survive is choline, a building block that cells use to make phospholipids. The researchers then treated their human APOE4 astrocyte cells with choline to promote phospholipid synthesis and found that it also reversed much of the damage they had seen in those cells, including the accumulation of cholesterol and lipid droplets."

SCIENCE TRANSLATIONAL MEDICINE 3 Mar 2021 Vol 13, Issue 583
DOI: 10.1126/scitranslmed.aaz4564

The Serotonin Connection

Depression & Alzheimer's

Aust N Z J Psychiatry. 2001 Dec;35(6):776-81.

History of depression as a risk factor for dementia: an updated review.

Jorm AF[1].

Author information

Abstract

OBJECTIVE: This review updates an earlier meta-analysis of the data on history of depression as a risk factor for dementia. It also considers the available evidence on the hypotheses proposed to explain the association between history of depression and dementia.

METHOD: A meta-analysis was carried out on results from seven case-control and six prospective studies. A qualitative review was carried out on the evidence related to the hypotheses to explain the association.

RESULTS: The meta-analysis found evidence to support an association from both case-control studies (estimated relative risk 2.01; 95% CI 1.16-3.50) and prospective studies (estimated relative risk 1.87; 95% CI 1.09-3.20). However, the evidence did not clearly support any one hypothesis explaining the association. The most likely contenders are: (i) depression can be an early prodrome of dementia, (ii) depression brings forward the clinical manifestation of dementing diseases, and (iii) depression leads to damage to the hippocampus through a glucocorticoid cascade.

CONCLUSIONS: The possibility that history of depression is a risk factor for dementia needs to be taken seriously and explanations of the association need to be further researched.

Arch Neurol. 2004 Aug;61(8):1290-3.

Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Modrego PJ[1], Ferrández J.

Abstract

BACKGROUND: Mild cognitive impairment has been regarded as a precursor to dementia of Alzheimer type, but not all patients with mild cognitive impairment develop dementia.

OBJECTIVE: To determine whether depression may increase the risk of developing dementia.

SETTING: The outpatient clinics of a community general hospital.

DESIGN: Prospective cohort study.

METHODS: A cohort of 114 patients with amnestic mild cognitive impairment was followed up for a mean period of 3 years. At baseline, the patients underwent memory tests, the Spanish version of the Mini-Mental State Examination, a verbal fluency test, the Geriatric Depression Scale, and the Clinical Dementia Rating Scale for staging purposes. Psychiatric examination for depression was based on structured interview and Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition criteria. We also carried out either computed tomography or magnetic resonance imaging of the brain.

MAIN OUTCOME MEASURES: We carried out periodic evaluations based on the Mini-Mental State Examination, verbal fluency test, Geriatric Depression Scale, Blessed Dementia Rating Scale, and Clinical Dementia Rating Scale. The end point was the development of probable Alzheimer disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

RESULTS: Depression was observed in 41 patients (36%) at baseline. After a mean period of 3 years, 59 patients (51.7%) developed dementia of Alzheimer type, and 6 died. Of the depressed patients, 35 (85%) developed dementia in comparison with 24 (32%) of the nondepressed patients (relative risk, 2.6; 95% confidence interval, 1.8-3.6). The survival analysis also showed that depressed patients developed dementia earlier than the nondepressed. Most patients with depression at baseline exhibited a poor response to antidepressants.

CONCLUSIONS: We conclude that patients with mild cognitive impairment and depression are at **more than twice the risk** of developing dementia of Alzheimer type as those without depression. Patients with a poor response to antidepressants are at an especially increased risk of developing dementia.

PMDD & Alzheimer's

Premenstrual Dysphoric Disorder (PMDD)

Neurotransmitters

The three main neurotransmitters implicated in PMDD are serotonin, GABA, and β-endorphin. Evidence currently suggests a leading role for altered serotonin levels in the etiology of PMDD. Central serotonin levels are typically low in women with PMDD, and symptoms worsen with depletion of the serotonin precursor tryptophan.[9, 10] Notably, many women report benefiting from selective serotonin reuptake inhibitors (SSRIs).

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/premenstrual-dysphoric-disorder/

“I wish you were my daughter…”

Hormones & Alzheimer's

Rebecca Roentsch Montrone, BS

Biol Psychiatry. 2006 Dec 15;60(12):1287-94. Epub 2006 Sep 25.

The neurosteroid allopregnanolone is reduced in prefrontal cortex in Alzheimer's disease.

Marx CE[1], Trost WT, Shampine LJ, Stevens RD, Hulette CM, Steffens DC, Ervin JF, Butterfield MI, Blazer DG, Massing MW, Lieberman JA.

Abstract

BACKGROUND:

Few data are currently available investigating neurosteroids (NS) in Alzheimer's disease (AD). The NS allopregnanolone may be decreased in serum and plasma in patients with AD, but it is unclear if allopregnanolone is also reduced in brain. Because a number of NS exhibit neuroprotective effects and impact cognitive performance in rodent models, these molecules may be relevant to the pathophysiology of neurodegenerative disorders. We therefore investigated prefrontal cortex (PFC) NS levels in AD.

METHODS:

Neurosteroid levels (allopregnanolone, pregnenolone, dehydroepiandrosterone [DHEA]) were determined in postmortem PFC in 14 male subjects with AD and 15 cognitively intact male control subjects by gas chromatography/mass spectrometry preceded by high-performance liquid chromatography purification.

RESULTS:

Subjects with AD exhibit significant reductions in allopregnanolone compared with cognitively intact control subjects (median levels = 2.50 ng/g vs. 5.59 ng/g, respectively; p = .02). Allopregnanolone levels are inversely correlated with neuropathological disease stage (Braak), r = -.49, p = .007. Median DHEA levels are elevated in subjects with AD (p = .01).

CONCLUSIONS:

Subjects with AD demonstrate significant reductions in PFC allopregnanolone levels, a finding that may be relevant to neuropathological disease stage severity. Neurosteroids may have utility as candidate biomarkers in AD.

Rebecca Roentsch Montrone, BS

Neuroprotective effects of dehydroepiandrosterone (DHEA) in rat model of Alzheimer's disease.

Aly HF[1], Metwally FM, Ahmed HH.

