Some reports looking at choline, fish oil, antioxidants and other in Trisomy 13

Cathy Breedon


Fish oil improves gene targets of Down syndrome in C57BL and BALB/c mice.

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We have considered a novel gene targeting approach for treating pathologies and conditions whose genetic bases are defined using diet and nutrition. One such condition is Down syndrome, which is linked to overexpression of RCAN1 on human chromosome 21 for some phenotypes. We\textit{ hypothesize that a decrease in RCAN1 expression with dietary supplements in individuals with Down syndrome represents a potential treatment.} Toward this, we used in vivo studies and bioinformatic analysis to identify potential healthy dietary RCAN1 expression modulators. We observed Rcan1 isoform 1 (Rcan1-1) protein reduction in mice pup hippocampus after a 4-week curcumin and fish oil supplementation, with only fish oil reduction being statistically significant. Focusing on fish oil, we observed a 17\% Rcan1-1 messenger RNA (mRNA) and 19\% Rcan1-1 protein reduction in BALB/c mice after 5 weeks of fish oil supplementation. Fish oil supplementation starting at conception and in a different mouse strain (C57BL) led to a 27\% reduction in hippocampal Rcan1-1 mRNA and a 34\% reduction in spleen Rcan1-1 mRNA at 6 weeks of age. Hippocampal protein results revealed a modest 11\% reduction in RCAN1-1, suggesting translational compensation. Bioinformatic mining of human fish oil studies also revealed reduced RCAN1 mRNA expression, consistent with the above studies. These results suggest the potential use of fish oil in treating Down syndrome and support our strategy of using select healthy dietary agents to treat genetically defined pathologies, an approach that we believe is simple, healthy, and cost-effective.


Maternal choline supplementation differentially alters the basal forebrain cholinergic system of young-adult Ts65Dn and disomic mice.

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Down syndrome (DS), trisomy 21, is a multifaceted condition marked by intellectual disability and early presentation of Alzheimer's disease (AD) neuropathological lesions including degeneration of the basal forebrain cholinergic neuron (BFCN) system. Although DS is diagnosable during gestation, there is no treatment option for expectant mothers or DS individuals. Using the Ts65Dn mouse model of DS that displays age-related degeneration of the BFCN system, we investigated the effects of maternal choline supplementation on the BFCN system in adult Ts65Dn mice and disomic (2N) littermates at 4.3-7.5 months of age. Ts65Dn dams were maintained on a choline-supplemented diet (5.1 g/kg choline chloride) or a control,
unsupplemented diet with adequate amounts of choline (1 g/kg choline chloride) from conception until weaning of offspring; post weaning, offspring were fed the control diet. Mice were transcardially perfused with paraformaldehyde, and brains were sectioned and immunolabeled for choline acetyltransferase (ChAT) or p75-neurotrophin receptor (p75(NTR)). BFCN number and size, the area of the regions, and the intensity of hippocampal labeling were determined. Ts65Dn-unsupplemented mice displayed region- and immunolabel-dependent increased BFCN number, larger areas, smaller BFCNs, and overall increased hippocampal ChAT intensity compared with 2N unsupplemented mice. These effects were partially normalized by maternal choline supplementation. Taken together, the results suggest a developmental imbalance in the Ts65Dn BFCN system. Early maternal-diet choline supplementation attenuates some of the genotype-dependent alterations in the BFCN system, suggesting this naturally occurring nutrient as a treatment option for pregnant mothers with knowledge that their offspring is trisomy 21.


Maternal choline supplementation improves spatial mapping and increases basal forebrain cholinergic neuron number and size in aged Ts65Dn mice.

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Down syndrome (DS) is marked by intellectual disability (ID) and early-onset of Alzheimer's disease (AD) neuropathology, including basal forebrain cholinergic neuron (BFCN) degeneration. The present study tested the hypothesis that maternal choline supplementation (MCS) improves spatial mapping and protects against BFCN degeneration in the Ts65Dn mouse model of DS and AD. During pregnancy and lactation, dams were assigned to either a choline sufficient (1.1g/kg choline chloride) or choline supplemented (5.0g/kg choline chloride) diet. Between 13 and 17 months of age, offspring were tested in the radial arm water maze (RAWM) to examine spatial mapping followed by unbiased quantitative morphometry of BFCNs. Spatial mapping was significantly impaired in unsupplemented Ts65Dn mice relative to normal disomic (2N) littermates. Additionally, a significantly lower number and density of medial septum (MS) hippocampal projection BFCNs was also found in unsupplemented Ts65Dn mice. Notably, MCS significantly improved spatial mapping and increased number, density, and size of MS BFCNs in Ts65Dn offspring. Moreover, the density and number of MS BFCNs correlated significantly with spatial memory proficiency, providing support for a functional relationship between these behavioral and morphometric effects of MCS for trisomic offspring. Thus, increasing maternal choline intake during pregnancy may represent a safe and effective treatment approach for expectant mothers carrying a DS fetus, as well as a possible means of BFCN neuroprotection during aging for the population at large.
Perinatal choline supplementation improves cognitive functioning and emotion regulation in the Ts65Dn mouse model of Down syndrome.

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In addition to mental retardation, individuals with Down syndrome (DS) also develop the neuropathological changes typical of Alzheimer's disease (AD) and the majority of these individuals exhibit dementia. The Ts65Dn mouse model of DS exhibits key features of these disorders, including early degeneration of cholinergic basal forebrain (CBF) neurons and impairments in functions dependent on the two CBF projection systems; namely, attention and explicit memory. \textbf{Herein, we demonstrate that supplementing the maternal diet with excess choline during pregnancy and lactation dramatically improved attentional function of the adult trisomic offspring.} Specifically, the adult offspring of choline-supplemented Ts65Dn dams performed significantly better than unsupplemented Ts65Dn mice on a series of 5 visual attention tasks, and in fact, on some tasks did not differ from the normosomic (2N) controls. A second area of dysfunction in the trisomic animals, heightened reactivity to committing an error, was partially normalized by the early choline supplementation. The 2N littermates also benefited from increased maternal choline intake on 1 attention task. \textbf{These findings collectively suggest that perinatal choline supplementation might significantly lessen cognitive dysfunction in DS and reduce cognitive decline in related neurodegenerative disorders such as AD.}

Erythrocyte phospholipid molecular species and fatty acids of Down syndrome children compared with non-affected siblings.

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The majority of children with Down syndrome (DS) develop Alzheimer's disease (AD) at an early age. Although long-chain n-3 fatty acids (FA) are protective of neurodegeneration, little is known about the FA status in DS. In the present study, we aimed to investigate whether children with DS presented altered plasma and erythrocyte membrane phospholipids (PL) FA composition, when compared with their non-affected siblings. Venous blood samples were analysed for plasma and erythrocyte membrane FA composition by TLC followed by GC techniques. Lipid molecular species were determined by electrospray ionisation/tandem MS (ESI-MS/MS). FA analysis measured by standard GC showed an increased concentration of MUFA and a decreased concentration of plasmalogens in major PL fractions, but there were no differences in the concentrations of arachidonic acid or DHA. However, as identified by ESI-MS/MS, children
with DS had increased levels of the following erythrocyte PL molecular species: 16:0-16:0, 16:0-18:1 and 16:0-18:2n-6, with reduced levels of 16:0-20:4n-6 species. Children with DS presented significantly higher levels of MUFA in both plasma and erythrocyte membrane, as well as higher levels of saturated and monounsaturated molecular species. Of interest was the almost double proportion of 16:0-18:2n-6 and nearly half the proportion of 16:0-20:4n-6 of choline phosphoacylglycerol species in children with DS compared with their non-affected siblings. These significant differences were only revealed by ESI-MS/MS and were not observed in the GC analysis. Further investigations are needed to explore molecular mechanisms and to test the association between the pathophysiology of DS and the risk of AD.

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HNE-modified proteins in Down syndrome: Involvement in development of Alzheimer disease neuropathology.

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Down syndrome (DS), trisomy of chromosome 21, is the most common genetic form of intellectual disability. The neuropathology of DS involves multiple molecular mechanisms, similar to AD, including the deposition of beta-amyloid (Aβ) into senile plaques and tau hyperphosphorylation in neurofibrillary tangles. Interestingly, many genes encoded by chromosome 21, in addition to being primarily linked to amyloid-beta peptide (Aβ) pathology, are responsible for increased oxidative stress (OS) conditions that also result as a consequence of reduced antioxidant system efficiency. However, redox homeostasis is disturbed by overproduction of Aβ, which accumulates into plaques across the lifespan in DS as well as in AD, thus generating a vicious cycle that amplifies OS-induced intracellular changes. The present review describes the current literature that demonstrates the accumulation of oxidative damage in DS with a focus on the lipid peroxidation by-product, 4-hydroxy-2-nonenal (HNE). HNE reacts with proteins and can irreversibly impair their functions. We suggest that among different post-translational modifications, HNE-adducts on proteins accumulate in DS brain and play a crucial role in causing the impairment of glucose metabolism, neuronal trafficking, protein quality control and antioxidant response. We hypothesize that dysfunction of these specific pathways contribute to accelerated neurodegeneration associated with AD neuropathology.


Redox proteomics analysis of HNE-modified proteins in Down syndrome brain: clues for understanding the development of Alzheimer disease.
Down syndrome (DS) is the most common genetic cause of intellectual disability, due to partial or complete triplication of chromosome 21. DS subjects are characterized by a number of abnormalities including premature aging and development of Alzheimer disease (AD) neuropathology after approximately 40 years of age. Several studies show that oxidative stress plays a crucial role in the development of neurodegeneration in the DS population. Increased lipid peroxidation is one of the main events causing redox imbalance within cells through the formation of toxic aldehydes that easily react with DNA, lipids, and proteins. In this study we used a redox proteomics approach to identify specific targets of 4-hydroxynonenal modifications in the frontal cortex from DS cases with and without AD pathology. We suggest that a group of identified proteins followed a specific pattern of oxidation in DS vs young controls, probably indicating characteristic features of the DS phenotype; a second group of identified proteins showed increased oxidation in DS/AD vs DS, thus possibly playing a role in the development of AD. The third group of comparison, DS/AD vs old controls, identified proteins that may be considered specific markers of AD pathology. All the identified proteins are involved in important biological functions including intracellular quality control systems, cytoskeleton network, energy metabolism, and antioxidant response. Our results demonstrate that oxidative damage is an early event in DS, as well as dysfunctions of protein-degradation systems and cellular protective pathways, suggesting that DS subjects are more vulnerable to oxidative damage accumulation that might contribute to AD development. Further, considering that the majority of proteins have been already demonstrated to be oxidized in AD brain, our results strongly support similarities with AD in DS.


An investigation of the molecular mechanisms engaged before and after the development of Alzheimer disease neuropathology in Down syndrome: a proteomics approach.

Down syndrome (DS) is one of the most common causes of intellectual disability, owing to trisomy of all or part of chromosome 21. DS is also associated with the development of Alzheimer disease (AD) neuropathology after the age of 40 years. To better clarify the cellular and metabolic pathways that could contribute to the differences in DS brain, in particular those involved in the onset of neurodegeneration, we analyzed the frontal cortex of DS subjects with or without significant AD pathology in comparison with age-matched controls, using a proteomics approach. Proteomics represents an advantageous tool to investigate the molecular mechanisms underlying the disease. From these analyses, we investigated the effects that age, DS, and AD neuropathology could have on protein expression levels. Our results show overlapping and independent molecular pathways (including energy metabolism, oxidative damage, protein synthesis, and autophagy) contributing to DS, to aging, and to the presence of AD pathology in DS. Investigation of pathomechanisms involved in DS with AD may provide putative targets for therapeutic approaches to slow the development of AD.


Association between frontal cortex oxidative damage and beta-amyloid as a function of age in Down syndrome.

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Down syndrome (DS) is the most common genetic cause of intellectual disability in children, and the number of adults with DS reaching old age is increasing. By the age of 40 years, virtually all people with DS have sufficient neuropathology for a postmortem diagnosis of Alzheimer disease (AD). Trisomy 21 in DS leads to an overexpression of many proteins, of which at least two are involved in oxidative stress and AD: superoxide dismutase 1 (SOD1) and amyloid precursor protein (APP). In this study, we tested the hypothesis that DS brains with neuropathological hallmarks of AD have more oxidative and nitrosative stress than those with DS but without significant AD pathology, as compared with similarly aged-matched non-DS controls. The frontal cortex was examined in 70 autopsy cases (n=29 control and n=41 DS). By ELISA, we quantified soluble and insoluble Aβ40 and Aβ42, as well as oligomers. Oxidative and nitrosative stress levels (protein carbonyls, 4-hydroxy-2-trans-nonenal (HNE)-bound proteins, and 3-nitrotyrosine) were measured by slot-blot. We found that soluble and insoluble amyloid beta peptide (Aβ) and oligomers increase as a function of age in DS frontal cortex. Of the oxidative stress markers, HNE-bound proteins were increased overall in DS. Protein carbonyls were correlated with Aβ40 levels. These results suggest that oxidative damage, but not nitrosative stress, may contribute to the onset and progression of AD pathogenesis in DS. Conceivably, treatment with antioxidants may provide a point of intervention to slow pathological alterations in DS.


Oxidative modification of lipoic acid by HNE in Alzheimer disease brain.

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Alzheimer disease (AD) is an age-related neurodegenerative disease characterized by the presence of three pathological hallmarks: synapse loss, extracellular senile plaques (SP) and intracellular neurofibrillary tangles (NFTs). The major component of SP is amyloid β-peptide (Aβ), which has been shown to induce oxidative stress. The AD brain shows increased levels of lipid peroxidation products, including 4-hydroxy-2-nonenal (HNE). HNE can react covalently with Cys, His, or Lys residues on proteins, altering structure and function of the latter. In the present study we measured the levels of the HNE-modified lipoic acid in brain of subjects with AD and age-matched controls. Lipoic acid is a key co-factor for a number of proteins including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, key complexes for cellular energetics. We observed a significant decrease in the levels of HNE-lipoic acid in the AD brain compared to that of age-matched controls. To investigate this phenomenon further, the levels and activity of lipoamide dehydrogenase (LADH) were measured in AD and control brains. Additionally, LADH activities were measured after in-vitro HNE-treatment to mice brains. Both LADH levels and activities were found to be significantly reduced in AD brain compared to age-matched control. HNE-treatment also reduced the LADH activity in mice brain. These data are consistent with a two-hit hypothesis of AD: oxidative stress leads to lipid peroxidation that, in turn, causes oxidative dysfunction of key energy-related complexes in mitochondria, triggering neurodegeneration. This study is consonant with the notion that lipoic acid supplementation could be a potential treatment for the observed loss of cellular energetics in AD and potentiate the antioxidant defense system to prevent or delay the oxidative stress in and progression of this devastating dementing disorder.


Aging in Down Syndrome and the Development of Alzheimer's Disease Neuropathology.

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Chromosome 21, triplicated in Down Syndrome, contains several genes that are thought to play a critical role in the development of AD neuropathology. The overexpression of the gene for the amyloid precursor protein (APP), on chromosome 21, leads to early onset beta-amyloid (Aβ) plaques in DS. In addition to Aβ accumulation, middle-aged people with DS develop neurofibrillary tangles, cerebrovascular pathology, white matter pathology, oxidative damage, neuroinflammation and neuron loss. There is also evidence of potential compensatory responses in DS that benefit the brain and delay the onset of dementia after there is sufficient neuropathology for a diagnosis of AD. This review describes some of the existing literature and also highlights gaps in our knowledge regarding AD neuropathology in DS. It will be critical in the future to develop networked brain banks with standardized collection procedures to fully characterize the regional and temporal pathological events associated with aging in DS. As more information is acquired regarding AD evolution in DS, there will be opportunities to develop interventions that are age-appropriate to delay AD in DS.
Chronic Melatonin Administration Reduced Oxidative Damage and Cellular Senescence in the Hippocampus of a Mouse Model of Down Syndrome.

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Previous studies have demonstrated that melatonin administration improves spatial learning and memory and hippocampal long-term potentiation in the adult Ts65Dn (TS) mouse, a model of Down syndrome (DS). This functional benefit of melatonin was accompanied by protection from cholinergic neurodegeneration and the attenuation of several hippocampal neuromorphological alterations in TS mice. Because oxidative stress contributes to the progression of cognitive deficits and neurodegeneration in DS, this study evaluates the antioxidant effects of melatonin in the brains of TS mice. Melatonin was administered to TS and control mice from 6 to 12 months of age and its effects on the oxidative state and levels of cellular senescence were evaluated. Melatonin treatment induced antioxidant and antiaging effects in the hippocampus of adult TS mice. Although melatonin administration did not regulate the activities of the main antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase) in the cortex or hippocampus, melatonin decreased protein and lipid oxidative damage by reducing the thiobarbituric acid reactive substances (TBARS) and protein carbonyls (PC) levels in the TS hippocampus due to its ability to act as a free radical scavenger. Consistent with this reduction in oxidative stress, melatonin also decreased hippocampal senescence in TS animals by normalizing the density of senescence-associated β-galactosidase positive cells in the hippocampus. These results showed that this treatment attenuated the oxidative damage and cellular senescence in the brain of TS mice and support the use of melatonin as a potential therapeutic agent for age-related cognitive deficits and neurodegeneration in adults with DS.

Chronic melatonin treatment rescues electrophysiological and neuromorphological deficits in a mouse model of Down syndrome.

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The Ts65Dn mouse (TS), the most commonly used model of Down syndrome (DS), exhibits several key phenotypic characteristics of this condition. In particular, these animals present hypocellularity in different areas of their CNS due to impaired neurogenesis and have alterations in synaptic plasticity that compromise their cognitive performance. In addition, increases in oxidative stress during adulthood contribute to the age-related progression of cognitive and neuronal deterioration. We have previously demonstrated that chronic melatonin treatment improves learning and memory and reduces cholinergic neurodegeneration in TS mice.
However, the molecular and physiological mechanisms that mediate these beneficial cognitive effects are not yet fully understood. In this study, we analyzed the effects of chronic melatonin treatment on different mechanisms that have been proposed to underlie the cognitive impairments observed in TS mice: reduced neurogenesis, altered synaptic plasticity, enhanced synaptic inhibition and oxidative damage. Chronic melatonin treatment rescued both impaired adult neurogenesis and the decreased density of hippocampal granule cells in trisomic mice. In addition, melatonin administration reduced synaptic inhibition in TS mice by increasing the density and/or activity of glutamatergic synapses in the hippocampus. These effects were accompanied by a full recovery of hippocampal LTP in trisomic animals. Finally, melatonin treatment decreased the levels of lipid peroxidation in the hippocampus of TS mice. These results indicate that the cognitive-enhancing effects of melatonin in adult TS mice could be mediated by the normalization of their electrophysiological and neuromorphological abnormalities and suggest that melatonin represents an effective treatment in retarding the progression of DS neuropathology.


Is Serum Antioxidant Status Impaired in Pregnant Women at High Risk for Carrying a Down Syndrome-affected Fetus?

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Objective: The present study aims to establish the oxidant/antioxidant status in serum samples from pregnant women above the threshold for Down syndrome (DS) risk according to the quadruple test. Methods: Thirty maternal serum samples that were above threshold for DS risk (study group) were chosen from pregnant women whose quadruple tests were studied at Ankara University İbni Sina Hospital Central Laboratory. They have been matched with control group consisting of 30 pregnant women whose DS risk were below threshold. Malondialdehyde (MDA) level, glutathione peroxidase (GSH-Px) and non-enzymatic superoxide radical scavenger activities (NSSA) were detected in all serum samples. Results: It was found that NSSA was significantly decreased in the study group as compared to the control group (p = 0.006). Malondialdehyde levels had a tendency to increase with gestational week in both groups (p = 0.042 in the study group and p < 0.001 in the control group). Conclusion: There is a significant decrease in non-enzymatic antioxidant capacity in pregnant women that were above the threshold for DS risk as compared to the control group. In the context of these results, dietary antioxidant supplementation might be a useful approach during early gestation especially around the time of conception possibly to prevent bearing a DS fetus.


Antioxidants in Down syndrome.

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Individuals with Down syndrome (DS) have high levels of oxidative stress throughout the lifespan. Mouse models of DS share some structural and functional abnormalities that parallel findings seen in the human phenotype. Several of the mouse models show evidence of cellular oxidative stress and have provided a platform for antioxidant intervention. Genes that are overexpressed on chromosome 21 are associated with oxidative stress and neuronal apoptosis. The lack of balance in the metabolism of free radicals generated during processes related to oxidative stress may have a direct role in producing the neuropathology of DS including the tendency to Alzheimer disease (AD). Mitochondria are often a target for oxidative stress and are considered to be a trigger for the onset of the AD process in DS. Biomarkers for oxidative stress have been described in DS and in AD in the general population. However, intervention trials using standard antioxidant supplements or diets have failed to produce uniform therapeutic effect. This chapter will examine the biological role of oxidative stress in DS and its relationship to abnormalities in both development and aging within the disorder. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.


**Oxidative stress and Down syndrome. Do antioxidants play a role in therapy?**

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Oxidative stress is a phenomenon associated with imbalance between production of free radicals and reactive metabolites (e.g. superoxide and hydrogen peroxide) and the antioxidant defences. Oxidative stress in individuals with Down syndrome (DS) has been associated with trisomy of the 21st chromosome resulting in DS phenotype as well as with various morphological abnormalities, immune disorders, intellectual disability, premature aging and other biochemical abnormalities. Trisomy 21 in patients with DS results in increased activity of an important antioxidant enzyme Cu/Zn superoxide dismutase (SOD) which gene is located on the 21st chromosome along with other proteins such as transcription factor Ets-2, stress inducing factors (DSCR1) and precursor of beta-amyloid protein responsible for the formation of amyloid plaques in Alzheimer disease. Mentioned proteins are involved in the management of mitochondrial function, thereby promoting mitochondrial theory of aging also in people with DS. In defence against toxic effects of free radicals and their metabolites organism has built antioxidant defence systems. Their lack and reduced function increases oxidative stress resulting in disruption of the structure of important biomolecules, such as proteins, lipids and nucleic acids. This leads to their dysfunctions affecting pathophysiology of organs and the whole organism. This paper examines the impact of antioxidant interventions as well as positive effect of physical exercise on cognitive and learning disabilities of individuals with DS. Potential therapeutic targets on the molecular level (oxidative stress markers, gene for DYRK1A, neutrophic factor BDNF) after intervention of natural polyphenols are also discussed.
α-Tocopherol supplementation reduces biomarkers of oxidative stress in children with Down syndrome: a randomized controlled trial.

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BACKGROUND: Down syndrome (DS) is the most common human chromosomal abnormality. It is characterized by mental retardation and several metabolic disturbances, including elevated oxidative stress, which may be causally linked. Treatment with dietary antioxidants has been suggested as a potential method to alleviate the oxidative damage and retardation of DS patients, but prior supplementation work has been equivocal. AIM: To evaluate the effects of supplementation with antioxidants α-tocopherol and α-lipoic acid (ALA) on oxidative stress biomarkers in DS children.METHODS: Ninety-three DS children aged 7-15 years from both sexes were randomly allocated to three groups: α-tocopherol (400 IU/day), ALA (100 mg/day) and placebo. The intervention period was 4 months. A healthy control group consisted 26 non-DS siblings. Serum thiobarbituric acid reactive substances (TBARS) and urinary 8-hydroxy-2'-deoxyguanosine (8OHdG) were used as biomarkers of oxidative stress. RESULTS: DS children had greater levels of baseline oxidative stress than their siblings. Moreover, males had greater levels of 8OHdG than females (P<0.001) but there was no significant association between age and biomarkers of oxidative stress. Serum levels of TBARS did not change significantly over time, or relative to placebo. Although urinary 8OHdG concentrations decreased significantly in both α-tocopherol and ALA, groups compared with the baseline levels (P<0.001), mean final levels of urinary 8OHdG concentrations differed significantly only between α-tocopherol and placebo groups (P<0.01). CONCLUSIONS: α-Tocopherol supplementation of the diets of DS children may attenuate oxidative stress at the DNA level.

Antioxidant intervention attenuates oxidative stress in children and teenagers with Down syndrome.

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We previously demonstrated that systemic oxidative stress is present in Down syndrome (DS) patients. In the present study we investigated the antioxidant status in the peripheral blood of DS children and teenagers comparing such status before and after an antioxidant supplementation. Oxidative stress biomarkers were evaluated in the blood of DS patients (n=21) before and after a daily antioxidant intervention (vitamin E 400mg, C 500 mg) during 6 months. Healthy children (n=18) without DS were recruited as control group. The activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), gamma-glutamyltransferase (GGT), glucose-6-phosphate
dehydrogenase (G6PD) and myeloperoxidase (MPO), as well as the contents of reduced glutathione (GSH), uric acid, vitamin E, thiobarbituric acid reactive substances (TBARS), and protein carbonyls (PC) were measured. Before the antioxidant therapy, DS patients presented decreased GST activity and GSH depletion; elevated SOD, CAT, GR, GGT and MPO activities; increased uric acid levels; while GPx and G6PD activities as well as vitamin E and TBARS levels were unaltered. After the antioxidant supplementation, SOD, CAT, GPx, GR, GGT and MPO activities were downregulated, while TBARS contents were strongly decreased in DS. Also, the antioxidant therapy did not change G6PD and GST activities as well as uric acid and PC levels, while it significantly increased GSH and vitamin E levels in DS patients. Our results clearly demonstrate that the antioxidant intervention with vitamins E and C attenuated the systemic oxidative damage present in DS patients.


Persistence of the benefit of an antioxidant therapy in children and teenagers with Down syndrome.

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This study examined the effect of an antioxidant intervention in biomarkers of inflammation and oxidative stress (OS) in the blood of Down syndrome (DS) children and teenagers during four different stages. A control group was composed by healthy children (n=18), assessed once, and a Down group composed by DS patients (n=21) assessed at the basal period (t0), as well as after 6 months of antioxidant supplementation (t1), after 12 months (after interruption of the antioxidant intervention for 6 months) (t2), and again after further 6 months of antioxidant supplementation (t3). Biomarkers of inflammation (myeloperoxidase activity - MPO and levels of IL-1β and TNF-α) and OS (thiobarbituric acid reactive substances - TBARS, protein carbonyls - PC), reduced glutathione (GSH), uric acid (UA) and vitamin E levels, as well as antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and gamma-glutamyltransferase (GGT) activities, were measured after each period. After the antioxidant supplementation, the activities of SOD, CAT, GPx, GR, GGT and MPO were downregulated, while TBARS contents were strongly decreased, the contents of GSH and vitamin E were significantly increased, and no changes in G6PD and GST activity as well as in UA and PC levels were detected. After the interruption of the antioxidant therapy for 6 months, DS patients showed elevated GPx and GGT activities and also elevated UA and TBARS levels. No changes in SOD, CAT, GR, GST, G6PD and MPO activities as well as in GSH, vitamin E, PC, TNF-α and IL-1β levels were detected. The results showed that the antioxidant intervention persistently attenuated the systemic oxidative damage in DS patients even after a relatively long period of cessation of the antioxidant intervention.
Plasma antioxidant enzymes and lipoperoxidation status in children with Down syndrome.

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OBJECTIVES: Oxidative stress (OS) may play a critical role in cell aging and neurologic disorders that are often seen in Down syndrome (DS) patients. The aim of this study was to determine the antioxidant enzyme level and lipoperoxidation status in blood from DS children.

DESIGN AND METHODS: In a cross-sectional study, we recruited a total of 36 DS children and 40 healthy controls (HCs). All subjects were free of infection according to the C reactive protein (CRP) value and routine peripheral blood profile. The activities of total superoxide dismutases (SODs), extracellular glutathione peroxidase (GPx3), malondialdehyde (MDA) and nitric oxide synthase (NOS) concentrations in peripheral blood were measured by spectrophotometric methods. The relationship of SOD and GPx3 was analyzed in the two groups.

RESULTS: The two groups were similar with respect to age, gender and peripheral blood profiles. The total SOD activity was significantly increased, while the GPx3 activity was significantly reduced in the DS group compared to the HCs (p=0.000, p=0.033 respectively). The MDA level was higher in DS children (p=0.013). There was no significant difference in NOS between DS and HCs (p=0.708). A significant negative correlation between GPx3 and SOD activity was identified in DS (r=-0.14, p=0.018) but not in the HC group.

CONCLUSIONS: Abnormal redox metabolism takes place in DS individuals. Reducing GPx3 may be a compensatory mechanism of protection against intracellular OS. Moreover, monitoring of decreases in GPx3 activity may be a useful biomarker for evaluating OS in DS patients.

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Antioxidants and biomarkers of oxidative damage in the saliva of patients with Down's syndrome.

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BACKGROUND: The aim of this study was to investigate enzymatic and non-enzymatic antioxidant systems and levels of biomarker levels of oxidative damage in the saliva of patients with Down's syndrome (DS).

METHODS: Saliva samples were collected from 30 patients with DS and control group (age: 14-24 years). Subsequently, the concentrations of superoxide dismutase, concentration of malondialdehyde, carbonylated proteins, uric acid, vitamin C and total protein, peroxidase activity and total antioxidant capacity were analyzed.

RESULTS: Patients with DS presented significantly higher concentrations of superoxide dismutase, higher
levels of malondialdehyde and salivary total protein content than controls (p<0.05). Conversely, no difference in carbonylated proteins or antioxidants (uric acid, vitamin C, peroxidase, and total antioxidant capacity) was observed between DS patients and controls (p>0.05). CONCLUSION: Patients with DS are more vulnerable to oxidative stress in saliva as indicated by the significant increase in malondialdehyde and superoxide dismutase concentrations found in this study.


Choline metabolic pathway gene polymorphisms and risk for Down syndrome: An association study in a population with folate-homocysteine metabolic impairment.

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BACKGROUND/OBJECTIVES: Choline is an essential nutrient involved in one-carbon metabolism, but its role in mechanisms underlying meiotic non-disjunction is poorly known. The relationship between folate-homocysteine metabolic pathway gene polymorphism and Down syndrome (DS) risk has been widely analyzed, but there are limited reports on its correlation with choline metabolism. In the present case-control association study, we investigated the relationship of three single-nucleotide polymorphisms (SNPs) (phosphatidylethanolamine N-methyltransferase (PEMT) rs12325817, choline dehydrogenase (CHDH) rs12676 and homocysteine methyltransferase (BHMT) rs3733890) of choline metabolism with risk for DS.

SUBJECT/METHODS: Genotyping of 228 mothers of a down syndrome child (DSM) and 200 control mothers (CMs) for all SNPs was performed by PCR coupled with restriction fragment length polymorphism method. RESULTS: A significantly increased risk for BHMT +742AA genotype with an odds ratio of 4.96 (95% confidence interval (CI): 1.66-14.88, P=0.0036) was observed. For PEMT rs12325817 and CHDH rs12676, no significant difference in allelic and genotypic frequencies was observed. In genotypic combination analysis considering PEMT -744GG/CHDH +432GG/BHMT +742GG as the reference combination, PEMT -744GC/CHDH +432GG/BHMT +742GG genotypic combination was significantly higher in DSM compared with that in CMs with an odds ratio of 2.061 (95% CI: 1.10-3.86, P=0.0342). We also observed an epistatic interaction between methylenetetrahydrofolate reductase (MTHFR) rs1801133 and choline metabolic pathway gene variants. CONCLUSIONS: Our findings indicate impaired choline metabolism showing a greater risk for DS, especially in a population associated with homocysteine-folate impairment. Further studies are required to confirm our findings.European Journal of Clinical Nutrition advance online publication, 28 September 2016;


Intracellular oxidant activity, antioxidant enzyme defense system, and cell senescence in fibroblasts with trisomy 21.
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Down's syndrome (DS) is characterized by a complex phenotype associated with chronic oxidative stress and mitochondrial dysfunction. Overexpression of genes on chromosome-21 is thought to underlie the pathogenesis of the major phenotypic features of DS, such as premature aging. Using cultured fibroblasts with trisomy 21 (T21F), this study aimed to ascertain whether an imbalance exists in activities, mRNA, and protein expression of the antioxidant enzymes SOD1, SOD2, glutathione-peroxidase, and catalase during the cell replication process in vitro. T21F had high SOD1 expression and activity which led to an interenzymatic imbalance in the antioxidant defense system, accentuated with replicative senescence. Intracellular ROS production and oxidized protein levels were significantly higher in T21F compared with control cells; furthermore, a significant decline in intracellular ATP content was detected in T21F. Cell senescence was found to appear prematurely in DS cells as shown by SA-β-Gal assay and p21 assessment, though not apoptosis, as neither p53 nor the proapoptotic proteins cytochrome c and caspase 9 were altered in T21F. These novel findings would point to a deleterious role of oxidatively modified molecules in early cell senescence of T21F, thereby linking replicative and stress-induced senescence in cultured cells to premature aging in DS.

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The contribution of the citrate pathway to oxidative stress in Down syndrome.
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Inflammatory conditions and oxidative stress have a crucial role in Down syndrome (DS). Emerging studies have also reported an altered lipid profile in the early stages of DS. Our previous works demonstrate that citrate pathway activation is required for oxygen radical production during inflammation. Here, we find up-regulation of the citrate pathway and down-regulation of carnitine/acylcarnitine carrier and carnitine palmitoyl-transferase 1 genes in cells from children with DS. Interestingly, when the citrate pathway is inhibited, we observe a reduction in oxygen radicals as well as in lipid peroxidation levels. Our preliminary findings provide evidence for a citrate pathway dysregulation, which could be related to some phenotypic traits of people with DS.