Abstract

The current study was undertaken to elucidate a possible neuroprotective role of dehydroepiandrosterone (DHEA) against the development of Alzheimer's disease in experimental rat model. Alzheimer's disease was produced in young female ovariectomized rats by intraperitoneal administration of AlCl(3) (4.2 mg/kg body weight) daily for 12 weeks. Half of these animals also received orally DHEA (250 mg/kg body weight, three times weekly) for 18 weeks. Control groups of animals received either DHAE alone, or no DHEA, or were not ovariectomized. After such treatment the animals were analyzed for oxidative stress biomarkers such as hydrogen peroxide, nitric oxide and malondialdehyde, total antioxidant capacity, reduced glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase and catalase activities, antiapoptotic marker Bcl-2 and brain derived neurotrophic factor.

Also brain cholinergic markers (acetylcholinesterase and acetylcholine) were determined. The results revealed significant increase in oxidative stress parameters associated with significant decrease in the antioxidant enzyme activities in Al-intoxicated ovariectomized rats. Significant depletion in brain Bcl-2 and brain-derived neurotrophic factor levels were also detected. Moreover, significant elevations in brain acetylcholinesterase activity accompanied with significant reduction in acetylcholine level were recorded. Significant amelioration in all investigated parameters was detected as a result of treatment of Al-intoxicated ovariectomized rats with DHEA. These results were confirmed by histological examination of brain sections. These results clearly indicate a neuroprotective effect of DHEA against Alzheimer's disease.

Acta Biochim Pol. 2011;58(4):513-20. Epub 2011 Dec 6.

Biol Psychiatry. 2000 Jan 15;47(2):161-3.

DHEA-S plasma levels and incidence of Alzheimer's disease.

Hillen T[1], Lun A, Reischies FM, Borchelt M, Steinhagen-Thiessen E, Schaub RT.

Abstract

BACKGROUND:

Cross-sectional studies controlling for age and gender reported a relationship between Alzheimer's disease and low dehydroepiandrosterone sulphate (DHEA-S) plasma levels. Prospective data with sufficient control for confounding factors are lacking.

METHODS:

A nested case-control study examined baseline DHEA-S in participants of the Berlin Aging Study. Cases (n = 14) developed dementia of the Alzheimer type within 3 years. Control group A (n = 14) was matched for gender, age, multimorbidity, and immobility. Control group B (n = 13) was matched for gender and age and comprised participants free from multimorbidity, immobility, multimedication, need of help, incontinence, visual impairment, hearing impairment, and depression.

RESULTS:

The mean plasma DHEA-S concentration of case subjects was 1.02 +/- 0.61 mumol/L. Both control groups had higher mean DEHA-S levels, in control group A, it was 1.89 +/- 1.24 mumol/L (p = .012) and in control group B 1.70 +/- 1.38 mumol/L (p = .093).

CONCLUSIONS:

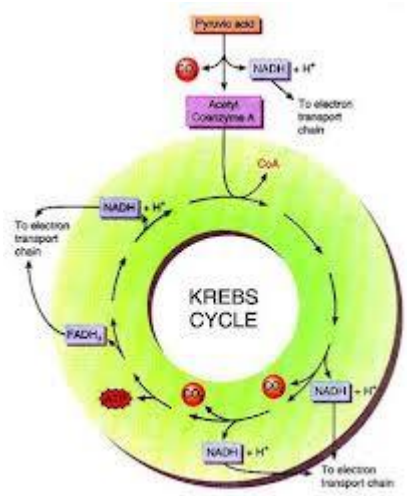
This population-based prospective study supports the role of DHEA-S as a risk factor for Alzheimer's disease.

Progesterone and Estrogen Regulate Alzheimer-Like Neuropathology in Female 3xTg-AD Mice Jenna C. Carroll, Emily R. Rosario, Lilly Chang, Frank Z. Stanczyk, Salvatore Oddo, Frank M. LaFerla, Christian J. Pike

Estrogen depletion in postmenopausal women is a significant risk factor for the development of Alzheimer's disease (AD), and estrogen-based hormone therapy may reduce this risk. However, the effects of progesterone both alone and in combination with estrogen on AD neuropathology remain unknown. In this study, we used the triple transgenic mouse model of AD (3xTg-AD) to investigate the individual and combined effects of estrogen and progesterone on β-amyloid (Aβ) accumulation, tau hyperphosphorylation, and hippocampal-dependent behavioral impairments. In gonadally intact female 3xTg-AD mice, AD-like neuropathology was apparent by 3 months of age and progressively increased through age 12 months, a time course that was paralleled by behavioral impairment. Ovariectomy-induced depletion of sex steroid hormones in adult female 3xTg-AD mice significantly increased Aβ accumulation and worsened memory performance.

Treatment of ovariectomized 3xTg-AD mice with estrogen, but not progesterone, prevented these effects. When estrogen and progesterone were administered in combination, progesterone blocked the beneficial effect of estrogen on Aβ accumulation but not on behavioral performance. Interestingly, progesterone significantly reduced tau hyperphosphorylation when administered both alone and in combination with estrogen. These results demonstrate that estrogen and progesterone independently and interactively regulate AD-like neuropathology and suggest that an optimized hormone therapy may be useful in reducing the risk of AD in postmenopausal women.

Mitochondrial Energy & Alzheimer's



Rebecca Roentsch Montrone, BS

PNAS **August 25, 2009** vol. 106 no. 34 **14670-14675**

Mitochondrial dysfunction has been proposed to play a pivotal role in neurodegenerative diseases, including Alzheimer's disease (AD). To address whether mitochondrial dysfunction precedes the development of AD pathology, we conducted mitochondrial functional analyses in female triple transgenic Alzheimer's mice (3xTg-AD) and age-matched nontransgenic (nonTg). Mitochondrial dysfunction in the 3xTg-AD brain was evidenced by decreased mitochondrial respiration and decreased pyruvate dehydrogenase (PDH) protein level and activity as early as 3 months of age.

3xTg-AD mice also exhibited increased oxidative stress as manifested by increased hydrogen peroxide production and lipid peroxidation. Mitochondrial amyloid beta (Aβ) level in the 3xTg-AD mice was significantly increased at 9 months and temporally correlated with increased level of Aβ binding to alcohol dehydrogenase (ABAD). Embryonic neurons derived from 3xTg-AD mouse hippocampus exhibited significantly decreased mitochondrial respiration and increased glycolysis. Results of these analyses indicate that compromised mitochondrial function is evident in embryonic hippocampal neurons, continues unabated in females throughout the reproductive period, and is exacerbated during reproductive senescence.

In nontransgenic control mice, oxidative stress was coincident with reproductive senescence and accompanied by a significant decline in mitochondrial function. Reproductive senescence in the 3xTg-AD mouse brain markedly exacerbated mitochondrial dysfunction. Collectively, the data indicate significant mitochondrial dysfunction occurs early in AD pathogenesis in a female AD mouse model. **Mitochondrial dysfunction provides a plausible mechanistic rationale for the hypometabolism in brain** that precedes AD diagnosis and suggests therapeutic targets for prevention of AD.