The effect of acetyl-L-carnitine administration on persons with Down syndrome.
Pueschel SM1.
Since previous investigations reported improvements in cognition of patients with dementia after acetyl-L-carnitine therapy and since there is an increased risk for persons with Down syndrome to develop Alzheimer disease, this study was designed to investigate the effect of acetyl-L-carnitine administration on neurological, intellectual, and social functions in adults with Down syndrome. In this double-blind study we enrolled 40 individuals with Down syndrome and administered acetyl-L-carnitine to the study group during a six months period. Specified examinations and psychological tests were given to persons in both the study and control groups at the start of the investigation and at 3, 6, and 9 months. A detailed analysis of the data revealed that acetyl-L-carnitine administration did not enhance central nervous system functions and that it did not benefit persons with Down syndrome.


Can cognitive deterioration associated with Down syndrome be reduced?
Thiel R¹, Fowkes SW.

Individuals with Down syndrome have signs of possible brain damage prior to birth. In addition to slowed and reduced mental development, they are much more likely to have cognitive deterioration and develop dementia at an earlier age than individuals without Down syndrome. Some of the cognitive impairments are likely due to post-natal hydrogen peroxide-mediated oxidative stress caused by overexpression of the superoxide dismutase (SOD-1) gene, which is located on the triplicated 21st chromosome and known to be 50% overexpressed. However, some of this disability may also be due to early accumulation of advanced protein glycation end-products, which may play an adverse role in prenatal and postnatal brain development. This paper suggests that essential nutrients such as folate, vitamin B6, vitamin C, vitamin E, selenium, and zinc, as well as alpha-lipoic acid and carnosine may possibly be partially preventive. Acetyl-L-carnitine, aminoguanidine, cysteine, and N-acetylcysteine are also discussed, but have possible safety concerns for this population. This paper hypothesizes that nutritional factors begun prenatally, in early infancy, or later may prevent or delay the onset of dementia in the Down syndrome population. Further examination of these data may provide insights into nutritional, metabolic and pharmacological treatments for dementias of many kinds. As the Down syndrome population may be the largest identifiable group at increased risk for developing dementia, clinical research to verify the possible validity of the prophylactic use of anti-glycation nutrients should be performed. Such research might also help those with glycation complications associated with diabetes or Alzheimer's.

Nutr Metab (Lond). 2012 Jan 5;9:1. d
γ-Tocotrienol does not substantially protect DS neurons from hydrogen peroxide-induced oxidative injury.

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BACKGROUND: Down syndrome (DS) neurons are more susceptible to oxidative stress and previous studies have shown that vitamin E was able to reduce oxidative stress and improve DS neurons' viability. Therefore, this study was done to investigate the protective role of γ-tocotrienol (γT3) in DS neurons from hydrogen peroxide (H2O2) -induced oxidative stress. The pro-apoptosis tendency of γT3 was compared to α-tocopherol (αT) in non-stress condition as well. METHODS: Primary culture of DS and euploid neurons were divided into six groups of treatment: control, H2O2, γT3 pre-treatment with H2O2, γT3 only, αT pre-treatment with H2O2 and αT only. The treatments were assessed by MTS assay and apoptosis assay by single-stranded DNA (ssDNA) apoptosis ELISA assay, Hoechst and Neu-N immunofluorescence staining. The cellular uptake of γT3 and αT was determined by HPLC while protein expressions were determined by Western blot. Comparison between groups was made by the Student's t test, one-way ANOVA and Bonferroni adjustment as well as two-way ANOVA for multiple comparisons. RESULTS: One day incubation of γT3 was able to reduced apoptosis of DS neurons by 10%, however γT3 was cytotoxic at longer incubation period (14 days) and at concentrations ≥ 100 μM. Pre-treatment of αT and γT3 only attenuate apoptosis and increase cell viability in H2O2-treated DS and euploid neurons by 10% in which the effects were minimal to maintain most of the DS cells' morphology. γT3 act as a free radical scavenger by reducing ROS generated by H2O2. In untreated controls, DS neurons showed lower Bcl-2/Bax ratio and p53 expression compared to normal neurons, while cPKC and PKC-δ expressions were higher in DS neurons. On the other hand, pre-treatment of γT3 in H2O2-treated DS neurons have reduced Bcl-2/Bax ratio, which was not shown in euploid neurons. This suggests that pre-treatment of γT3 did not promote DS cell survival. Meanwhile γT3 and αT treatments without H2O2 as well as pre-treatment of γT3 and αT induced changes in cPKC and PKC-δ expression in DS neurons suggesting interaction of γT3 and αT with PKC activity. CONCLUSION: Our study suggests that γT3 pre-treatment are not sufficient to protect DS neurons from H2O2-induced oxidative assault, instead induced the apoptosis process.

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Plant polyphenols as natural drugs for the management of Down syndrome and related disorders.

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Polyphenols are secondary metabolites of plants largely found in fruits, vegetables, cereals and beverages, and therefore represent important constituents of the human diet. Increasing studies have demonstrated the potential beneficial effects of polyphenols on human health. Extensive reviews have discussed the protective effects of polyphenols against a series of diseases such as cancer, cardio-vascular diseases, diabetes, and neurodegenerative disorders. Limited studies have investigated the potential therapeutic effects of these natural compounds on neurodevelopmental disorders associated with intellectual disability, such as Down syndrome (DS), for which mitochondrial dysfunctions and oxidative stress are hallmarks and contribute to the deleterious symptoms and cognitive decline. This review, starting from the structure, source, bioavailability and pharmacokinetics of relevant polyphenols, highlights recent studies on the effect and potential molecular mechanism(s) of action of the phenolic compounds epigallocatechin-3-gallate, resveratrol and hydroxytyrosol in restoring mitochondrial energy deficit and in reversing phenotypical alteration in DS. The clinical implications of plant polyphenol dietary supplements as therapeutic tools in managing DS and other intellectual disability-related diseases, is also discussed.


The polyphenols resveratrol and epigallocatechin-3-gallate restore the severe impairment of mitochondria in hippocampal progenitor cells from a Down syndrome mouse model.

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Mitochondrial dysfunctions critically impair nervous system development and are potentially involved in the pathogenesis of various neurodevelopmental disorders, including Down syndrome (DS), the most common genetic cause of intellectual disability. Previous studies from our group demonstrated impaired mitochondrial activity in peripheral cells from DS subjects and the efficacy of epigallocatechin-3-gallate (EGCG) - a natural polyphenol major component of green tea - to counteract the mitochondrial energy deficit. In this study, to gain insight into the possible role of mitochondria in DS intellectual disability, mitochondrial functions were analyzed in neural progenitor cells (NPCs) isolated from the hippocampus of Ts65Dn mice, a widely used model of DS which recapitulates many major brain structural and functional phenotypes of the syndrome, including impaired hippocampal neurogenesis. We found that, during NPC proliferation, mitochondrial bioenergetics and mitochondrial biogenic program were strongly compromised in Ts65Dn cells, but not associated with free radical accumulation. These data point to a central role of mitochondrial dysfunction as an inherent feature of DS and not as a consequence of cell oxidative stress. Further, we disclose that, besides EGCG, also the natural polyphenol resveratrol, which displays a neuroprotective action in various human diseases but never tested in DS, restores oxidative phosphorylation efficiency and mitochondrial biogenesis, and improves proliferation of NPCs. These effects were associated with the activation of PGC-1α/Sirt1/AMPK axis by both polyphenols. This research paves the way for using nutraceuticals as a potential therapeutic tool in preventing or managing some energy deficit-associated DS clinical manifestations.
OBJECTIVE: To determine whether vitamin E would slow the progression of cognitive deterioration and dementia in aging persons with Down syndrome (DS). METHODS: A randomized, double-blind controlled clinical trial was conducted at 21 clinical sites, and researchers trained in research procedures recruited adults with DS older than 50 years to participate. Participants were randomly assigned to receive 1,000 IU of vitamin E orally twice daily for 3 years or identical placebo. The primary outcome was change on the Brief Praxis Test (BPT). Secondary outcomes included incident dementia and measures of clinical global change, cognition, function, and behavior. RESULTS: A total of 337 individuals were randomized, 168 to vitamin E and 169 to placebo. Both groups demonstrated deterioration on the BPT with no difference between drug and placebo. At baseline, 26% were diagnosed with dementia and there was an overall rate of incident dementia of 11%/year with no difference between groups. There was no effect on the secondary outcome measures. Though numerically higher in the treatment group, there was no difference in the number of adverse events (p = 0.079) and deaths (p = 0.086) between groups. CONCLUSIONS: Vitamin E did not slow the progression of cognitive deterioration in older individuals with DS.CLASSIFICATION OF EVIDENCE: This
study provides Class II evidence that vitamin E does not significantly slow the progression of cognitive deterioration in aging persons with DS.

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Down syndrome--genetic and nutritional aspects of accompanying disorders.
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Down syndrome (DS) is one of the more commonly occurring genetic disorders, where mental retardation is combined with nutritional diseases. It is caused by having a third copy of chromosome 21, and there exist 3 forms; Simple Trisomy 21, Translocation Trisomy and Mosaic Trisomy. Symptoms include intellectual disability/mental retardation, early onset of Alzheimer's disease and the appearance of various phenotypic features such as narrow slanted eyes, flat nose and short stature. In addition, there are other health problems throughout the body, consisting in part of cardiac defects and thyroid function abnormalities along with nutritional disorders (ie. overweight, obesity, hypercholesterolemia and deficiencies of vitamins and minerals). Those suffering DS have widespread body frame abnormalities and impaired brain development and function; the latter leading to impaired intellectual development. Many studies indicate excessive or deficient nutrient uptakes associated with making inappropriate foodstuff choices, food intolerance, (eg. celiac disease) or malabsorption. DS persons with overweight or obesity are linked with a slow metabolic rate, abnormal blood leptin concentrations and exhibit low levels of physical activity. Vitamin B group deficiencies and abnormal blood homocysteine levels decrease the rate of intellectual development in DS cases. Zinc deficiencies result in short stature, thyroid function disorders and an increased appetite caused by excessive supplementation. Scientific advances in the research and diagnosis of DS, as well as preventing any associated conditions, have significantly increased life expectancies of those with this genetic disorder. Early dietary interventions by parents or guardians of DS children afford an opportunity for decreasing the risk or delaying some of the DS associated conditions from appearing, thus beneficially impacting on their quality of life.


Role of folate-homocysteine pathway gene polymorphisms and nutritional cofactors in Down syndrome: A triad study.
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STUDY QUESTION: Do gene-gene and gene-environment interactions in folate-homocysteine (Hcy) pathway have a predisposing role for Down syndrome (DS)? SUMMARY ANSWER: The
study provides evidence that in addition to advanced age, maternal genotype, micronutrient deficiency and elevated Hcy levels, individually and in combination, are risk factors for Down syndrome. WHAT IS KNOWN ALREADY: Polymorphisms in certain folate-Hcy-pathway genes (especially the T allele of MTHFR C677T), elevated Hcy and poor folate levels in mothers during pregnancy have been shown to be risk factors for Down syndrome in certain Asian populations (including the eastern region of India), while the same SNPs are not a risk factor in European populations. This conflicting situation alludes to differential gene-environment (nutrition) interactions in different populations which needs to be explored. STUDY DESIGN, SIZE, DURATION: Between 2008 and 2012, 151 Down syndrome triads and 200 age-matched controls (Control mothers n = 186) were included in the study. Seven polymorphisms in six genes of folate-Hcy metabolic pathway, along with Hcy, cysteine (Cys), vitamin B12 (vit-B12) and folate levels, were analysed and compared among the case and control groups.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Genotyping was performed by the PCR-RFLP technique. Levels of homocysteine and cysteine were measured by HPLC while vitamin B12 and folate were estimated by chemiluminescence. MAIN RESULTS AND THE ROLE OF CHANCE: We demonstrate that polymorphisms in the folate-Hcy pathway genes in mothers collectively constitute a genotypic risk for DS which is effectively modified by interactions among genes and by the environment affecting folate, Hcy and vitamin B12 levels. The study also supports the idea that these maternal risk factors provide an adaptive advantage during pregnancy supporting live birth of the DS child. LIMITATIONS AND REASONS FOR CAUTION: Our inability to obtain genotype and nutritional assessments of unaffected siblings of the DS children was an important limitation of the study. Also, its confinement to a specific geographic region (the eastern part) of India, and relatively small sample size is a limitation. A parallel investigation on another population could add greater authenticity to the data. WIDER IMPLICATIONS OF THE FINDINGS: For mothers genetically susceptible to deliver a DS child (particularly in South Asia), peri-conceptional nutritional supplementation and antenatal care could potentially reduce the risk of a DS child. Additionally, nutritional strategies could possibly be used for better management of the symptoms of DS children.

STUDY FUNDING/COMPETING INTERESTS: The work is funded through Programme support for Genetic disorders by Dept. of Biotechnology, Government of India to R.R. The authors declare no conflict of interest.


Determinants of vitamin d levels in children and adolescents with down syndrome.

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Background. Poor studies have evaluated 25-hydroxycholecalciferol (25(OH)D) levels in Down syndrome (DS). Objective. To assess in DS subjects serum 25(OH)D value, to identify risk factors for vitamin D deficiency, and to evaluate whether a normal 25(OH)D value can be restored with a 400 I.U. daily supplement of cholecalciferol in respect to controls. Methods. We have longitudinally evaluated 31 DS patients (aged 4.5-18.9 years old) and 99 age- and sex-matched healthy controls. In these subjects, we analysed calcium, phosphate, parathyroid hormone (PTH), 25(OH)D concentrations, and calcium and 25(OH)D dietary intakes, and we quantified outdoor exposure. After 12.3 months (range 8.1-14.7 months) of 25(OH)D
supplementation, we reevaluated these subjects. Results. DS subjects showed reduced 25(OH)D levels compared to controls (P < 0.0001), in particular DS subjects with obesity (P < 0.05) and autoimmune diseases history (P < 0.005). PTH levels were significantly higher in DS subjects than controls (P < 0.0001). After cholecalciferol supplementation, 25(OH)D levels were significantly ameliorated (P < 0.05), even if reduced compared to controls (P < 0.0001), in particular in DS subjects with obesity (P < 0.05) and autoimmune diseases (P < 0.001).

Conclusions. Hypovitaminosis D is very frequent in DS subjects, in particular in presence of obesity and autoimmune diseases. In these subjects, there could be a need for higher cholecalciferol supplementation.


Characteristics associated with bone mineral density screening in adults with intellectual disabilities.

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BACKGROUND: Certain health characteristics place adults with intellectual disability at increased risk for osteoporosis. However, little data exist to describe how comorbid disease or medications affect screening patterns for these patients. METHODS: We evaluated the relationship between bone density screening and the presence of risk factors using a secondary cross-sectional analysis of 5520 adults aged 19 years and older with the diagnosis of intellectual disability. RESULTS: Of the sample, 22.9% received one or more bone density screenings (34.4% women, 13.3% men). Low screening rates in men prohibited the construction of a valid sex-specific multivariate model of the association between bone density screening and risk factors for osteoporosis. In women, when controlling for age the following factors were significantly associated with ever having bone density screening: use of antiepileptic medication (odds ratio [OR], 1.5) and vitamin D (OR, 3.4); recent receipt of a flu vaccine (OR, 1.4); and living in a 24-hour supported residential setting (OR, 1.3). A diagnosis of Down syndrome (OR, 0.72) was associated with decreased likelihood of screening. CONCLUSIONS: Many known risk factors for osteoporosis affected the likelihood of an adult with intellectual disability receiving screening, yet overall screening rates for adults with intellectual disabilities were lower than screening rates in the general population. Results suggest a need for increased provider awareness about bone density screenings in high-risk adults with intellectual disability, especially men, as well as men and women with Down syndrome.


Hypocalcemic seizure in an adolescent with Down syndrome: a manifestation of unrecognized celiac disease.

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Celiac disease (CD) affects up to 1% of the general population. Classically, it manifests with intestinal symptoms (diarrhea, steatorrhea, abdominal pain or discomfort) associated with weight loss and anemia. Seizure is a rare form of presentation of CD. A 13-year-old female patient with Down syndrome was admitted to the pediatric emergency dept. with generalized tonicclonic seizure in addition to numbness around the mouth, paresthesias, and muscular cramping for seven days. Investigations revealed severe hypocalcemia and vitamin D deficiency, which were a consequence of malabsorption secondary to histopathologically confirmed CD. Physicians should be aware that unrecognized CD can cause severe hypocalcemia.


Effect of the one-carbon unit cycle on overall DNA methylation in children with Down's syndrome.

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DNA methylation is a major epigenetic mechanism regulating gene expression. In order to analyze the impact of the one-carbon unit cycle on the overall level of DNA methylation in children with Down's syndrome (DS), the levels of indicators associated with the one-carbon unit cycle, including folic acid (FA), vitamin B12 (VB12) and homocysteine (Hcy), and the overall DNA methylation level of DS and healthy controls (HCs) were determined in the present study. A total of 36 DS children and 40 age- and gender-matched HCs were included in the present study to determine the levels of FA, VB12, Hcy and overall DNA methylation. The effect of the one-carbon unit cycle on the overall level of DNA methylation within the DS group was analyzed. The results demonstrated that the level of VB12 was decreased (P=0.008), while the Hcy level was increased (P=0.000) in DS patients compared with the HCs. FA and VB12 levels decreased with increasing age in DS patients (P<0.05). DNA hypermethylation and hypomethylation were observed in DS patients with VB12 deficiency and hyperhomocysteinemia, respectively (P=0.031, P=0.021). Abnormalities in the one-carbon unit cycle tend to worsen with increasing age in DS children. Thus, one-carbon unit cycle-associated alterations in DNA methylation may be important in the neuropathological alterations observed in DS.

Role of metal ions in the cognitive decline of Down syndrome.

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Down syndrome (DS), caused by trisomy of whole or part of chromosome 21 is the most common mental impairment. All people with DS suffer from cognitive decline and develop Alzheimer's disease (AD) by the age of 40. The appearance of enlarged early endosomes, followed by Amyloid βpeptide deposition, the appearance of tau-containing neurofibrillary tangles and basal forebrain cholinergic neuron (BFCN) degeneration are the neuropathological characteristics of this disease. In this review we will examine the role of metal ion dyshomeostasis and the genes which may be involved in these processes, and relate these back to the manifestation of age-dependent cognitive decline in DS.


Low heart-type fatty acid binding protein level during aging may protect down syndrome people against atherosclerosis.

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BACKGROUND: Aging is considered an important independent risk factor for atherosclerosis. Down syndrome people (DS) display an accelerated aging process compared to healthy subjects, anyway they are relatively resistant to developing atherosclerosis. The mechanisms involved in such protective effect are not well known. Since heart-type fatty acid binding protein (H-FABP) is a protein involved in the transport of fatty acids and it has been recently correlated with the presence of atherosclerosis, we aimed to measure H-FABP level both in DS and in healthy subjects during aging to evaluate the association between this molecule, aging and atherosclerosis. FINDINGS: We quantified plasmatic H-FABP level in three groups of male DS and age-matched healthy subjects (children, age 2-14 years; adults, age 20-50 years; elderly, > 60 years) using a biochip array analyzer. We observed that aging is associated with increased H-FABP level in healthy subjects but not in DS which display both the same protein level in the different ages of life and have also lower level compared to their age-matched healthy subjects. CONCLUSION: Reduced H-FABP level during aging in DS may play a protective role against atherosclerosis. The potential involvement of H-FABP in the relationship between aging, atherosclerosis and development of coronary artery disease needs further investigations.

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Astrocytes of the murine model for Down Syndrome Ts65Dn display reduced intracellular ionic zinc.
Zinc is an essential trace element that is critical for a large number of structural proteins, enzymatic processes and transcription factors. In the brain, zinc ions are involved in synaptic transmission. The homeostasis of zinc is crucial for cell survival and function, and cells have developed a wide variety of systems to control zinc concentration. Alterations in free zinc concentration have been related with brain dysfunction. Down Syndrome individuals present alterations in free zinc concentration and in some of the proteins related with zinc homeostasis. We have analyzed the amount of free zinc and the zinc chelating protein metallothionein 3 in the astrocytes using primary cultures of the murine model Ts65Dn. We have observed a higher number of zinc positive spots in the cytoplasm of trisomic astrocytes but a decrease in the total concentration of total intracellular free zinc concentration (including the spots) respect to control astrocytes. Using FM1-43 staining, we found that the endocytic function remains unaltered. Therefore, a possible explanation for this lower concentration of free zinc could be the higher concentration of metallothionein 3 present in the cytoplasm of trisomic astrocytes. The blockade of metallothionein 3 expression using an specific siRNA induced an increase in the concentration of free zinc in basal conditions but failed to increase the uptake of zinc after incubation with zinc ions.


Evaluation of extracellular adenine nucleotides hydrolysis in platelets and biomarkers of oxidative stress in Down syndrome individuals.
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PURPOSE: Down syndrome (DS) is caused by the triplication of chromosome 21. Studies have demonstrated platelet abnormalities and oxidative stress in DS subjects. The enzymes NTPDase, 5'-nucleotidase, and adenosine deaminase (ADA) represent an important therapeutic target since they interfere in the extracellular nucleotide pool altering platelet functions. In this study, we evaluated the ectonucleotidase activities and oxidative stress parameters in samples of DS and healthy individuals.

METHODS AND RESULTS: The population consisted of 28 subjects with DS and 28 healthy subjects as a control group. Blood was obtained from each subject and used for platelet and serum preparation. NTPDase activity using ATP as substrate was increased in platelets of DS patients in relation to the control group; however, no alterations were observed in the ADP hydrolysis. A decrease in the 5'-nucleotidase activity and an increase in the ADA activity was observed in platelet of DS subjects when compared to healthy individuals (P<0.05). The lipid peroxidation and total thiol content was decreased in serum of DS individuals. Furthermore, superoxide dismutase and catalase activities were increased in whole blood of this group (P<0.05). CONCLUSION: Alterations in the ectonucleotidase activities in platelets as well as changes in the oxidative stress parameters may contribute to the clinical features of DS.

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Thyroid Function and its Implications in Oxidative Stress Influencing the Pathogenesis of Osteoporosis in Adults with Down Syndrome: A Cohort Study.

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People with Down syndrome (DS) show lower bone mass density (BMD) and a higher prevalence of hypothyroidism compared to general population. Furthermore, DS is a well-known high oxidative stress (OS) condition because genes involved in OS map on chromosome 21. Thyroid function too is involved in OS. Since both thyroid function and OS lead to lower BMD and osteoporotic fractures, we have explored correlations among BMD, thyroid hormones, and parameters of OS in DS adults. A total of 105 DS patients (48 males; 21-71 years; mean BMI 28.88±7.12 kg/m²) were enrolled in a cohort study, 48 of them undergoing thyroid replacement therapy. We evaluated thyroid function, BMD, and total antioxidant capacity (TAC) in blood plasma. TAC was assayed by H2O2-metmyoglobin system, as source of radicals, and by the chromogenous ABTS, with a latency time (LAG) in the appearance of its cation ABTS+ proportional to antioxidant concentration. BMD was evaluated with DEXA, using WHO criteria to classify osteoporosis. Low BMD was found in 83.78% of patients. TSH and LAG did not correlate with BMD. Nevertheless, LAG significantly correlates to Z-scores estimated at the lumbar spine (r²=0.558; p=0.03) in hypothyroid patients. Our data show that low TAC could be more associated with reduced BMD rather than TSH itself in DS patients and that the OS could have a role in the pathogenesis of osteoporosis regarding the hypothyroid subgroup.

**Green tea EGCG plus fish oil omega-3 dietary supplements rescue mitochondrial dysfunctions and are safe in a Down's syndrome child.**

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**Maternal choline supplementation programs greater activity of the phosphatidylethanolamine N-methyltransferase (PEMT) pathway in adult Ts65Dn trisomic mice.**

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**Maternal choline supplementation (MCS) induces lifelong cognitive benefits in the Ts65Dn mouse, a trisomic mouse model of Down syndrome and Alzheimer’s disease.** To gain insight into the mechanisms underlying these beneficial effects, we conducted a study to test the hypothesis that MCS alters choline metabolism in adult Ts65Dn offspring. Deuterium-labeled methyl-d₉-choline was administered to adult Ts65Dn and disomic (2N) female littermates born to choline-unsupplemented or choline-supplemented Ts65Dn dams. Enrichment of d₉-choline metabolites (derived from intact choline) and d₃ + d₆-choline metabolites [produced when choline-derived methyl groups are used by phosphatidylethanolamine N-methyltransferase (PEMT)] was measured in harvested tissues. Adult offspring (both Ts65Dn and 2N) of choline-supplemented (vs. choline-unsupplemented) dams exhibited 60% greater (P≤0.007) activity of hepatic PEMT, which functions in de novo choline synthesis and produces phosphatidylcholine (PC) enriched in docosahexaenoic acid. Higher (P<0.001) enrichment of PEMT-derived d₃ and d₆ metabolites was detected in liver, plasma, and brain in both genotypes but to a greater extent in the Ts65Dn adult offspring. MCS also yielded higher (P<0.05) d₉ metabolite enrichments in liver, plasma, and brain. **These data demonstrate that MCS exerts lasting effects on offspring choline metabolism, including up-regulation of the hepatic PEMT pathway and enhanced provision of choline and PEMT-PC to the brain.**


**Persistence of the benefit of an antioxidant therapy in children and teenagers with Down syndrome.**

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This study examined the effect of an antioxidant intervention in biomarkers of inflammation and oxidative stress (OS) in the blood of Down syndrome (DS) children and teenagers during four different stages. A control group was composed by healthy children (n=18), assessed once, and a Down group composed by DS patients (n=21) assessed at the basal period (t₀), as well as after 6 months of antioxidant supplementation (t₁), after 12 months (after interruption of the antioxidant intervention for 6 months) (t₂), and again after further 6 months of antioxidant supplementation (t₃). Biomarkers of inflammation (myeloperoxidase activity - MPO and levels of IL-1β and TNF-α) and OS (thiobarbituric acid reactive substances - TBARS, protein carbonyls - PC), reduced glutathione (GSH), uric acid (UA) and vitamin E levels, as well as antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione-S-transferase (GST) and gamma-glutamyltransferase (GGT) activities, were measured after each period. After the antioxidant supplementation, the activities of SOD, CAT, GPx, GR, GGT and MPO were downregulated, while TBARS contents were strongly decreased, the contents of GSH and vitamin E were significantly increased, and no changes in G6PD and GST activity as well as in UA and PC levels were detected. After the interruption of the antioxidant therapy for 6 months, DS patients showed elevated GPx and GGT activities and also elevated UA and TBARS levels. No changes in SOD, CAT, GR, GST, G6PD and MPO activities as well as in GSH, vitamin E, PC, TNF-α and IL-1β levels were detected. The results showed that the antioxidant intervention persistently attenuated the systemic oxidative damage in DS patients even after a relatively long period of cessation of the antioxidant intervention.
levels were unaltered. After the antioxidant supplementation, SOD, CAT, GPx, GR, GGT and MPO activities were downregulated, while TBARS contents were strongly decreased in DS. Also, the antioxidant therapy did not change G6PD and GST activities as well as uric acid and PC levels, while it significantly increased GSH and vitamin E levels in DS patients. Our results clearly demonstrate that the antioxidant intervention with vitamins E and C attenuated the systemic oxidative damage present in DS patients.


Systemic oxidative stress in children and teenagers with Down syndrome.
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AIMS: The aim of this study was to evaluate the antioxidant status and oxidative stress biomarkers in the blood of children and teenagers with Down syndrome. MAIN METHODS: The analysis of enzymatic antioxidant defenses, such as the activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione transferase (GST), non-enzymatic antioxidants, such as levels of reduced glutathione (GSH), uric acid (UA) and vitamin E, as well as oxidative damage indicators, such as protein carbonyls (PC) levels and lipoperoxidation (TBARS), of DS individuals (n=20) compared to healthy controls (n=18). Except the vitamin E was measured by HPLC, all other markers were measured spectrophotometrically. KEY FINDINGS: Antioxidant enzymes analysis showed significant increases in the SOD (47.2%), CAT (24.7%) and GR (49.6%) activities in DS subjects. No significant difference in GPx activity was detected while GST activity (61.2%) was decreased, and both responses may be consequence of the depletion of GSH (24.9%) levels. There were no significant differences in TBARS levels, while PC levels showed decreased (31.7%) levels compared to healthy controls, which may be related to the increase (16.1%) found in serum UA. Levels of vitamin E showed no significant differences between DS individuals compared to controls. SIGNIFICANCE: The results revealed a systemic pro-oxidant status in DS individuals, evidenced by the increased activity of some important antioxidant enzymes, together with decreased GSH levels in whole blood and elevated UA levels in plasma, probably as an antioxidant compensation related to the redox imbalance in DS individuals.


Down syndrome individuals with Alzheimer’s disease have a distinct neuroinflammatory phenotype compared to sporadic Alzheimer’s disease.
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Down syndrome (DS) is the most common genetic cause of intellectual disability and is primarily caused by the triplication of chromosome 21. The overexpression of amyloid precursor protein gene may be sufficient to drive Alzheimer's disease (AD) neuropathology that is observed in virtually all individuals with DS by the age of 40 years. There is relatively little information about inflammation in the DS brain and how the genetics of DS may alter inflammatory responses and modify the course of AD pathogenesis in this disorder. Using the macrophage classification system of M1, M2a, M2b, and M2c inflammatory phenotypes, we have shown that the early stages of AD are associated with a bias toward an M1 or M2a phenotype. In later stages of AD, markers of M1, M2a and M2c are elevated. We now report the inflammatory phenotype in a DS autopsy series to compare this with the progression in sporadic AD. Tissue from young DS cases (under 40 years of age, pre-AD) show a bias toward M1 and M2b states with little M2a or M2c observed. Older DS cases (over 40 with AD pathology) show a distinct bias toward an M2b phenotype. Importantly, this is distinct from sporadic AD where the M2b phenotype has been rarely, if ever observed in postmortem studies. Stimulated by immune complex activation of microglial cells and toll-like receptor activation, the M2b phenotype represents a unique neuroinflammatory state in diseased brain and may have significant implications for therapeutic intervention for persons with DS.

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Pathways to cognitive deficits in Down syndrome.
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Major efforts in Down syndrome (DS) research have been directed at the identification and functional characterization of genes encoded by human chromosome 21 (HSA21). In parallel with this, tissue samples and cell lines derived from individuals with DS have been examined for abnormalities in gene expression and cellular morphology, and mouse models of DS have been characterized for abnormalities at the molecular, cellular, electrophysiological, and behavioral level. One goal of such investigations has been the identification of effective targets for pharmacotherapies that can prevent or correct the abnormalities and, by extension to human clinical trials, prevent or lessen aspects of the cognitive deficits seen in people with DS. Because it is caused by an extra copy of an entire chromosome, DS has been considered by some as too complicated a genetic perturbation to be amenable to postnatal pharmacological interventions. However, recent data from experiments with one mouse model, the Ts65Dn, have clearly demonstrated that several pharmacological interventions can indeed rescue DS-relevant learning and memory deficits. Extension of mouse data to successful human clinical trials will be aided by understanding the molecular basis of successful drug treatments, that is, how increased expression of HSA21 genes perturbs molecular mechanisms that are targeted and rescued by specific drugs. Here, we review information on HSA21 genes, their expression and their likely contributions to the DS phenotype. We then describe results of a bioinformatics effort that integrates information on genes known to cause intellectual disability when mutated, the pathways in which these genes function, and how these pathways are impacted by HSA21 encoded proteins. This pathway approach to the molecular basis of ID in DS aids in understanding why some drug therapies have been successful in the Ts65Dn and in predicting whether these same drugs are likely to be successful in treating ID in DS. These data can be used to design new experiments and interpret information for prediction of additional ta


Role of folate-homocysteine pathway gene polymorphisms and nutritional cofactors in Down syndrome: A triad study.

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STUDY QUESTION: Do gene-gene and gene-environment interactions in folate-homocysteine (Hcy) pathway have a predisposing role for Down syndrome (DS)? SUMMARY ANSWER: The
study provides evidence that in addition to advanced age, maternal genotype, micronutrient deficiency and elevated Hcy levels, individually and in combination, are risk factors for Down syndrome. WHAT IS KNOWN ALREADY: Polymorphisms in certain folate-Hcy-pathway genes (especially the T allele of MTHFR C677T), elevated Hcy and poor folate levels in mothers during pregnancy have been shown to be risk factors for Down syndrome in certain Asian populations (including the eastern region of India), while the same SNPs are not a risk factor in European populations. This conflicting situation alludes to differential gene-environment (nutrition) interactions in different populations which needs to be explored. STUDY DESIGN, SIZE, DURATION: Between 2008 and 2012, 151 Down syndrome triads and 200 age-matched controls (Control mothers n = 186) were included in the study. Seven polymorphisms in six genes of folate-Hcy metabolic pathway, along with Hcy, cysteine (Cys), vitamin B12 (vit-B12) and folate levels, were analysed and compared among the case and control groups.

Participants/Materials, Setting, Methods: Genotyping was performed by the PCR-RFLP technique. Levels of homocysteine and cysteine were measured by HPLC while vitamin B12 and folate were estimated by chemiluminescence. Main Results and the Role of Chance: We demonstrate that polymorphisms in the folate-Hcy pathway genes in mothers collectively constitute a genotypic risk for DS which is effectively modified by interactions among genes and by the environment affecting folate, Hcy and vitamin B12 levels. The study also supports the idea that these maternal risk factors provide an adaptive advantage during pregnancy supporting live birth of the DS child. Limitations and Reasons for Caution: Our inability to obtain genotype and nutritional assessments of unaffected siblings of the DS children was an important limitation of the study. Also, its confinement to a specific geographic region (the eastern part) of India, and relatively small sample size is a limitation. A parallel investigation on another population could add greater authenticity to the data. Wider Implications of the Findings: For mothers genetically susceptible to deliver a DS child (particularly in South Asia), peri-conceptional nutritional supplementation and antenatal care could potentially reduce the risk of a DS child. Additionally, nutritional strategies could possibly be used for better management of the symptoms of DS children. Study Funding Competing Interests: The work is funded through Programme support for Genetic disorders by Dept. of Biotechnology, Government of India to R.R. The authors declare no conflict of interest.