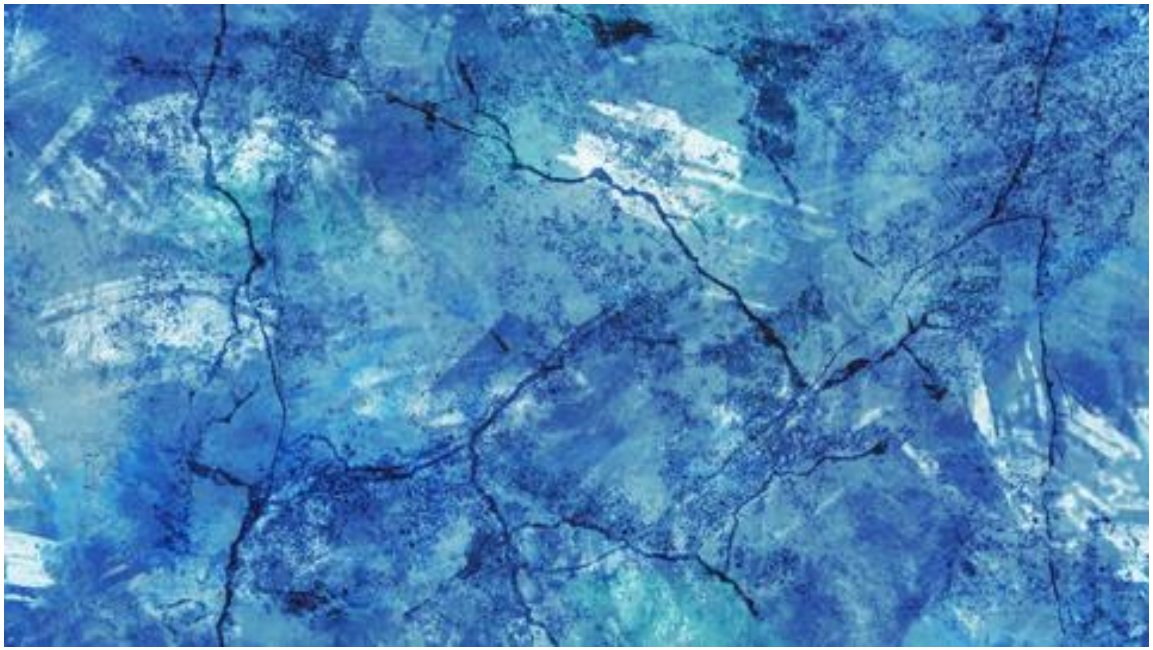
Rebecca Roentsch Montrone, BS

J Alzheimers Dis. 2006 Jul;9(2):119-26.

Mitochondrial alterations in Alzheimer's disease. Baloyannis SJ[1].

- **Abstract**
- Morphological alterations of mitochondria may be related to metabolic and energy deficiency in neurons in Alzheimer's disease and other neurodegenerative disorders. Mitochondrial dysfunction is also a hallmark of beta peptide induced neuronal toxicity in Alzheimer's disease. A general change in glucose utilization, increased oxidative stress, and Ca;{2+} deregulation are additional metabolic defects in the AD brain that may also be associated with defective mitochondrial function the result is a cycle of increased mitochondrial dysfunction causing increased oxidative damage until the cellular energy supply falls below the threshold for cellular survival. In a series of studies on the morphological and morphometric estimation of mitochondria in Alzheimer's disease, by electron microscopy we noticed substantial morphological and morphometric changes in the neurons of the hippocampus, the acoustic cortex, the frontal cortex, the cerebellar cortex, the climbing fibers, the thalamus, the globus pallidus, the red nucleus and the locus coeruleus. The morphological alterations consisted of considerable changes of the mitochondrial cristae, accumulation of osmiophilic material, and decrease of their size, in comparison with the normal controls. Mitochondrial alterations were particularly prominent in neurons, which showed loss of dendritic spines and abbreviation of the dendritic arborization. The ultrastructural study of large number of neurons in the thalamus and the red nucleus revealed that the mitochondrial alterations did not coexist with cytoskeletal pathology and accumulation of amyloid deposits, though they were prominent in neurons, which demonstrated fragmentation of the cisternae of the Golgi apparatus. Morphometric analysis showed that mitochondria are significantly reduced in Alzheimer's disease. The relationship between the site and extent of mitochondrial abnormalities and the synaptic alterations suggests an intimate and early association between these features in Alzheimer's disease.

Methylene Blue!



"Methylene blue (MB) and its compounds are investigated for their potential benefits in the management of Alzheimer's disease (AD). AD is a widely seen neuropathological disorder characterized by the gradual decline of cognitive abilities, ultimately leading to the development of severe dementia. It is anticipated that there will be a significant increase in the prevalence of AD due to the aging population. Histopathologically, AD is distinguished by the presence of intracellular tangles of neurofibrillary tissues (NFTs) and extracellular amyloid plaques within the brain. MB is a thiophenazine dye with FDA approval for treating several illnesses. Its ease in crossing the blood-brain barrier and potential therapeutic use in central nervous system diseases have increased interest in its application for treating AD. The literature review includes randomized clinical trials investigating MB's potential benefits in treating AD. ***The findings of the studies indicate that the administration of MB has demonstrated enhancements in cognitive function, reductions in the accumulation of plaques containing beta-amyloid, improvements in memory and cognitive function in animal subjects, and possesses antioxidant properties that can mitigate oxidative stress and inflammation within the brain.*** *This review evaluates the modern and latest research on the application of MB for treating AD."*

Cureus. **2023** Oct; 15(10): e46732.
Published online 2023 Oct 9. doi: 10.7759/cureus.46732

Rebecca Roentsch Montrone, BS

Proteolytic Enzymes & Alzheimer's

Hum Exp Toxicol. 2013 Jul;32(7):721-35. doi: 10.1177/0960327112467040.

Serrapeptase and nattokinase intervention for relieving Alzheimer's disease pathophysiology in rat model.

Fadl NN[1], Ahmed HH, Booles HF, Sayed AH.