Oxidative Stress -a Phenotypic Hallmark of Fanconi Anemia and Down Syndrome: The Effect of Antioxidants.


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BACKGROUND: Oxidative stress plays a major role in the pathogenesis of leukemia-prone diseases such as Fanconi anemia (FA) and Down syndrome (DS). AIM: To explore the oxidative stress state in children with DS and FA by estimating the levels of antioxidants (e.g.,
malondialdehyde [MDA], total antioxidant capacity, and superoxide dismutase [SOD] activity) and DNA damage, and to evaluate the effect of antioxidant treatment on these patients.

SUBJECTS AND METHODS: The study included 32 children clinically diagnosed with (15 patients) and FA (17 patients) in addition to 17 controls matched for age and sex. MDA, total antioxidant capacity, SOD activity, and DNA damage were measured. Antioxidants including Vitamin A, E, and C were given to the patients according to the recommended daily allowance for 6 months. Clinical follow-up and re-evaluation were conducted for all patients. Laboratory tests including complete blood count, karyotyping, DNA damage, and oxidative stress were re-evaluated. Statistical analysis was performed using statistical computer program Statistical Package for the Social Sciences version 14.0. RESULTS:

Children with FA and DS had elevated levels of oxidative stress and more DNA damage than controls. Oxidative stress parameters and DNA damage improved in FA and DS patients after antioxidant administration. CONCLUSION: Early administration of antioxidants to FA and DS patients is recommended for slowing of the disease course with symptoms amelioration and improvement of general health.


Antioxidant intervention attenuates oxidative stress in children and teenagers with Down syndrome.

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We previously demonstrated that systemic oxidative stress is present in Down syndrome (DS) patients. In the present study we investigated the antioxidant status in the peripheral blood of DS children and teenagers comparing such status before and after an antioxidant supplementation. Oxidative stress biomarkers were evaluated in the blood of DS patients (n=21) before and after a daily antioxidant intervention (vitamin E 400mg, C 500 mg) during 6 months. Healthy children (n=18) without DS were recruited as control group. The activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), gamma-glutamyltransferase (GGT), glucose-6-phosphate dehydrogenase (G6PD) and myeloperoxidase (MPO), as well as the contents of reduced glutathione (GSH), uric acid, vitamin E, thiobarbituric acid reactive substances (TBARS), and protein carbonyls (PC) were measured. Before the antioxidant therapy, DS patients presented decreased GST activity and GSH depletion; elevated SOD, CAT, GR, GGT and MPO activities; increased uric acid levels; while GPx and G6PD activities as well as vitamin E and TBARS levels were unaltered. After the antioxidant supplementation, SOD, CAT, GR, GGT and MPO activities were downregulated, while TBARS contents were strongly decreased in DS. Also, the antioxidant therapy did not change G6PD and GST activities as well as uric acid and PC levels, while it significantly increased GSH and vitamin E levels in DS patients. Our results clearly demonstrate that the antioxidant intervention with vitamins E and C attenuated the systemic oxidative damage present in DS patients.
Vitamin D deficiency exacerbates atypical antipsychotic-induced metabolic side effects in rats: Involvement of the INSIG/SREBP pathway.

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Metabolic syndrome is a major concern in psychotic patients receiving atypical antipsychotics. Recent evidence suggests that sterol regulatory element-binding proteins (SREBPs) and insulin-induced genes (INSIGs) are implicated in the antipsychotic-induced metabolic side-effects. Vitamin D (VD) deficiency, a highly prevalent phenomenon among patients with psychosis, might also predispose individuals to metabolic syndrome. Considering that VD has modulating effects on the INSIG/SREBP pathway, it is possible that VD may have a role in the antipsychotic-induced metabolic disturbances involving its effects on the INSIG/SREBP system. Thus, the present study aimed to evaluate the effects of VD deficiency and VD supplementation on antipsychotic-induced metabolic changes in rats. After 4-week administration, clozapine (10mg/kg/d) and risperidone (1mg/kg/d) both caused glucose intolerance and insulin resistance in VD deficient rats, but not in rats with sufficient VD status. Antipsychotic treatments, especially clozapine, elevated serum lipid levels, which were most apparent in VD deficient rats, but alleviated in VD-supplemented rats. Additionally, antipsychotic treatments down-regulated INSIGs and up-regulated SREBPs expression in VD deficient rats, and these effects were attenuated when VD status was more sufficient. Collectively, this study disclose the novel findings that antipsychotic-induced metabolic disturbances is exacerbated by VD deficiency and can be alleviated by VD supplementation, providing new evidence for the promising role of VD in prevention and treatment of metabolic disorders caused by antipsychotic medications. Furthermore, our data also suggest the involvement of INSIG/SREBP pathway in the antipsychotic-induced hyperlipidemia and beneficial effects of VD on lipid profile.
Background. Poor studies have evaluated 25-hydroxycholecalciferol (25(OH)D) levels in Down syndrome (DS). Objective. To assess in DS subjects serum 25(OH)D value, to identify risk factors for vitamin D deficiency, and to evaluate whether a normal 25(OH)D value can be restored with a 400 I.U. daily supplement of cholecalciferol in respect to controls. Methods. We have longitudinally evaluated 31 DS patients (aged 4.5-18.9 years old) and 99 age- and sex-matched healthy controls. In these subjects, we analysed calcium, phosphate, parathyroid hormone (PTH), 25(OH)D concentrations, and calcium and 25(OH)D dietary intakes, and we quantified outdoor exposure. After 12.3 months (range 8.1-14.7 months) of 25(OH)D supplementation, we reevaluated these subjects. Results. DS subjects showed reduced 25(OH)D levels compared to controls (P < 0.0001), in particular DS subjects with obesity (P < 0.05) and autoimmune diseases history (P < 0.005). PTH levels were significantly higher in DS subjects than controls (P < 0.0001). After cholecalciferol supplementation, 25(OH)D levels were significantly ameliorated (P < 0.05), even if reduced compared to controls (P < 0.0001), in particular in DS subjects with obesity (P < 0.05) and autoimmune diseases (P < 0.001).

Conclusions. Hypovitaminosis D is very frequent in DS subjects, in particular in presence of obesity and autoimmune diseases. In these subjects, there could be a need for higher cholecalciferol supplementation.

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Antioxidants and biomarkers of oxidative damage in the saliva of patients with Down's syndrome.

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BACKGROUND:

The aim of this study was to investigate enzymatic and non-enzymatic antioxidant systems and levels of biomarker levels of oxidative damage in the saliva of patients with Down's syndrome (DS). METHODS: Saliva samples were collected from 30 patients with DS and control group (age: 14-24 years). Subsequently, the concentrations of superoxide dismutase, concentration of malondialdehyde, carbonylated proteins, uric acid, vitamin C and total protein, peroxidase activity and total antioxidant capacity were analyzed. RESULTS: Patients with DS presented significantly higher concentrations of superoxide dismutase, higher levels of malondialdehyde and salivary total protein content than controls (p<0.05). Conversely, no difference in
carbonylated proteins or antioxidants (uric acid, vitamin C, peroxidase, and total antioxidant capacity) was observed between DS patients and controls (p>0.05). CONCLUSION: Patients with DS are more vulnerable to oxidative stress in saliva as indicated by the significant increase in malondialdehyde and superoxide dismutase concentrations found in this study.


α-Tocopherol supplementation reduces biomarkers of oxidative stress in children with Down syndrome: a randomized controlled trial.
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BACKGROUND: Down syndrome (DS) is the most common human chromosomal abnormality. It is characterized by mental retardation and several metabolic disturbances, including elevated oxidative stress, which may be causally linked. Treatment with dietary antioxidants has been suggested as a potential method to alleviate the oxidative damage and retardation of DS patients, but prior supplementation work has been equivocal. AIM: To evaluate the effects of supplementation with antioxidants α-tocopherol and α-lipoic acid (ALA) on oxidative stress biomarkers in DS children. METHODS: Ninety-three DS children aged 7-15 years from both sexes were randomly allocated to three groups: α-tocopherol (400 IU/day), ALA (100 mg/day) and placebo. The intervention period was 4 months. A healthy control group consisted 26 non-DS siblings. Serum thiobarbituric acid reactive substances (TBARS) and urinary 8-hydroxy-2'-deoxyguanosine(8OHdG) were used as biomarkers of oxidative stress. RESULTS: DS children had greater levels of baseline oxidative stress than their siblings. Moreover, males had greater levels of 8OHdG than females (P<0.001) but there was no significant association between age and biomarkers of oxidative stress. Serum levels of TBARS did not change significantly over time, or relative to placebo. Although urinary 8OHdG concentrations decreased significantly in both α-tocopherol and ALA, groups compared with the baseline levels (P<0.001), mean final levels of urinary 8OHdG concentrations differed significantly only between α-tocopherol and placebo groups (P<0.01). CONCLUSIONS: α-Tocopherol supplementation of the diets of DS children may attenuate oxidative stress at the DNA level.


One-carbon metabolism in neurodevelopmental disorders: using broad-based nutraceuticals to treat cognitive deficits in complex spectrum disorders.
Folate and choline, two nutrients involved in the one-carbon metabolic cycle, are intimately involved in regulating DNA integrity, synthesis, biogenic amine synthesis, and methylation. In this review, we discuss evidence that folate and choline play an important role in normal cognitive development, and that altered levels of these nutrients during periods of high neuronal proliferation and synaptogenesis can result in diminished cognitive function. We also discuss the use of these nutrients as therapeutic agents in a spectrum of developmental disorders in which intellectual disability is a prominent feature, such as in Fragile-X, Rett syndrome, Down syndrome, and Autism spectrum disorders. A survey of recent literature suggests that nutritional supplements have mild, but generally consistent, effects on improving cognition. Intervening with supplements earlier rather than later during development is more effective in improving cognitive outcomes. Given the mild improvements seen after treatments using nutrients alone, and the importance of the genetic profile of parents and offspring, we suggest that using nutraceutics early in development and in combination with other therapeutics are likely to have positive impacts on cognitive outcomes in a broad spectrum of complex neurodevelopmental disorders.


Pregnant Canadian Women Achieve Recommended Intakes of One-Carbon Nutrients through Prenatal Supplementation but the Supplement Composition, Including Choline, Requires Reconsideration.


BACKGROUND: Folate, vitamin B-6, vitamin B-12, and choline are involved in one-carbon metabolism and play critical roles in pregnancy including prevention of birth defects and promotion of neurodevelopment. However, excessive intakes may adversely affect disease susceptibility in offspring. Intakes of these nutrients during pregnancy are not well characterized. OBJECTIVE: Our aim was to determine dietary and supplemental intakes and major dietary sources of one-carbon nutrients during pregnancy. METHODS: In pregnant women (n = 368) at
≤16 wk postconception, supplement use >30 d before pregnancy was assessed by maternal recall and supplement and dietary intakes in early (0-16 wk) and late pregnancy (23-37 wk) were assessed by food-frequency questionnaire. RESULTS: Preconception, 60.1% (95% CI: 55.8, 64.3) of women used B vitamin-containing supplements. This increased to 92.8% (95% CI: 89.6, 95.2) in early and 89.0% (95% CI: 85.0, 92.3) in late pregnancy. Median supplemental folic acid, vitamin B-12, and vitamin B-6 were 1000 μg/d, 2.6 μg/d, and 1.9 mg/d, respectively. Forty-one percent and 50% of women had dietary intakes of folate and vitamin B-6 less than the estimated average requirement (520 mg/d dietary folate equivalents and 1.6 mg/d, respectively). Eight-seven percent of women had choline intakes less than the Adequate Intake (450 mg/d). Dietary intakes did not change appreciably during pregnancy. Fruits and vegetables and fortified foods contributed ~57% to total dietary folate intake. Fruits and vegetables contributed ~32% to total dietary vitamin B-6 intake and dairy and egg products contributed ~37% to total dietary vitamin B-12 intake. CONCLUSIONS: Vitamin supplements were an important source of one-carbon nutrients during pregnancy in our sample. Without supplements, many women would not have consumed quantities of folate and vitamin B-6 consistent with recommendations. Given the importance of choline in pregnancy, further research to consider inclusion in prenatal supplements is warranted. This trial was registered at clinicaltrials.gov as NCT02244684.


Combined folate gene MTHFD and TC polymorphisms as maternal risk factors for Down syndrome in China.

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We examined whether polymorphisms in the methylenetetrahydrofolate dehydrogenase (MTHFD) and transcobalamin (TC) genes, which are involved in folate metabolism, affect maternal risk for Down syndrome. We investigated 76 Down syndrome mothers and 115 control mothers from Bengbu, China. Genomic DNA was isolated from the peripheral lymphocytes. Polymerase chain reaction and restriction fragment length polymorphism were used to examine the polymorphisms of MTHFD G1958A and TC C776G. The frequencies of the polymorphic alleles were 24.3 and 19.1% for MTHFD 1958A, 53.9 and 54.2% for TC 776G, in the case and control groups, respectively. No significant differences were found between two groups in relation to either the allele or the genotype frequency for both polymorphisms. However, when gene-gene interactions between these two polymorphisms together with previous studied C677T and A1298C polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene were analyzed, the combined MTHFR 677CT/TT and MTHFD 1958AA/GA genotype was found to be significantly associated with the risk of having a Down syndrome child [odds ratio (OR) = 3.11; 95% confidence interval (95%CI) = 1.07-9.02]. In addition, the combined TC 776CG and MTHFR 677TT genotype increased the risk of having a child with Down syndrome 3.64-fold (OR = 3.64; 95%CI = 1.28-10.31). In conclusion, neither MTHFD G1958A nor TC C776G polymorphisms are an independent risk factor for Down syndrome. However, the combined MTHFD/MTHFR, TC/MTHFR genotypes play a role in the risk of bearing a Down syndrome child in the Chinese population.

**Gamma tocotrienol, a potent radioprotector, preferentially upregulates expression of anti-apoptotic genes to promote intestinal cell survival.**

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Gamma tocotrienol (GT3) has been reported as a potent ameliorator of radiation-induced gastrointestinal (GI) toxicity when administered prophylactically. This study aimed to evaluate the role of GT3 mediated pro- and anti-apoptotic gene regulation in protecting mice from radiation-induced GI damage. Male 10- to 12-weeks-old CD2F1 mice were administered with a single dose of 200 mg/kg of GT3 or equal volume of vehicle (5% Tween-80) 24 h before exposure to 11 Gy of whole-body γ-radiation. Mouse jejunum was surgically removed 4 and 24h after radiation exposure, and was used for PCR array, histology, immunohistochemistry, and immunoblot analysis. Results were compared among vehicle pre-treated no radiation, vehicle pre-treated irradiated, and GT3 pre-treated irradiated groups. GT3 pretreated irradiated groups, both 4h and 24h after radiation, showed greater upregulation of anti-apoptotic gene expression than vehicle pretreated irradiated groups. TUNEL staining and intestinal crypt analysis showed protection of jejunum after GT3 pre-treatment and immunoblot results were supportive of PCR data. Our study demonstrated that GT3-mediated protection of intestinal cells from a GI-toxic dose of radiation occurred via upregulation of antiapoptotic and downregulation of pro-apoptotic factors, both at the transcript as well as at the protein levels.


**Preconception folic acid supplementation and risk for chromosome 21 nondisjunction: a report from the National Down Syndrome Project.**

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Both a lack of maternal folic acid supplementation and the presence of genetic variants that reduce enzyme activity in folate pathway genes have been linked to meiotic nondisjunction of chromosome 21; however, the findings in this area of research have been inconsistent. To better understand these inconsistencies, we asked whether maternal use of a folic acid-containing supplement before conception reduces risk for chromosome 21 nondisjunction. Using questionnaire data from the National Down Syndrome Project, a population-based case-control study, we compared the use of folic acid-containing supplements among mothers of infants with full trisomy 21 due to maternal nondisjunction (n = 702) and mothers of infants born with no major birth defects (n = 983). Using logistic regression, adjusting for maternal age, race/ethnicity, and infant age at maternal interview, we found no evidence of an association.
between lack of folic acid supplementation and maternal nondisjunction among all case mothers (OR = 1.16; 95% CI: 0.90-1.48). In analyses stratified by meiotic stage and maternal age (<35 or ≥35 years), we found an association among older mothers experiencing meiosis II nondisjunction errors (OR = 2.00; 95% CI: 1.08-3.71). These data suggest that lack of folic acid supplementation may be associated specifically with MII errors in the aging oocyte. If confirmed, these results could account for inconsistencies among previous studies, as each study sample may vary by maternal age structure and proportion of meiotic errors.