Abstract

Serrapeptase (SP) and nattokinase (NK) are proteolytic enzymes belonging to serine proteases. In this study, we hypothesized that SP and NK could modulate certain factors that are associated with Alzheimer's disease (AD) pathophysiology in the experimental model. Oral administration of aluminium chloride (AlCl3) in a dose of 17 mg/kg body weight (bw) daily for 45 days induced AD-like pathology in male rats with a significant increase in brain acetylcholinesterase (AchE) activity, transforming growth factor β (TGF-β), Fas and interleukin-6 (IL-6) levels. Meanwhile, AlCl3 supplementation produced significant decrease in brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) when compared with control values. Also, AlCl3 administration caused significant decline in the expression levels of disintegrin and metalloproteinase domain 9 (ADAM9) and a disintegrin and metalloproteinase domain 10 (ADAM10) genes in the brain. Histological investigation of brain tissue of rat model of AD showed neuronal degeneration in the hippocampus and focal hyalinosis with cellular as well as a cellular amyloid plaques formation. Oral administration of SP or NK in a rat model of AD daily for 45 days resulted in a significant decrease in brain AchE activity, TGF-β, Fas and IL-6 levels. Also, the treatment with these enzymes produced significant increase in BDNF and IGF-1 levels when compared with the untreated AD-induced rats. Moreover, both SP and NK could markedly increase the expression levels of ADAM9 and ADAM10 genes in the brain tissue of the treated rats. These findings were well confirmed by the histological examination of the brain tissue of the treated rats. The present results support our hypothesis that the oral administration of proteolytitc enzymes, SP and/or NK, would have an effective role in modulating certain factors characterizing AD. Thus, these enzymes may have a therapeutic application in the treatment of AD.

Ecklonia cava extract – (Seanol/Fibroboost)

Memory & Acetylcholine – a natural acetylcholinesterase inhibitor

Memory is related to the neurotransmitter acetylcholine (ACh). In an animal study, ECE increased rodent acetylcholine by 140% in the brain regions responsible for learning and memory in just 7 days. Memory augmentation increased by 100-200% at a dose as low as 0.2-1mg/kg.

With regard to mechanism, it is contemplation that ECE works by slightly inhibiting an enzyme that breaks down acetylcholine called acetylcholinesterase. By inhibiting this enzyme, the availability and utilization of acetylcholine in the body would be enhanced.

Greatly Improved Blood Flow

Since Ecklonia Cava is fat-soluble, it has the capability to cross the blood-brain barrier and considerably improves blood flow to the brain. This is another way ECE improves memory. More specifically, Dr. Lee's group found that ECE increases the rate of blood flow in the carotid artery (the main artery to the brain) from an average of 36.68 cm/ sec. to 40.09 cm/sec., while the placebo had no improvement.

Glutathione & Alzheimer's

J Alzheimers Dis. 2014;40(3):519-29. doi: 10.3233/JAD-132483.

The emerging role of glutathione in Alzheimer's disease.

Saharan S[1], Mandal PK[2].

Abstract

With millions of older individuals presently suffering from Alzheimer's disease (AD) worldwide, AD is an unduly common form of dementia that exacts a heavy toll on affected individuals and their families. One of the emerging causative factors associated with AD pathology is oxidative stress. This AD-related increase in oxidative stress has been attributed to decreased levels of the brain antioxidant, glutathione (GSH). In this article, we review the role of GSH in AD from a pathological as well as a diagnostic point of view. We recapitulate the literature that has assessed the role of GSH in AD onset and progression. We discuss the various methodologies through which alterations in GSH levels might be monitored, and highlight the yet uncharted potential of assaying GSH levels in vivo with magnetic resonance spectroscopy in AD therapeutics and prognostics. Finally, the present manuscript integrates findings from various studies to elucidate the possible molecular mechanisms through which disruptions in GSH homeostasis may contribute to AD pathology.

Elevation of glutathione as a therapeutic strategy in Alzheimer disease ☆

Chava B. Pocernich[a, b],
D. Allan Butterfield[a, b, c],

Abstract

Oxidative stress has been associated with the onset and progression of mild cognitive impairment (MCI) and Alzheimer disease (AD). AD and MCI brain and plasma display extensive oxidative stress as indexed by protein oxidation, lipid peroxidation, free radical formation, DNA oxidation, and decreased antioxidants. The most abundant endogenous antioxidant, glutathione, plays a significant role in combating oxidative stress. The ratio of oxidized to reduced glutathione is utilized as a measure of intensity of oxidative stress. Antioxidants have long been considered as an approach to slow down AD progression. In this review, we focus on the elevation on glutathione through N-acetyl-cysteine (NAC) and γ-glutamylcysteine ethyl ester (GCEE) as a potential therapeutic approach for Alzheimer disease. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease
Volume 1822, Issue 5, May 2012, Pages 625–630
Antioxidants and Antioxidant Treatment in Disease

Beta-amyloidolysis and glutathione in Alzheimer's disease

- **Authors** Lasierra-Cirujeda J, Coronel P, Aza MJ, Gimeno M
- **Published Date** April 2013 Volume 2013:4 Pages 31—38
- **DOI** http://dx.doi.org/10.2147/JBM.S35496

Abstract: In this review, we hypothesized the importance of the interaction between the brain glutathione (GSH) system, the proteolytic tissue plasminogen activator (t-PA)/plasminogen/plasmin system, regulated by plasminogen activator inhibitor (PAI-1), and neuroserpin in the pathogenesis of Alzheimer's disease. The histopathological characteristic hallmark that gives personality to the diagnosis of Alzheimer's disease is the accumulation of neurofibroid tangles located intracellularly in the brain, such as the protein tau and extracellular senile plaques made primarily of amyloidal substance. These formations of complex etiology are intimately related to GSH, brain protective antioxidants, and the proteolytic system, in which t-PA plays a key role. There is scientific evidence that suggests a relationship between aging, a number of neurodegenerative disorders, and the excessive production of reactive oxygen species and accompanying decreased brain proteolysis. The plasminogen system in the brain is an essential proteolytic mechanism that effectively degrades amyloid peptides ("beta-amyloidolysis") through action of the plasmin, and this physiologic process may be considered to be a means of prevention of neurodegenerative disorders. In parallel to the decrease in GSH levels seen in aging, there is also a decrease in plasmin brain activity and a progressive decrease of t-PA activity, caused by a decrease in the expression of the t-PA together with an increase of the PAI-1 levels, which rise to an increment in the production of amyloid peptides and a lesser clearance of them. Better knowledge of the GSH mechanism and cerebral proteolysis will allow us to hypothesize about therapeutic practices.

"Targeting oxidative stress-induced brain hypometabolism and brain mitochondrial failure as new and effective strategies for the prevention and treatment of cognitive decline in elderly demented/depressed patients and those with Alzheimer's disease: New scents on the trail?"

From *Alzheimer's & Dementia – the Journal of the Alzheimer's Disease Association*
Gjumrakch Aliev, , Hector H. Palacios, et.al . **July 2010**Volume 6, Issue 4, Supplement, Page S579

Metal involvement in the Alzheimer's Brain

_N_-Aryl-substituted 3-(β-D-glucopyranosyloxy)-2-methyl-4(1_H_)-pyridinones as agents for Alzheimer's therapy ***Chem. Sci.***, 2011,**2**, 642-648

DOI: 10.1039/C0SC00544D
Received 27 Oct 2010, Accepted 03 Dec 2010
First published online 23 Dec 2010

Molecules designed to sequester, redistribute and/or remove metal ions are attractive therapeutic agents in neurodegenerative diseases such as Alzheimer's disease. The multifactorial nature of the condition and the generally poor target specificity associated with metal ion-binding therapy has led to the development of multifunctional 3-hydroxy-4-(1*H*)-pyridinone pro-ligands. The excellent qualities of the basic 3-hydroxy-4-pyridinone framework as a low toxicity metal chelator and an antioxidant, as well as its antibacterial and analgesicproperties among other functions, inspired us to functionalize it with a framework derived fromthioflavin-T, the well-known traditional dye used as a marker to detect amyloid deposits in tissue sections. Thus 2-methyl-3-hydroxy-1-(4-dimethylaminophenyl)-4(1*H*)-pyridinone (**HL_1**), 2-methyl-3-hydroxy-1-(4-methylaminophenyl)-4(1*H*)-pyridinone (**HL_2**), 1-(4-aminophenyl)-3-hydroxy-2-methyl-4(1*H*)-pyridinone (**HL_3**), 1-(6-benzothiazolyl)-3-hydroxy-2-methyl-4(1*H*)-pyridinone (**HL_4**), 1-(2-benzothiazolyl)-3-hydroxy-2-methyl-4(1*H*)-pyridinone (**HL_5**) and 2-methyl-3-hydroxy-1-[4-(4-bromophenyl)-2-thiazolyl]-4(1*H*)-pyridinone (**HL_6**) were obtained.Glycosylation, as well as incorporation of structures mimicking those of known amyloid imaging agents, may target drug action to the site of interest, the metal-overloaded amyloid plaques in the Alzheimer's brain. The pro-ligands were assessed for their antioxidant activity, cytotoxicity and ability to interfere with metal ion-induced amyloid peptide aggregation to screen promising lead compounds. Finally, in a brain uptake study with a radiolabeled glucoconjugate pyridinone,3-(β-D-glucopyranosyloxy)-1-[4-(4-[^{125}I]iodophenyl)-2-thiazolyl]-2-methyl-4(1*H*)-pyridinone(**[^{125}I]-GL_7**) was shown to cross the blood–brain barrier using an *in situ* rat brain perfusion technique.

In Summary…

- **Glutathione with regard to AD**
  - Metal detoxification
  - Prevents inflammation and damage due to oxidative stress
    - Increasing glucose metabolism
    - Improving mitochondrial energy production
  - Prevents and increases the degradation of beta-amyloid plaque

Anandamide, Cannabinoids, & Alzheimer's Disease

Rebecca Roentsch Montrone, BS

Neurobiol Aging. 2012 Aug;33(8):1522-32. doi: 10.1016/j.neurobiolaging.2011.03.012. Epub 2011 May 4. **An amyloid β42-dependent deficit in anandamide mobilization is associated with cognitive dysfunction in Alzheimer's disease.**

Jung KM[1], Astarita G, Yasar S, Vasilevko V, Cribbs DH, Head E, Cotman CW, Piomelli D.

Abstract

The endocannabinoids and their attending cannabinoid (CB)(1) receptors have been implicated in the control of cognition, but their possible roles in dementias are still unclear. In the present study, we used liquid chromatography/mass spectrometry to conduct an endocannabinoid-targeted lipidomic analysis of postmortem brain samples from 38 Alzheimer's disease (AD) patients and 17 control subjects, matched for age and postmortem interval. The analysis revealed that midfrontal and temporal cortex tissue from AD patients contains, relative to control subjects, significantly lower levels of the endocannabinoid anandamide and its precursor 1-stearoyl, 2-docosahexaenoyl-sn-glycero-phosphoethanolamine-N-arachidonoyl (NArPE). No such difference was observed with the endocannabinoid 2-arachidonoyl-sn-glycerol or 15 additional lipid species. In AD patients, but not in control subjects, statistically detectable positive correlations were found between (1) anandamide content in midfrontal cortex and scores of the Kendrick's Digit Copy test ($p = 0.004$, $r = 0.81$; $n = 10$), which measures speed of information processing; and (2) anandamide content in temporal cortex and scores of the Boston Naming test ($p = 0.027$, $r = 0.52$; $n = 18$), which assesses language facility. Furthermore, anandamide and NArPE levels in midfrontal cortex of the study subjects inversely correlated with levels of the neurotoxic amyloid peptide, amyloid β-protein (Aβ)(42), while showing no association with Aβ(40) levels, amyloid plaque load or tau protein phosphorylation. Finally, high endogenous levels of Aβ(42) in Swedish mutant form of amyloid precursor protein (APP(SWE))/Neuro-2a cells directly reduced anandamide and NArPE concentrations in cells lysates. The results suggest that an Aβ(42)-dependent impairment in brain anandamide mobilization contributes to cognitive dysfunction in AD.

Psychopharmacology August 2014, Volume 231, Issue 15, pp 3009-3017

Chronic cannabidiol treatment improves social and object recognition in double transgenic APP_{swe} /PS1ΔE9 mice

David Cheng, Jac Kee Low, Warren Logge, Brett Garner, Tim Karl

Abstract

Rationale - Patients suffering from Alzheimer's disease (AD) exhibit a decline in cognitive abilities including an inability to recognise familiar faces. Hallmark pathological changes in AD include the aggregation of amyloid-β (Aβ), tau protein hyperphosphorylation as well as pronounced neurodegeneration, neuroinflammation, neurotoxicity and oxidative damage.