The genetics of folate metabolism and maternal risk of birth of a child with Down syndrome and associated congenital heart defects.

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Almost 15 years ago it was hypothesized that polymorphisms of genes encoding enzymes involved in folate metabolism could lead to aberrant methylation of peri-centromeric regions of chromosome 21, favoring its abnormal segregation during maternal meiosis. Subsequently, more than 50 small case-control studies investigated whether or not maternal polymorphisms of folate pathway genes could be risk factors for the birth of a child with Down syndrome (DS), yielding conflicting and inconclusive results. However, recent meta-analyses of those studies suggest that at least three of those polymorphisms, namely MTHFR 677C>T, MTRR 66A>G, and RFC1 80G>A, are likely to act as maternal risk factors for the birth of a child with trisomy 21, revealing also complex gene-nutrient interactions. A large-cohort study also revealed that lack of maternal folic acid supplementation at peri-conception resulted in increased risk for a DS birth due to errors occurred at maternal meiosis II in the aging oocyte, and it was shown that the methylation status of chromosome 21 peri-centromeric regions could favor recombination errors during meiosis leading to its malsegregation. In this regard, two recent case-control studies revealed association of maternal polymorphisms or haplotypes of the DNMT3B gene, coding for an enzyme required for the regulation of DNA methylation at centromeric and peri-centromeric regions of human chromosomes, with risk of having a birth with DS. Furthermore, congenital heart defects (CHD) are found in almost a half of DS births, and increasing evidence points to a possible contribution of lack of folic acid supplementation at peri-conception, maternal polymorphisms of folate pathway genes, and resulting epigenetic modifications of several genes, at the basis of their occurrence. This review summarizes available case-control studies and literature meta-analyses in order to provide a critical and up to date overview of what we currently know in this field.
Antioxidant effects of potassium ascorbate with ribose therapy in a case with Prader Willi Syndrome.

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Oxidative stress (OS) is involved in several human diseases, including obesity, diabetes, atherosclerosis, carcinogenesis, as well as genetic diseases. We previously found that OS occurs in Down Syndrome as well as in Beckwith-Wiedemann Syndrome (BWS). Here we describe the clinical case of a female patient with Prader Willi Syndrome (PWS), a genomic imprinting disorder, characterized by obesity, atherosclerosis and diabetes mellitus type 2, pathologies in which a continuous and important production of free radicals takes place. We verified the presence of OS by measuring a redox biomarkers profile including total hydroperoxides (TH), non protein-bound iron (NPBI), thiols (SH), advanced oxidation protein products (AOPP) and isoprostanes (IPs). Thus we introduced in therapy an antioxidant agent, namely potassium ascorbate with ribose (PAR), in addition to GH therapy and we monitored the redox biomarkers profile for four years. A progressive decrease in OS biomarkers occurred until their normalization. In the meantime a weight loss was observed together with a steady growth in standards for age and sex.

Proposed remedies for some developmental disorders.

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Developmental disorders (DDs) are important leading cause of disability in developed countries and also in the United States. DDs are a group of individual conditions that result from abnormal nervous system development and cause altered function. They can begin at any time from prenatal to 22 years of age and the disability usually presents itself throughout a person's life time. Down syndrome, autism, neural tube defects, schizophrenia, cretinism, and attention-deficit hyperactivity disorder are among the most common DDs that currently plague numerous countries and have varying incidence rates. Their occurrence may be partially attributable to the lack of certain dietary nutrients. Notably, essential vitamins, minerals, and ω-3 fatty acids are often deficient in the general population of America and developed countries and are exceptionally deficient in patients suffering from mental disorders. Typically, most of these disorders are treated with prescription drugs, but many of these drugs cause unwanted side effects. Therefore, psychiatrists recommend alternative or complementary nutritional remedies to overcome the adverse effects of those drugs. Studies have shown that daily supplements of vital nutrients, such as that contain amino acids, often effectively reduce symptoms of the patients, because they are converted into neurotransmitters that alleviate depression and other mental disorders. The aim of this article is to discuss the role of dietary imbalances in the
incidence of DD and to emphasize which dietary supplements can aid in the treatment of the above-mentioned DD.


How nutritional status, diet and dietary supplements can affect autism. A review.

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Autism is a neurodevelopmental disorder with symptoms arising that are apparent throughout the patient's lifespan. Autism Spectrum Disorders (ASD) are characterised by impaired social and communication interactions as well as restricted, repetitive interests and behaviour. Currently in Poland, about 50,000 people suffer from autism, of which 1/5 are children. Epidemiological studies show that the incidence of autism is increasing, which may be due to the diagnostic category of ASD having been developed. Of vital importance in the treatment of autism, is early diagnosis which is conducive to more rapidly improving the quality of patients' health. It is believed that both genetic and environmental factors may affect the development of the disease. Moreover, expert opinion emphasises the importance of making an adequate diagnosis when the first symptoms of autism start appearing which can be both psychological, gastro-intestinal and metabolic ones. Conventional treatment is based on the combination of behavioural and dietary therapy together with pharmacotherapy. For example, adapting an appropriate diet could help alleviate the disease severity, as well as the psychological and gastrointestinal symptoms. Much scientific research has indicated that pathogenesis of autism may have a beginning already in foetal life. During pregnancy, specialists should take special heed of metabolic disorders, which can increase the risk of ASD in children. One of the dietician's tasks are to properly assess the nutritional status of mothers before and during pregnancy, thereby allowing changes in nutrition to be made wherever necessary in order that metabolic indicators be improved. Thus an important part of autism therapy is the improving patient's nutritional status to prevent the onset of gastrointestinal symptoms. Adopting diets and tailored to individual disease symptoms, is linked to the nutritional requirements and food preferences of the patient. Specialists also emphasise that continual monitoring of the diet and nutritional status of children with ASD is required. It is also essential to start adequate dietary management in autistic patients with overweight, obesity or wasting, caused by improper nutrition. Frequently only a dietary therapy is insufficient to effectively treat autism. Many studies demonstrate the need to supplement the nutritional deficiencies of autistic patients with fatty acids omega-3, probiotics, vitamins and minerals in combination with medical and psychological interventions. A properly designed elimination diet adapted to the patient's individual may also lead to relief of the autism symptoms and the occurrence of gastrointestinal disorders. Parents and caregivers should therefore be aware of the benefits of nutritional therapy and need for proper monitoring the treatment of patients with ASD. A review of nutritional factors, dietary treatments and diet supplementation in patients with ASD is presented.
Erythrocyte phospholipid molecular species and fatty acids of Down syndrome children compared with non-affected siblings.

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The majority of children with Down syndrome (DS) develop Alzheimer’s disease (AD) at an early age. Although long-chain n-3 fatty acids (FA) are protective of neurodegeneration, little is known about the FA status in DS. In the present study, we aimed to investigate whether children with DS presented altered plasma and erythrocyte membrane phospholipids (PL) FA composition, when compared with their non-affected siblings. Venous blood samples were analysed for plasma and erythrocyte membrane FA composition by TLC followed by GC techniques. Lipid molecular species were determined by electrospray ionisation/tandem MS (ESI-MS/MS). FA analysis measured by standard GC showed an increased concentration of MUFA and a decreased concentration of plasmalogens in major PL fractions, but there were no differences in the concentrations of arachidonic acid or DHA. However, as identified by ESI-MS/MS, children with DS had increased levels of the following erythrocyte PL molecular species: 16:0-16:0, 16:0-18:1 and 16:0-18:2n-6, with reduced levels of 16:0-20:4n-6 species. Children with DS presented significantly higher levels of MUFA in both plasma and erythrocyte membrane, as well as higher levels of saturated and monounsaturated molecular species. Of interest was the almost double proportion of 16:0-18:2n-6 and nearly half the proportion of 16:0-20:4n-6 of choline phosphoacylglycerol species in children with DS compared with their non-affected siblings. These significant differences were only revealed by ESI-MS/MS and were not observed in the GC analysis. Further investigations are needed to explore molecular mechanisms and to test the association between the pathophysiology of DS and the risk of AD.


The α7 nicotinic acetylcholine receptor: A mediator of pathogenesis and therapeutic target in autism spectrum disorders and Down syndrome.

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Currently, there are no medications that target core deficits of social communication and restrictive, repetitive patterns of behavior in persons with autism spectrum disorders (ASDs). Adults with Down syndrome (DS) display a progressive worsening of adaptive functioning, which is associated with Alzheimer's disease (AD)-like histopathological changes in brain.
Similar to persons with ASDs, there are no effective medication strategies to prevent or retard the progressive worsening of adaptive functions in adults with DS. Data suggest that the $\alpha_7$-subunit containing nicotinic acetylcholine receptor ($\alpha_7$nAChR) is implicated in the pathophysiology and serves as a promising therapeutic target of these disorders. In DS, production of the amyloidogenic A$\beta_{1-42}$ peptide is increased and binds to the $\alpha_7$nAChR or the lipid milieu associated with this receptor, causing a cascade that results in cytotoxicity and deposition of amyloid plaques. Independently of their ability to inhibit the complexing of A$\beta_{1-42}$ with the $\alpha_7$nAChR, $\alpha_7$nAChR agonists and positive allosteric modulators (PAMs) also possess procognitive and neuroprotective effects in relevant in vivo and in vitro models. The procognitive and neuroprotective effects of $\alpha_7$nAChR agonist interventions may be due, at least in part, to stimulation of the PI3K/Akt signaling cascade, cross-talk with the Wnt/β-catenin signaling cascade and both transcriptional and non-transcriptional effects of β-catenin, and effects of transiently increased intraneuronal concentrations of Ca$^{2+}$ on metabolism and the membrane potential. Importantly, $\alpha_7$nAChR PAMs are particularly attractive medication candidates because they lack intrinsic efficacy and act only when and where endogenous acetylcholine is released or choline is generated.


**Prenatal treatment of Down syndrome: a reality?**

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**PURPOSE OF REVIEW:** Down syndrome affects more than 5 million people globally. During the last 10 years, there has been a dramatic increase in the research efforts focused on therapeutic interventions to improve learning and memory in Down syndrome. **RECENT FINDINGS:** This review summarizes the different functional abnormalities targeted by researchers in mouse models of Down syndrome. Three main strategies have been used: neural stem cell implantation; environmental enrichment and physical exercise; and pharmacotherapy. Pharmacological targets include the choline pathway, GABA and NMDA receptors, DYRK1A protein, oxidative stress and pathways involved in development and neurogenesis. Many strategies have improved learning and memory as well as electrophysiological and molecular alterations in affected animals. To date, eight molecules have been tested in human adult clinical trials. No studies have yet been performed on infants. However, compelling studies reveal that permanent brain alterations originate during fetal life in Down syndrome. Early prenatal diagnosis offers a 28 weeks window to positively impact brain development and improve postnatal cognitive outcome in affected individuals. Only a few approaches (Epigallocatechine gallate, NAP/SAL, fluoxetine, and apigenin) have been used to treat mice in utero; these showed therapeutic effects that persisted to adulthood. **SUMMARY:** In this article, we discuss the challenges, recent progress, and lessons learned that pave the way for new therapeutic approaches in Down syndrome.

Prenatal pharmacotherapy rescues brain development in a Down's syndrome mouse model.


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Intellectual impairment is a strongly disabling feature of Down's syndrome, a genetic disorder of high prevalence (1 in 700-1000 live births) caused by trisomy of chromosome 21. Accumulating evidence shows that widespread neurogenesis impairment is a major determinant of abnormal brain development and, hence, of intellectual disability in Down's syndrome. This defect is worsened by dendritic hypotrophy and connectivity alterations. Most of the pharmacotherapies designed to improve cognitive performance in Down's syndrome have been attempted in Down's syndrome mouse models during adult life stages. Yet, as neurogenesis is mainly a prenatal event, treatments aimed at correcting neurogenesis failure in Down's syndrome should be administered during pregnancy. Correction of neurogenesis during the very first stages of brain formation may, in turn, rescue improper brain wiring. The aim of our study was to establish whether it is possible to rescue the neurodevelopmental alterations that characterize the trisomic brain with a prenatal pharmacotherapy with fluoxetine, a drug that is able to restore post-natal hippocampal neurogenesis in the Ts65Dn mouse model of Down's syndrome.

Pregnant Ts65Dn females were treated with fluoxetine from embryonic Day 10 until delivery. On post-natal Day 2 the pups received an injection of 5-bromo-2-deoxyuridine and were sacrificed after either 2 h or after 43 days (at the age of 45 days). Untreated 2-day-old Ts65Dn mice exhibited a severe neurogenesis reduction and hypocellularity throughout the forebrain (subventricular zone, subgranular zone, neocortex, striatum, thalamus and hypothalamus), midbrain (mesencephalon) and hindbrain (cerebellum and pons). In embryonically treated 2-day-old Ts65Dn mice, precursor proliferation and cellularity were fully restored throughout all brain regions. The recovery of proliferation potency and cellularity was still present in treated Ts65Dn 45-day-old mice. Moreover, embryonic treatment restored dendritic development, cortical and hippocampal synapse development and brain volume. Importantly, these effects were accompanied by recovery of behavioural performance. The cognitive deficits caused by Down's syndrome have long been considered irreversible. The current study provides novel evidence that a pharmacotherapy with fluoxetine during embryonic development is able to fully rescue the abnormal brain development and behavioural deficits that are typical of Down's syndrome. If the positive effects of fluoxetine on the brain of a mouse model are replicated in foetuses with Down's syndrome, fluoxetine, a drug usable in humans, may represent a breakthrough for the therapy of intellectual disability in Down's syndrome.


Long-term oral administration of melatonin improves spatial learning and memory and protects against cholinergic degeneration in middle-aged Ts65Dn mice, a model of Down syndrome.

Corrales A¹, Martínez P, García S, Vidal V, García E, Flórez J, Sanchez-Barceló EJ, Martínez-Cué C.
Ts65Dn mice (TS), the most commonly used model of Down syndrome (DS), exhibit phenotypic characteristics of this condition. Both TS mice and DS individuals present cognitive disturbances, age-related cholinergic degeneration, and increased brain expression of β-amyloid precursor protein (AβPP). These neurodegenerative processes may contribute to the progressive cognitive decline observed in DS. Melatonin is a pineal indoleamine that has been reported to reduce neurodegenerative processes and improve cognitive deficits in various animal models. In this study, we evaluated the potentially beneficial effects of long-term melatonin treatment on the cognitive deficits, cholinergic degeneration, and enhanced AβPP and β-amylloid levels of TS mice. Melatonin was administered for 5 months to 5- to 6-month-old TS and control (CO) mice. Melatonin treatment improved spatial learning and memory and increased the number of choline acetyltransferase (ChAT)-positive cells in the medial septum of both TS and CO mice. However, melatonin treatment did not significantly reduce AβPP or β-amylloid levels in the cortex or the hippocampus of TS mice. Melatonin administration did reduce anxiety in TS mice without inducing sensorimotor alterations, indicating that prolonged treatment with this indoleamine is devoid of noncognitive behavioral side effects (e.g., motor coordination, sensorimotor abilities, or spontaneous activity). Our results suggest that melatonin administration might improve the cognitive abilities of both TS and CO mice, at least partially, by reducing the age-related degeneration of basal forebrain cholinergic neurons. Thus, chronic melatonin supplementation may be an effective treatment for delaying the age-related progression of cognitive deterioration found in DS.


Chronic melatonin treatment rescues electrophysiological and neuromorphological deficits in a mouse model of Down syndrome.

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The Ts65Dn mouse (TS), the most commonly used model of Down syndrome (DS), exhibits several key phenotypic characteristics of this condition. In particular, these animals present hypocellularity in different areas of their CNS due to impaired neurogenesis and have alterations in synaptic plasticity that compromise their cognitive performance. In addition, increases in oxidative stress during adulthood contribute to the age-related progression of cognitive and neuronal deterioration. We have previously demonstrated that chronic melatonin treatment improves learning and memory and reduces cholinergic neurodegeneration in TS mice. However, the molecular and physiological mechanisms that mediate these beneficial cognitive effects are not yet fully understood. In this study, we analyzed the effects of chronic melatonin treatment on different mechanisms that have been proposed to underlie the cognitive impairments observed in TS mice: reduced neurogenesis, altered synaptic plasticity, enhanced synaptic inhibition and oxidative damage. Chronic melatonin treatment rescued both impaired adult neurogenesis and the decreased density of hippocampal granule cells in trisomic mice. In addition, melatonin administration reduced synaptic inhibition in TS mice by increasing the density and/or activity of glutamatergic synapses in the hippocampus. These effects were accompanied by a full recovery of hippocampal LTP in trisomic animals. Finally, melatonin
treatment decreased the levels of lipid peroxidation in the hippocampus of TS mice. These results indicate that the cognitive-enhancing effects of melatonin in adult TS mice could be mediated by the normalization of their electrophysiological and neuromorphological abnormalities and suggest that melatonin represents an effective treatment in retarding the progression of DS neuropathology.