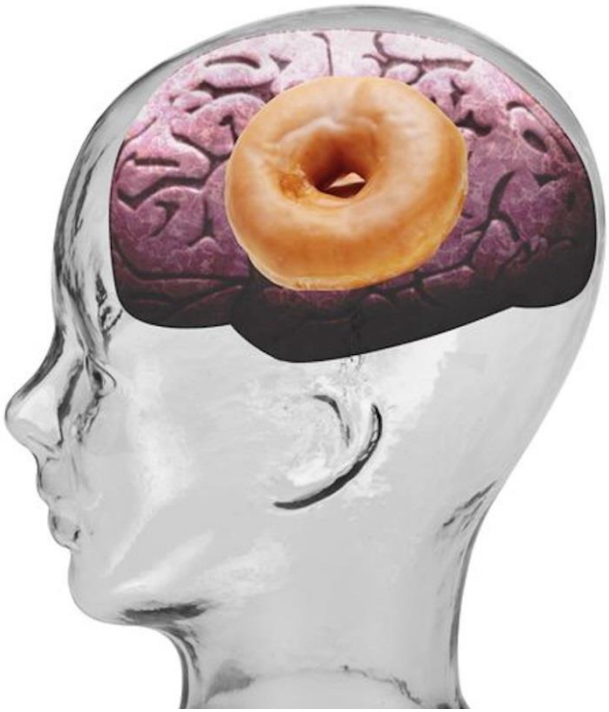
Objectives - The non-psychoactive phytocannabinoid cannabidiol (CBD) exerts neuroprotective, anti-oxidant and anti-inflammatory effects and promotes neurogenesis. CBD also reverses Aβ-induced spatial memory deficits in rodents.

Materials and methods - Thus we determined the therapeutic-like effects of chronic CBD treatment (20 mg/kg, daily intraperitoneal injections for 3 weeks) on the APP_{swe}/PS1ΔE9 (APPxPS1) transgenic mouse model for AD in a number of cognitive tests, including the social preference test, the novel object recognition task and the fear conditioning paradigm. We also analysed the impact of CBD on anxiety behaviours in the elevated plus maze.

Results - Vehicle-treated APPxPS1 mice demonstrated impairments in social recognition and novel object recognition compared to wild type-like mice. Chronic CBD treatment reversed these cognitive deficits in APPxPS1 mice without affecting anxiety-related behaviours.

Conclusions - This is the first study to investigate the effect of chronic CBD treatment on cognition in an AD transgenic mouse model. Our findings suggest that CBD may have therapeutic potential for specific cognitive impairments associated with AD.

Diet & Alzheimer's Disease



Rebecca Roentsch Montrone, BS

- “She fasts for more than 12 hours between dinner and the next day's breakfast, making sure there are at least three hours between dinner and bedtime. The idea behind fasting, said Bredesen, is that with the break the body begins a process called autophagy, which can help destroy amyloid-beta, a problematic protein that builds up in the brains of Alzheimer's patients.

- Gee has also cut out processed foods from her diet, including sugar, grains and other starches, since they can stir up inflammation in the brain. Her rule of thumb: "I don't buy any packaged, boxed or canned food.“

- A typical dinner for her includes mostly raw organic vegetables drizzled with extra virgin olive oil and wild caught fish. Occasionally she replaces the fish with grass-fed lean meats. She has integrated more fermented foods into her diet — research is beginning to correlate gut health with brain health.”

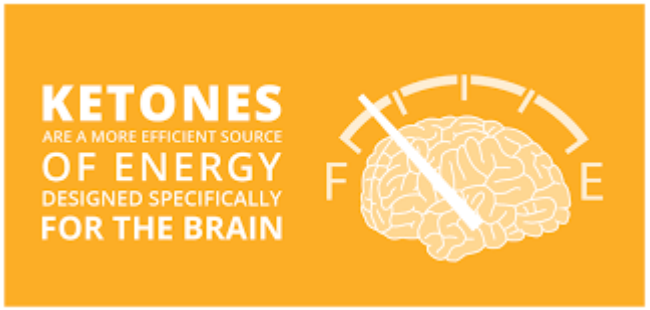
Could Gut Bacterial Imbalance Cause Brain Illness?

In a recent British study, researchers evaluated the diversity of organisms and presence of parasites in people from 192 countries and compared their results with the prevalence of Alzheimer's disease in those countries. Remarkably, they found that in those countries having the greatest degree of hygiene, in other words the least amount of parasites and microbial diversity, rates of Alzheimer's were dramatically increased in comparison to those countries in which harboring parasites was actually very common and the gut organisms were more diverse. The authors commented:

"Variation in hygiene may partly explain global patterns in AD rates. Microorganism exposure may be inversely related to AD risk. These results may help predict AD burden in developing countries where microbial diversity is rapidly diminishing. Epidemiological forecasting is important for preparing for future healthcare needs and research prioritization."

Evolution, Medicine, and Public Health - Molly Fox, Leslie A. Knapp, Paul W. Andrews, Corey L. Fincher

Ketone Energy & Alzheimer's



Rebecca Roentsch Montrone, BS

Neurotherapeutics. 2008 Jul;5(3):470-80. doi: 10.1016/j.nurt.2008.05.004.

Ketone bodies as a therapeutic for Alzheimer's disease. Henderson ST[1].

Abstract

An early feature of Alzheimer's disease (AD) is region-specific declines in brain glucose metabolism. Unlike other tissues in the body, the brain does not efficiently metabolize fats; hence the adult human brain relies almost exclusively on glucose as an energy substrate. Therefore, inhibition of glucose metabolism can have profound effects on brain function. The hypometabolism seen in AD has recently attracted attention as a possible target for intervention in the disease process. One promising approach is to supplement the normal glucose supply of the brain with ketone bodies (KB), which include acetoacetate, beta-hydroxybutyrate, and acetone. KB are normally produced from fat stores when glucose supplies are limited, such as during prolonged fasting. KB have been induced both by direct infusion and by the administration of a high-fat, low-carbohydrate, low-protein, ketogenic diets. Both approaches have demonstrated efficacy in animal models of neurodegenerative disorders and in human clinical trials, including AD trials. Much of the benefit of KB can be attributed to their ability to increase mitochondrial efficiency and supplement the brain's normal reliance on glucose. Research into the therapeutic potential of KB and ketosis represents a promising new area of AD research.

Effects of β-hydroxybutyrate on cognition in memory-impaired adults Mark A. Reger, et. al

Abstract

Glucose is the brain's principal energy substrate. In Alzheimer's disease (AD), there appears to be a pathological decrease in the brain's ability to use glucose. Neurobiological evidence suggests that ketone bodies are an effective alternative energy substrate for the brain. Elevation of plasma ketone body levels through an oral dose of medium chain triglycerides (MCTs) may improve cognitive functioning in older adults with memory disorders. On separate days, 20 subjects with AD or mild cognitive impairment consumed a drink containing emulsified MCTs or placebo. Significant increases in levels of the ketone body β-hydroxybutyrate (β-OHB) were observed 90 min after treatment (P=0.007) when cognitive tests were administered. β-OHB elevations were moderated by apolipoprotein E (APOE) genotype (P=0.036). For ε4+ subjects, β-OHB levels continued to rise between the 90 and 120 min blood draws in the treatment condition, while the β-OHB levels of ε4− subjects held constant (P<0.009). On cognitive testing, MCT treatment facilitated performance on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) for ε4− subjects, but not for ε4+ subjects (P=0.04). Higher ketone values were associated with greater improvement in paragraph recall with MCT treatment relative to placebo across all subjects (P=0.02). Additional research is warranted to determine the therapeutic benefits of MCTs for patients with AD and how APOE-ε4 status may mediate β-OHB efficacy.

Received: September 24, 2002; Received in revised form: **January 30, 2003**; Accepted: March 27, 2003;

Sugar and Your Brain: Is Alzheimer's Disease Actually Type 3 Diabetes? Dr. B.J. Hardick, D.C.

"Studies have shown that brain cells shrink and become tangled from high blood sugar levels over time. This means that your sugar intake could be drastically affecting long-term brain health, inherently increasing the likelihood of developing lesions in the brain, which are linked to the deadly disease process we call Alzheimer's."

"The good news is that the brain is very resilient. A handful of well-researched, holistic prevention tools have been shown to restore damaged brain cells, and return a dying brain to its fully functioning state."

Benfotiamine & Alzheimer's

Brain. 2010 May;133(Pt 5):1342-51. doi: 10.1093/brain/awq069. Epub 2010 Apr 12.

Powerful beneficial effects of benfotiamine on cognitive impairment and beta-amyloid deposition in amyloid precursor protein/presenilin-1 transgenic mice.

Pan X[1], Gong N, Zhao J, Yu Z, Gu F, Chen J, Sun X, Zhao L, Yu M, Xu Z, Dong W, Qin Y, Fei G, Zhong C, Xu TL.

Abstract

Reduction of glucose metabolism in brain is one of the main features of Alzheimer's disease. Thiamine (vitamin B1)-dependent processes are critical in glucose metabolism and have been found to be impaired in brains from patients with Alzheimer's disease. However, thiamine treatment exerts little beneficial effect in these patients. Here, we tested the effect of benfotiamine, a thiamine derivative with better bioavailability than thiamine, on cognitive impairment and pathology alterations in a mouse model of Alzheimer's disease, the amyloid precursor protein/presenilin-1 transgenic mouse. We show that after a chronic 8 week treatment, benfotiamine dose-dependently enhanced the spatial memory of amyloid precursor protein/presenilin-1 mice in the Morris water maze test. Furthermore, benfotiamine effectively reduced both amyloid plaque numbers and phosphorylated tau levels in cortical areas of the transgenic mice brains. Unexpectedly, these effects were not mimicked by another lipophilic thiamine derivative, fursultiamine, although both benfotiamine and fursultiamine were effective in increasing the levels of free thiamine in the brain. Most notably, benfotiamine, but not fursultiamine, significantly elevated the phosphorylation level of glycogen synthase kinase-3alpha and -3beta, and reduced their enzymatic activities in the amyloid precursor protein/presenilin-1 transgenic brain. Therefore, in the animal Alzheimer's disease model, benfotiamine appears to improve the cognitive function and reduce amyloid deposition via thiamine-independent mechanisms, which are likely to include the suppression of glycogen synthase kinase-3 activities. These results suggest that, unlike many other thiamine-related drugs, benfotiamine may be beneficial for clinical Alzheimer's disease treatment.

Vitamin D & Alzheimer's Disease

Neurology. 2014 Sep 2; 83(10): 920–928. PMCID: PMC4153851 **Vitamin D and the risk of dementia and Alzheimer disease**

Thomas J. Littlejohns, MSc, et. Al

Abstract

Objective: To determine whether low vitamin D concentrations are associated with an increased risk of incident all-cause dementia and Alzheimer disease.

Methods: One thousand six hundred fifty-eight elderly ambulatory adults free from dementia, cardiovascular disease, and stroke who participated in the US population–based Cardiovascular Health Study between 1992–1993 and 1999 were included. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were determined by liquid chromatography-tandem mass spectrometry from blood samples collected in 1992–1993. Incident all-cause dementia and Alzheimer disease status were assessed during follow-up using National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.

Results: During a mean follow-up of 5.6 years, 171 participants developed all-cause dementia, including 102 cases of Alzheimer disease. Using Cox proportional hazards models, the multivariate adjusted hazard ratios (95% confidence interval [CI]) for incident all-cause dementia in participants who were severely 25(OH)D deficient (<25 nmol/L) and deficient (≥25 to <50 nmol/L) were 2.25 (95% CI: 1.23–4.13) and 1.53 (95% CI: 1.06–2.21) compared to participants with sufficient concentrations (≥50 nmol/L). The multivariate adjusted hazard ratios for incident Alzheimer disease in participants who were severely 25(OH)D deficient and deficient compared to participants with sufficient concentrations were 2.22 (95% CI: 1.02–4.83) and 1.69 (95% CI: 1.06–2.69). In multivariate adjusted penalized smoothing spline plots, the risk of all-cause dementia and Alzheimer disease markedly increased below a threshold of 50 nmol/L.

Conclusion: Our results confirm that vitamin D deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer disease. This adds to the ongoing debate about the role of vitamin D in nonskeletal conditions.

Magnesium-l-Threonate & Alzheimer's Disease

- A Breakthrough Form of Magnesium
  - Better Function of Memory-Forming Synaptic Connections
  - Improvement in Spatial Short-Term Memory
  - Enhanced Spatial Long-Term Memory
  - Better Recall
  - Increased Brain Cell Signaling
  - Higher Memory- Forming Synaptic Plasticity and Density

Life Extension Magazine February 2012

Omega-3 & Alzheimer's Disease

Omega-3 fatty acids, energy substrates, and brain function during aging

Erika Freemantle[a], Milène Vandal[a], et. al Prostaglandins, Leukotrienes and Essential Fatty Acids
Volume 75, Issue 3, September 2006, Pages 213–220