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Overexpression of DYRK1A inhibits choline acetyltransferase induction by oleic acid in cellular models of Down syndrome.

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Histological brain studies of individuals with DS have revealed an aberrant formation of the cerebral cortex. Previous work from our laboratory has shown that oleic acid acts as a neurotrophic factor and induces neuronal differentiation. In order to characterize the effects of oleic acid in a cellular model of DS, immortalized cell lines derived from the cortex of trisomy Ts16 (CTb) and normal mice (CNh) were incubated in the absence or presence of oleic acid. Oleic acid increased choline acetyltransferase expression (ChAT), a marker of cholinergic differentiation in CNh cells. However, in trisomic cells (CTb line) oleic acid failed to increase ChAT expression. These results suggest that the overdose of specific genes in trisomic lines delays differentiation in the presence of oleic acid by inhibiting acetylcholine production mediated by ChAT. The dual-specificity tyrosine (Y) phosphorylation-regulated kinase 1A (DYRK1A) gene is located on human chromosome 21 and encodes a proline-directed protein kinase. It has been proposed that DYRK1A plays a prominent role in several biological functions, leading to mental retardation in DS patients. Here we explored the potential role of DYRK1A in the modulation of ChAT expression in trisomic cells and in the signaling pathways of oleic acid. Down-regulation of DYRK1A by siRNA in trisomic CTb cells rescued ChAT expression up to levels similar to those of normal cells in the presence of oleic acid. In agreement with these results, oleic acid was unable to increase ChAT expression in neuronal cultures of transgenic mice overexpressing DYRK1A. In summary, our results highlight the role played by DYRK1A in brain development through the control of ChAT expression. In addition, the overexpression of DYRK1A in DS models prevented the neurotrophic effect of oleic acid, a fact that may account for mental retardation in DS patients.


Peroxisomes: the neuropathological consequences of peroxisomal dysfunction in the developing brain.

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Peroxisomes are intracellular organelles that perform vital metabolic functions. They have been extensively studied in the hepatic and renal systems, yet their pivotal roles in facilitating central nervous system patterning and in disease pathogenesis are only recently being firmly established by the neuroscience community. Peroxisomal functions including the break-down of long chain fatty acids, the removal of H2O2, and the biosynthesis of ether lipids. The build up of long chain fatty acids and H2O2 is detrimental to cellular function, and ether lipids play roles in maintaining cell membrane structure. These findings have major implications for treatments for the full spectrum of peroxisomal disorders. Here, we provide a timely review highlighting the most important data in recent times linking peroxisomal functions to brain formation, and we describe how peroxisomal deficiency and pathway dysfunction results in neurological deficits, the more severe of which result in life changing disabilities and death.


Effect of Coenzyme Q10 in mitigating oxidative DNA damage in Down syndrome patients, a double blind randomized controlled trial.
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Down syndrome (DS) is a chromosomal abnormality (trisomy 21) associated with a complex phenotype. Oxidative stress is known to play a major role in this pathology both due to genetic and epigenetic factors, suggesting that oxidative imbalance contributes to the clinical manifestation of DS. In particular, the implications of oxidative DNA damage in Down syndrome has been linked with neurodegeneration. Here we report the results of a double blind controlled trial aimed at investigating the protective effect of Coenzyme Q(10) on DNA oxidation in this clinical setting using the single cell gel electrophoresis


Coenzyme Q10 and oxidative imbalance in Down syndrome: biochemical and clinical aspects.
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Down syndrome (DS) is a chromosomal abnormality (trisomy 21) associated with mental retardation and Alzheimer-like dementia, characteristic change of the individual's phenotype and premature ageing. Oxidative stress is known to play a major role in this pathology since a gene dose effect leads to elevated ratio of superoxide dismutase to catalase/glutathione peroxidase compared to controls in all age categories suggesting that oxidative imbalance contributes to the clinical manifestation of DS. Hyperuricemia is another feature of DS that has an interesting relationship with oxidative stress since uric acid represents an important free radical scavenger. However its formation is connected to the conversion of Xanthine dehydrogenase (XDH) to Xanthine oxidase (XO) which leads to concomitant production of free radicals. Here we report
that plasma samples from DS patients in pediatric age, despite an increased total antioxidant capacity, largely due to elevated Uric acid content (UA), present significantly elevated markers of oxidative damage such as increased allantoin levels. Moreover DS plasma samples do not differ from healthy control ones in terms of Coenzyme Q10 and susceptibility to peroxidative stimuli. On the contrary, lymphocyte and platelet CoQ10 content was significantly lower in DS patients, a fact that might underlie oxidative imbalance at a cellular level.


Coenzyme Q10 (ubiquinol-10) supplementation improves oxidative imbalance in children with trisomy 21.
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Endogenous coenzyme Q10 is an essential cofactor in the mitochondrial respiratory chain, a potent antioxidant, and a potential biomarker for systemic oxidative status. Evidence of oxidative stress was reported in individuals with trisomy 21. In this study, 14 children with trisomy 21 had significantly increased (P < 0.0001) plasma ubiquinone-10 (the oxidized component of coenzyme Q10) compared with 12 age- and sex-matched healthy children (historical controls). Also, the mean ratio of ubiquinol-10 (the biochemically reduced component):total coenzyme Q10 was significantly decreased (P < 0.0001). After 3 months of ubiquinol-10 supplementation (10 mg/kg/day) to 10 patients with trisomy 21, the mean ubiquinol-10:total coenzyme Q10 ratio increased significantly (P < 0.0001) above baseline values, and 80% of individual ratios were within normal range. No significant or unexpected adverse effects were reported by participants. To our knowledge, this is the first study to indicate that the pro-oxidant state in plasma of children with trisomy 21, as assessed by ubiquinol-10:total coenzyme Q10 ratio, may be normalized with ubiquinol-10 supplementation. Further studies are needed to determine whether correction of this oxidant imbalance improves clinical outcomes of children with trisomy 21.

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Beneficial effects of carnosine and carnosine plus vitamin E treatments on doxorubicin-induced oxidative stress and cardiac, hepatic, and renal toxicity in rats.
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OBJECTIVE: Oxidative stress plays an important role in doxorubicin (DOX)-induced toxicity. Carnosine (CAR) is a dipeptide with antioxidant properties. The aim of this study was to evaluate the decreasing or preventive effect of CAR alone or combination with vitamin E (CAR +
Vit E) on DOX-induced toxicity in heart, liver, and brain of rats. METHODS: Rats were treated with CAR (250 mg kg\(^{-1}\) day\(^{-1}\); intraperitoneally (i.p.)) or CAR + Vit E (equals 200 mg kg\(^{-1}\) \(\alpha\)-tocopherol; once every 3 days; intramuscularly) for 12 consecutive days. On the 8th day of treatment, rats were injected with a single dose of DOX (30 mg kg\(^{-1}\), i.p.). Serum cardiac troponin I (cTnI), urea, and creatinine levels; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities; and oxidative stress parameters in tissues were measured. We also determined thiobarbituric acid reactive substances, diene conjugate, protein carbonyl (PC), and glutathione levels and antioxidant enzyme activities. RESULTS: DOX resulted in increased serum cTnI, ALT, AST, urea, and creatinine levels and increased lipid peroxide and PC levels in tissues. CAR or CAR + Vit E treatments led to decreases in serum cTnI levels and ALT and AST activities. These treatments reduced prooxidant status and ameliorated histopathologic findings in the examined tissues. CONCLUSION: Our results may indicate that CAR alone, especially in combination with Vit E, protect against DOX-induced toxicity in heart, liver, and kidney tissues of rats. This was evidenced by improved cardiac, hepatic, and renal markers and restoration of the prooxidant state and amelioration of histopathologic changes.


Intrinsic carnosine metabolism in the human kidney.

Peters V\(^1\), Klessens CQ, Baelde HJ, Singler B, Veraar KA, Zutinic A, Drozak J, Zschocke J,

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Histidine-containing dipeptides like carnosine and anserine have protective functions in both health and disease. Animal studies suggest that carnosine can be metabolized within the kidney. The goal of this study was to obtain evidence of carnosine metabolism in the human kidney and to provide insight with regards to diabetic nephropathy. Expression, distribution, and localization of carnosinase-1 (CNDP1), carnosine synthase (CARNs), and taurine transporters (TauT) were measured in human kidneys. CNDP1 and CARNs activities were measured in vitro. CNDP1 and CARNs were located primarily in distal and proximal tubules, respectively. Specifically, CNDP1 levels were high in tubular cells and podocytes (20.3 ± 3.4 and 15 ± 3.2 ng/mg, respectively) and considerably lower in endothelial cells (0.5 ± 0.1 ng/mg). CNDP1 expression was correlated with the degradation of carnosine and anserine (r = 0.88 and 0.81, respectively). Anserine and carnosine were also detectable by HPLC in the renal cortex. Finally, TauT mRNA and protein were found in all renal epithelial cells. In diabetic patients, CNDP1 seemed to be reallocated to proximal tubules. We report compelling evidence that the kidney has an intrinsic capacity to metabolize carnosine. Both CNDP1 and CARNs are expressed in glomeruli and tubular cells. Carnosine-synthesizing and carnosine-hydrolyzing enzymes are localized in distinct compartments in the nephron and increased CNDP1 levels suggest a higher CNDP1 activity in diabetic kidneys.


Dietary supplemental vitamin B6 increases carnosine and anserine concentrations in the heart of rats.

Suidasari S\(^1\), Hasegawa T\(^1\), Yanaka N\(^1\), Kato N\(^1\).
This study was performed to examine the effect of dietary level of vitamin B6 on the concentrations of carnosine and anserine, antioxidants, in the heart of rats. Analysis using UPLC-MS/MS showed that the concentrations of these dipeptides in the 7 and 35 mg pyridoxine HCl/kg groups were significantly higher than those in the 1 mg pyridoxine HCl/kg group, implying the novel role of dietary vitamin B6 as a determinant of the dipeptides favorable for heart.

Recent Pat Drug Deliv Formul. 2015 Jun 17

Telomere Attrition in Human Lens Epithelial Cells Associated with Oxidative Stress Provide a New Therapeutic Target for the Treatment, Dissolving and Prevention of Cataract with N-Acetylcarnosine Lubricant Eye Drops. Kinetic, Pharmacological and Activity-Dependent Separation of Therapeutic Targeting: Transcorneal Penetration and Delivery of L-Carnosine in the Aqueous Humor and Hormone-Like Hypothalamic Antiaging Effects of the Instilled Ophthalmic Drug Through a Safe Eye Medication Technique.

Babizhayev MA1, Yegorov YE.

Visual impairment broadly impacts the ability of affected people to maintain their function and to remain independent during their daily occupations as they grow older. Visual impairment affects survival of older patients, quality of life, can affect a person’s self-ranking of health, may be associated with social and functional decline, use of community support services, depression, falls, nursing home placement, and increased mortality. It has been hypothesized that senile cataract may serve as a marker for generalised tissue aging, since structural changes occurring in the proteins of the lens during cataract formation are similar to those which occur elsewhere as part of the aging process. The published analysis revealed a strong age-dependent relationship between undergoing cataract surgery and subsequent mortality. Nuclear opacity, particularly severe nuclear opacity, and mixed opacities with nuclear were significant predictors of mortality independent of body mass index, comorbid conditions, smoking, age, race, and sex. The lens opacity status is considered as an independent predictor of 2-year mortality, an association that could not be explained by potential confounders. Telomeres have become important biomarkers for aging as well as for oxidative stress-related disease. The lens epithelium is especially vulnerable to oxidative stress. Oxidative damage to the cuboidal epithelial cells on the anterior surface of the lens mediated by reactive oxygen species and phospholipid hydroperoxides can precede and contribute to human lens cataract formation. The erosion and shortening of telomeres in human lens epithelial cells in the lack of telomerase activity has been recognized as a primary cause of premature lens senescence phenotype that trigger human cataractogenesis. In this study we aimed to be focused on research defining the mechanisms that underlie linkages among telomere attrition in human lens epithelial cells associated with oxidative stress, biology of the lens response to oxidative damages, aging and health, cataract versus neuroendocrine regulation and disease. The cumulative results demonstrate that carnosine, released ophthalmically from the patented 1% N-acetylcarnosine prodrug lubricant eye drops, at physiological concentration might remarkably reduce the rate of telomere shortening in the lens cells subjected to oxidative stress in the lack of efficient
antioxidant lens protection. Carnosine promotes the protection of normal cells from acquiring phenotypic characteristics of cellular senescence. The data of visual functions (visual acuity, glare sensitivity) in older adult subjects and older subjects with cataract treated with 1% N-acetylcarnosine lubricant eye drops showed significant improvement as compared, by contrast with the control group which showed generally no improvement in visual functions, with no difference from baseline in visual acuity and glare sensitivity readings. N-acetylcarnosine derived from the lubricant eye drops may be transported into the hypothalamic tuberomammillary nucleus (TMN) histamine neurons and gradually hydrolyzed. The resulting L-histidine may subsequently be converted into histamine, which could be responsible for the effects of carnosine on neurotransmission and hormone-like antiaging and anti-cataract physiological function. The research utilizing the N-acetylcarnosine lubricant eye drops powerful therapeutic platform provides the findings related to the intraocular uptake exposure sources as well as a timing dosage and duration systemic absorption of said preparation from the conjunctival sac reaching the hypothalamus with activities transfer into the hypothalamic-neuroendocrine pathways affecting across the hypothalamus metabolic pathway the telomere biology and cataract disease occurrence, reversal and prevention and the average expected lifespan of an individual. Such findings can be translated into clinical practice and may provide a basis for personalized cataract disease and aging prevention and treatment approaches.

Amino Acids. 2015 Jun 17.

Carnosine metabolism in diabetes is altered by reactive metabolites.

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Carnosinase 1 (CN1) contributes to diabetic nephropathy by cleaving histidine-dipeptides which scavenge reactive oxygen and carbonyl species and increase nitric oxide (NO) production. In diabetic mice renal CN1 activity is increased, the regulatory mechanisms are unknown. We therefore analysed the in vitro and in vivo regulation of CN1 activity using recombinant and human CN1, and the db/db mouse model of diabetes. Glucose, leptin and insulin did not modify recombinant and human CN1 activity in vitro, glucose did not alter renal CN1 activity of WT or db/db mice ex vivo. Reactive metabolite methylglyoxal and Fenton reagent carbonylated recombinant CN1 and doubled CN1 efficiency. NO S-nitrosylated CN1 and decreased CN1 efficiency for carnosine by 70% (p < 0.01), but not for anserine. Both CN1 cysteine residues were nitrosylated, the cysteine at position 102 but not at position 229 regulated CN1 activities. In db/db mice, renal CN1 mRNA and protein levels were similar as in non-diabetic controls, CN1 efficiency 1.9 and 1.6 fold higher for carnosine and anserine. Renal carbonyl stress was strongly increased and NO production halved, CN1 highly carbonylated and less S-nitrosylated compared to WT mice. GSH and NO\textsubscript{2/3} concentrations were reduced and inversely related with carnosine degradation rate (r = -0.82/-0.85). Thus, reactive metabolites of diabetes upregulate CN1 activity by post-translational modifications, and thus decrease the availability of reactive metabolite-scavenging histidine dipeptides in the kidney in a positive feedback loop. Interference with this vicious circle may represent a new therapeutic target for mitigation of DN.

J Gen Virol. 2015 Jul 31
Carnosine markedly ameliorates H9N2 swine influenza virus-induced acute lung injury.

Oxidative stress injury is an important pathogenesis of influenza virus in critically ill patients. The present study investigated the efficacy of carnosine, an antioxidant and free-radical scavenger, on a model of acute lung injury (ALI) induced by H9N2 swine influenza virus. A total of 320 female BALB/c mice were randomized into four groups and treated as follow: (1) mock-infected control, (2) carnosine control, (3) H9N2 group, and (4) H9N2 + carnosine treatment group. The H9N2 group mice were inoculated intranasally with A/Swine/Hebei/108/2002 (H9N2) virus (100 μL) in allantoic fluid (AF), while mock-infected animals were intranasally inoculated with noninfectious AF. Carnosine (10 mg/kg body weight) was administered orally (100 μL) for 7 consecutive days. The survival rate, lung water content, TNF-α, and interleukin (IL)-1β levels; lung histopathology; myeloperoxidase (MPO) activity; and toll-like receptor (TLR)-4 analyses were performed at 2, 4, 6, 8, and 14 days after inoculation. Carnosine treatment effectively decreased the mortality (43% vs 75%, \( P < 0.05 \)), significantly ameliorated pathological lesions in lungs, and decreased lung wet/dry weight ratio (\( P < 0.05 \)). It also inhibited MPO activity, suppressed TNF-α and IL-1β release, decreased H9N2 viral titer, and markedly inhibited levels of mRNA and protein of TLR-4 in the lungs of infected mice (\( P < 0.05 \)), which supported the use of carnosine for managing severe influenza cases.