Abstract

The maintenance of optimal cognitive function is a central feature of healthy aging. Impairment in brain glucose uptake is common in aging associated cognitive deterioration, but little is known of how this problem arises or whether it can be corrected or bypassed. Several aspects of the challenge to providing the brain with an adequate supply of fuel during aging seem to relate to omega-3 fatty acids. For instance, low intake of omega-3 fatty acids, especially docosahexaenoic acid (DHA), is becoming increasingly associated with several forms of cognitive decline in the elderly, particularly Alzheimer's disease. Brain DHA level seems to be an important regulator of brain glucose uptake, possibly by affecting the activity of some but not all the glucose transporters. DHA synthesis from either α-linolenic acid (ALA) or eicosapentaenoic acid (EPA) is very low in humans begging the question of whether these DHA precursors are likely to be helpful in maintaining cognition during aging. We speculate that ALA and EPA may well have useful supporting roles in maintaining brain function during aging but not by their conversion to DHA. ALA is an efficient ketogenic fatty acid, while EPA promotes fatty acid oxidation. By helping to produce ketone bodies, the effects of ALA and EPA could well be useful in strategies intended to use ketones to bypass problems of impaired glucose access to the brain during aging. Hence, it may be time to consider whether the main omega-3 fatty acids have distinct but complementary roles in brain function.

Iodine & Alzheimer's Disease

The Journal of Orthomolecular Medicine Vol. 14, 3rd Quarter 1999
Article

Parkinson's Disease, Multiple Sclerosis and Amyotrophic Lateral Sclerosis: The Iodine-Dopachrome-Glutamate Hypothesis Harold D. Foster, Ph.D.

Abstract

Background. *Globally, Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis mortalities tends to increase with latitude. These disorders also display a north-south gradient in the coterminous United States. This spatial distribution suggests their etiologies are significantly influenced by one or more geographical variables.*

Methods. *Pearson's correlation was used to compare mortalities, at the state scale, in the United States, from these three neurologic disorders and the spatial patterns of 81 other diseases and 219 environmental variables.*

Results. *The resulting correlations suggest that mortality from Parkinsonism, multiple sclerosis and amyotrophic lateral sclerosis occurs most often in recently glaciated, iodine deficient regions, that were formerly marked by elevated goiter prevalence.*

Conclusions. *Long-term iodine deficiency appears linked to abnormalities in the dopaminergic system that include an increased number of dopamine receptors. It is argued that this raises susceptibility to dopamine oxidation which, in turn, causes deficiencies of the antioxidant enzymes Cu/Zn superoxide dismutase, glutathione peroxidase and catalase. Dopamine deficiency also leads to elevated cytotoxic glutamate levels. Implications of the iodine-dopachrome-glutamate hypothesis, for treatment of these three neurologic disorders, are then discussed. Possible interventions include the use of levodopa, vitamin B3, Coenzyme Q10, various antioxidants, amino acids, iodine and glutamate antagonists.*

"The current author was not the first to recognize a spatial association between amyotrophic lateral sclerosis and goiter. Gajdusek and Salazar[21] noted that in south west New Guinea, amyotrophic lateral sclerosis, endemic goiter and cretinism all had analogous spatial distributions. To test the possibility of a relationship between amyotrophic lateral sclerosis and iodine deficiency further, Snow[9] collected questionnaire data from 50 British Columbian amyotrophic lateral sclerosis patients and a similar number of gender and age matched controls. He concluded that the risk of developing amyotrophic lateral sclerosis was significantly increased ($p=0.001$, $rr=3.807$) when blood relatives of patients had been afflicted by those diseases that Foster[22] had claimed were linked to iodine deficiency, namely multiple sclerosis, goiter, Alzheimer's disease, Parkinson's disease and cancers of the central nervous system and thyroid."

Gerovital GH3 & Alzheimer's

"Also influenced are a series of ailments affecting children and young people: post-encephalitic disturbances with children, mental retardation, arrested growth or intellectual development. With adults, improvement was obtained with Alzheimer's disease, senile dementia, multiple sclerosis. The treatment slows down the aging process and helps the regeneration process."

Interview with Ana Aslan, MD, Romania

Autoimmunity & Alzheimer's Disease

Med Hypotheses. 2005;64(3):458-63.

Add Alzheimer's disease to the list of autoimmune diseases. D'Andrea MR[1].

Abstract

A sole pathological event leading to Alzheimer's disease (AD) remains undiscovered in spite of decades of costly research. In fact, it is more probable that the causes of AD are the result of a myriad of intertwining pathologies. However, hope remains that a single awry event could lead to the many pathological events observed in AD brain tissues thereby creating the presentation of simultaneous pathologies. Age-related vascular diseases, which include an impaired blood-brain barrier (BBB), are a common denominator associated with various degrees of dementia, including AD. Recently, a key finding not only demonstrated the anomalous presence of immunoglobulin (Ig) detection in the brain parenchyma of AD tissues but, most importantly, specific neurons that showed degenerative, apoptotic features contained these vascular-derived antibodies. In addition, subsequent studies detected classical complement components, C1q and C5b-9, in these Ig-positive neurons, which also were spatially more associated with reactive microglia over the Ig-negative neurons. Thus, it is possible that the mere presence of anti-neuronal autoantibodies in the serum, whose importance had been previously dismissed, may be without pathological consequence until there is a BBB dysfunction to allow the deleterious effects of these autoantibodies access on their targets. Hence, these observations suggest autoimmunity-induced cell death in AD.

A Place for MODUCARE in the Slap-It-Silly Approach? Beck thinks so!

Moducare® taken orally at 3 capsules per day (each capsule contains 20.2 mg sterols/sterolins) restores weakened or reduced T cell activity in a balanced proportion of TH1 and TH2 cells. This enables the immune system to effectively counteract viral diseases (common cold, hepatitis, HIV, etc.) and various microbial diseases (tuberculosis, etc.). Moducare® also corrects a variety of autoimmune conditions (e.g. rheumatoid arthritis) usually arising from an excess secretion of inflammatory factors. However, Moducare® is not a drug: it does not interfere with any metabolic processes of either the patient or an infecting agent but it is rather a catalyst or messenger initiating a correction of existing immune system imbalances or maintaining adequate existing balances. It thereby helps an individual to maintain good health or fight a disease effectively. The use of Moducare® is ideal in conjunction with drug treatments.

Wrapping Up!

I have so much more to say regarding both topics here; **Cancer** & **Alzheimer's disease**. The highlights in this particular presentation are used primarily as examples of epigenetics – how we can alter the expression of our genes through changes we make in lifestyle, diet, hormones, nutrients, and more.

Epigenetics is a new, exciting and very promising frontier! You have so much more control than you know or even your doctor knows. ***"Knowledge is power"*** - Embrace it and use it, starting today!