Intravitreal injection of forskolin, homotaurine, and L-carnosine affords neuroprotection to retinal ganglion cells following retinal ischemic injury.
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PURPOSE: Retinal ganglion cell (RGC) death is the final event leading to visual impairment in glaucoma; therefore, identification of neuroprotective strategies able to slow down or prevent the process is one of the main challenges for glaucoma research. The purpose of this study was to evaluate the neuroprotective potential of RGC death induced by the in vivo transient increase in intraocular pressure (IOP) of a combined treatment with forskolin, homotaurine, and L-carnosine. Forskolin (7β-acetoxy-8, 13-epoxy-1α, 6β, 9α-trihydroxy-labd-14-en-11-one) is an activator of adenylylate cyclase that decreases IOP by reducing aqueous humor production and functions as a neuroprotector due to its neurotrophin-stimulating activity. Homotaurine is a natural aminosulfonate compound endowed with neuromodulatory effects, while the dipeptide L-carnosine is known for its antioxidant properties. METHODS: Retinal ischemia was induced in
the right eye of adult male Wistar rats by acutely increasing the IOP. Forskolin, homotaurine, and L-carnosine were intravitreally injected and RGC survival evaluated following retrograde labeling with FluoroGold. Total and phosphorylated Akt and glycogen synthase kinase-3β (GSK-3β) protein levels, as well as calpain activity, were analyzed with western blot. Protein kinase A (PKA) was inhibited by intravitreal injection of H89. RESULTS: A synergic neuroprotective effect on RGC survival was observed following the combined treatment with forskolin, homotaurine, and L-carnosine compared to forskolin alone. The observed neuroprotection was associated with reduced calpain activity, upregulation of phosphoinositide 3-kinase (PI3K)/Akt pathway, and inhibition of GSK-3β but was independent from PKA activation and distinct from the hypotensive effects of forskolin. CONCLUSIONS: A multidrug/multitarget approach, by interfering with several pathways involved in RGC degeneration, may be promising to achieve glaucoma neuroprotection.


**Prevalence of cataract in adult Down's syndrome patients aged 28 to 83 years.**

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**BACKGROUND:** Age-related cataract is the major cause of blindness in humans throughout the world. The majority of previous studies of cataract in Down's syndrome (which usually results from trisomy 21) have reported that the prevalence of this ocular abnormality is higher for a given age range than in the general population. The objective of the present study was to study the prevalence of cataract in a well-defined population of adults with Down's syndrome.

**METHODS:** An in-patient population of 68 adults (35 males and 33 females) with Down's syndrome, aged between 28.9 and 83.3 years, underwent ophthalmological examination for the presence of cataracts. RESULTS: Overall, the prevalence of cataract was 16.2%, with no significant difference in the prevalence between males (17.1%) and females (15.2%). In those aged between 45 and 64 years, the prevalence was 16.7%, rising in those aged between 65 and 75 years to 28.6%. CONCLUSION: Compared with the general population, the prevalence of cataract in Down's syndrome was raised in those aged 45 to 64 years, but not in those aged 65 to 75 years; the latter might be a function of the relatively small number of patients in this age group. The increased prevalence of cataract found in those in the 45- to 64-year-old age group may be the result of increased levels of the copper- and zinc-containing superoxide dismutase enzyme (CuZnSOD), in turn resulting from the location of the associated five exons of SOD1 on chromosome 21. These elevated levels of superoxide dismutase may give rise to increased levels of reactive species, including hydrogen peroxide and hydroxyl radicals, which may increase the risk of cataractogenesis. It is suggested that nutritional supplementation with antioxidants may therefore help reduce the prevalence of cataract in Down's syndrome.


**Evidence for an increase in trisomy 21 (Down syndrome) in Europe after the Chernobyl reactor accident.**

Sperling K¹, Neitzel H, Scherb H.
The objective of this study is to investigate the prevalence of Down syndrome (DS) associated with Chernobyl fallout. Maternal age-adjusted DS data and corresponding live birth data from the following seven European countries or regions were analyzed: Bavaria and West Berlin in Germany, Belarus, Hungary, the Lothian Region of Scotland, North West England, and Sweden from 1981 to 1992. To assess the underlying time trends in the DS occurrence, and to investigate whether there have been significant changes in the trend functions after Chernobyl, we applied logistic regression allowing for peaks and jumps from January 1987 onward. The majority of the trisomy 21 cases of the previously reported, highly significant January 1987 clusters in Belarus and West Berlin were conceived when the radioactive clouds with significant amounts of radionuclides with short physical half-lives, especially (131)iodine, passed over these regions. Apart from this, we also observed a significant longer lasting effect in both areas. Moreover, evidence for long-term changes in the DS prevalence in several other European regions is presented and explained by exposure, especially to (137)Cs. In many areas, (137)Cs uptake reached its maximum one year after the Chernobyl accident. Thus, the highest increase in trisomy 21 should be observed in 1987/1988, which is indeed the case. Based on the fact that maternal meiosis is an error prone process, the assumption of a causal relationship between low-dose irradiation and nondisjunction is the most likely explanation for the observed increase in DS after the Chernobyl reactor accident.


Mother’s Happiness with Cognitive - Executive Functions and Facial Emotional Recognition in School Children with Down Syndrome.
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BACKGROUND: According to the mother's key roles in bringing up emotional and cognitive abilities of mentally retarded children and respect to positive psychology in recent decades, this research is administered to assess the relation between mother's happiness level with cognitive-executive functions (i.e. attention, working memory, inhibition and planning) and facial emotional recognition ability as two factors in learning and adjustment skills in mentally retarded children with Down syndrome. METHODS: This study was an applied research and data were analyzed by Pearson correlation procedure. Population is included all school children with Down syndrome (9-12 yr) that come from Tehran, Iran. Overall, 30 children were selected as an in access sample. After selection and agreement of parents, the Wechsler Intelligence Scale for Children-Revised (WISC-R) was performed to determine the student's IQ, and then mothers were invited to fill out the Oxford Happiness Inventory (OHI). Cognitive-executive functions were evaluated by tests as followed: Continues Performance Test (CPT), N-Back, Stroop test (day and night version) and Tower of London. Ekman emotion facial expression test was also
accomplished for assessing facial emotional recognition in children with Down syndrome, individually. RESULTS: Mother's happiness level had a positive relation with cognitive-executive functions (attention, working memory, inhibition and planning) and facial emotional recognition in her children with Down syndrome, significantly. CONCLUSION: Parents' happiness (especially mothers) is a powerful predictor for cognitive and emotional abilities of their children.


Pain perception in people with Down syndrome: a synthesis of clinical and experimental research.
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People with an intellectual disability experience both acute and chronic pain with at least the same frequency as the general population. However, considerably less is known about the pain perception of people with Down syndrome. In this review paper, we evaluated the available clinical and experimental evidence. Some experimental studies of acute pain have indicated that pain threshold was higher than normal but only when using a reaction time method to measure pain sensitivity. However, when reaction time is not part of the calculation of the pain threshold, pain sensitivity in people with Down syndrome is in fact lower than normal (more sensitive to pain). Clinical studies of chronic pain have shown that people with an intellectual disability experience chronic pain and within that population, people with Down syndrome also experience chronic pain, but the precise prevalence of chronic pain in Down syndrome has yet to be established. Taken together, the literature suggests that people with Down syndrome experience pain, both acute and chronic, with at least the same frequency as the rest of the population. Furthermore, the evidence suggests that although acute pain expression appears to be delayed, once pain is registered, there appears to be a magnified pain response. We conclude by proposing an agenda for future research in this area.

Food Nutr Res. 2015 Feb 3;59:25487.

Dietary aspects related to health and obesity in Williams syndrome, Down syndrome, and Prader-Willi syndrome.
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BACKGROUND: Dietary aspects that might contribute to development of obesity and secondary conditions are not well documented in genetic subgroups associated with intellectual disability. OBJECTIVE: To describe the intake frequencies of selected foods in participants with Prader-
Willi syndrome (PWS), Down syndrome (DS), and Williams syndrome (WS), and investigate the association with body mass index (BMI). To explore food-related autonomy and intake frequencies among persons with DS in different living arrangements. METHODS:

Self-reported intake frequencies and measurement of plasma carotenoids and erythrocyte content of omega-3 fatty acids (FAs) were investigated in persons aged 16-42 years, with WS (n=21), DS (n=40), and PWS (n=20). RESULTS: A larger proportion of participants with PWS showed high-frequency intake of fruits (p=0.012) and vegetables (p=0.004), and had higher plasma carotenoids (p<0.001) compared to participants with DS and WS. Furthermore, a larger proportion of participants with WS were low-frequency consumers of fish (p=0.005), less likely to use omega-3 FA supplements (p=0.023), and had reduced erythrocyte concentrations of long-chain omega-3 FAs (p<0.001), compared to participants with PWS and DS. In DS, BMI was negatively associated with plasma carotenoids. Increased proportions of participants living in communities showed high-frequency intake of precooked meals (p=0.030), and a tendency toward high-frequency consumption of soft drinks (p=0.079), when compared to peers living with relatives. Participants in community residences were also more likely to participate frequently in food-related decisions and preparations. CONCLUSIONS: Persons with WS had a less-favorable dietary pattern when compared to persons with PWS. A larger proportion of persons living in communities frequently consumed precooked meals and showed a tendency of high-frequency soft drink consumption. Otherwise, their intake frequencies of the investigated foods were similar to those living with relatives, but they participated more frequently in decisions and preparations of foods.

Dev Med Child Neurol. 2015 Aug 18.

Morbidity and medication in a large population of individuals with Down syndrome compared to the general population.

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AIM: The aim of this study was to describe the incidence of morbidities and the prevalence of medical prescriptions in a large Down syndrome population. METHOD: A retrospective cohort study was carried out using the UK Clinical Practice Research Datalink from 1 January 2004 to 31 December 2013. We matched individuals with Down syndrome to randomly selected control participants by practice site, sex, birth year, and recording period. RESULTS: A total of 6430 individuals with Down syndrome (3009 females, 3421 males) and 19 176 controls (8966 females, 10 210 males) were included in the study. The incidence of cardiovascular disorders, gastrointestinal diseases (incidence rate ratio [IRR] 7.9 at 3 to <6y: yearly prevalence ratio [YPR] for laxatives 4.7), and sleeping disorders (IRR 4.8 in 3 to <6y) was increased in children with Down syndrome versus control participants. New onset of congenital heart malformation, ear diseases, eye disorders, autism, hypothyroidism, diabetes, and obesity were more frequent in childhood and remained elevated in adulthood (overall IRR 35.5, 1.7, 3.1, 4.4, 13.1, 1.3, and
2.6 respectively), whereas the gap widened in adulthood for epilepsy and intellectual disability (IRR 15.2 and 158 respectively, in participants older than 30y). At ≥30 years, the incidence of hypotension and dementia was raised (IRR 3.0 and 92.1 respectively; YPR for dementia drugs: 76.3); and that of hypertension, depression and anxiety was lowered (IRR 0.2, 0.5, and 0.4 respectively).

INTERPRETATION: The profile of newly occurring morbidities in Down syndrome varies across the developmental lifespan.


**The relationship between craniofacial development and hypodontia in patients with Down syndrome.**

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Background/Objective: Hypodontia is often seen in people with Down syndrome (DS). In the normal population, persons with hypodontia have a shorter cranial base and a hypoplastic maxilla, leading to a skeletal Class III tendency and a reduced face height. The purpose of this study was to examine craniofacial morphology in patients with DS at different ages and the influence of hypodontia on their craniofacial morphology.

Materials/Methods A comparative cross-sectional study was conducted in 63 children with DS (6-19 years old; 28 males and 35 females) at a Centre for Special Care Dentistry in Rotterdam, the Netherlands (CBT Rijnmond). Digital lateral cephalograms were obtained from all subjects and a cephalometric analysis was performed. The subjects were divided into a group with hypodontia (13 males and 25 females) and a group without hypodontia (15 males and 10 females).

RESULTS: Significant results included a decrease in antero-posterior relationship of upper and lower jaw (ANB angle -0.331° per year, P = 0.044) and a decrease in vertical dimension (S-N_Go-Gn angle -0.72° per year, P = 0.039) over the years in subjects with hypodontia compared to subjects without hypodontia.

Conclusion: The process of growth in DS patients is towards a reversed overjet. Hypodontia seems to have an additional effect on this development. The management of hypodontia as part of the complete treatment of dental development in DS children is important because it strongly influences the jaw relationship.

Glob Heart. 2015 Aug 11.

**DS-Connect: A Promising Tool to Improve Lives and Engage Down Syndrome Communities Worldwide.**

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Down syndrome (DS) is the most common genetic cause of intellectual and developmental disabilities in the United States with an estimated birth prevalence of 1:691 births; however, worldwide estimates of the number of individuals with intellectual and developmental disabilities, including DS, remain speculative. Little is known about the global health impact of DS, such as heart defects, gastrointestinal malformations, and other medical and behavioral issues. Further research is needed to develop the next generation of novel therapies and compounds aimed at improving cognition, reducing dementia, and mitigating other manifestations of DS. To address these challenges, the National Institutes of Health has created the first web-based, voluntary registry and data resource called DS-Connect: The Down Syndrome Registry to collect demographic and health information about individuals with DS.


Bidirectional Regulation of Amyloid Precursor Protein-Induced Memory Defects by Nebula/DSCR1: A Protein Upregulated in Alzheimer's Disease and Down Syndrome.

Shaw JL, Zhang S, Chang KT.

Aging individuals with Down syndrome (DS) have an increased risk of developing Alzheimer's disease (AD), a neurodegenerative disorder characterized by impaired memory. Memory problems in both DS and AD individuals usually develop slowly and progressively get worse with age, but the cause of this age-dependent memory impairment is not well understood. This study examines the functional interactions between Down syndrome critical region 1 (DSCR1) and amyloid-precursor protein (APP), proteins upregulated in both DS and AD, in regulating memory. Using Drosophila as a model, we find that overexpression of nebula (fly homolog of DSCR1) initially protects against APP-induced memory defects by correcting calcineurin and cAMP signaling pathways but accelerates the rate of memory loss and exacerbates mitochondrial dysfunction in older animals. We report that transient upregulation of Nebula/DSCR1 or acute pharmacological inhibition of calcineurin in aged flies protected against APP-induced memory loss. Our data suggest that calcineurin dyshomeostasis underlies age-dependent memory impairments and further imply that chronic Nebula/DSCR1 upregulation may contribute to age-dependent memory impairments in AD in DS. SIGNIFICANCE STATEMENT: Most Down syndrome (DS) individuals eventually develop Alzheimer's disease (AD)-like dementia, but mechanisms underlying this age-dependent memory impairment remain poorly understood. This study examines Nebula/Down syndrome critical region 1 (DSCR1) and amyloid-precursor protein (APP), proteins upregulated in both DS and AD, in regulating memory. We uncover a previously unidentified role for Nebula/DSCR1 in modulating APP-induced memory defects during aging. We show that upregulation of Nebula/DSCR1, an inhibitor of calcineurin, rescues APP-induced memory defects in young flies but enhances memory loss of older flies. Excitingly, transient Nebula/DSCR1 overexpression or calcineurin
inhibition in aged flies ameliorates APP-mediated memory problems. These results suggest that chronic Nebula/DSCR1 upregulation may contribute to age-dependent memory loss in DS and AD and points to correcting calcineurin signaling as a means to improve memory during aging.

**Nutr Rev.** 2012 Mar;70(3):153-64.

**Suboptimal magnesium status in the United States: are the health consequences underestimated?**

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In comparison with calcium, magnesium is an "orphan nutrient" that has been studied considerably less heavily. Low magnesium intakes and blood levels have been associated with type 2 diabetes, metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer. Almost half (48%) of the US population consumed less than the required amount of magnesium from food in 2005-2006, and the figure was down from 56% in 2001-2002. Surveys conducted over 30 years indicate rising calcium-to-magnesium food-intake ratios among adults and the elderly in the United States, excluding intake from supplements, which favor calcium over magnesium. The prevalence and incidence of type 2 diabetes in the United States increased sharply between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0. Dietary Reference Intakes determined by balance studies may be misleading if subjects have chronic latent magnesium deficiency but are assumed to be healthy. Cellular magnesium deficit, perhaps involving TRPM6/7 channels, elicits calcium-activated inflammatory cascades independent of injury or pathogens. Refining the magnesium requirements and understanding how low magnesium status and rising calcium-to-magnesium ratios influence the incidence of type 2 diabetes, metabolic syndrome, osteoporosis, and other inflammation-related disorders are research priorities.


**Remineralization of primary tooth enamel from individuals with Down syndrome.**

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**PURPOSE:** The purpose of this study was to clarify the characteristics of primary tooth enamel of Down syndrome patients (DSPs). We examined 9 primary teeth of Down syndrome children and 11 primary teeth of normally developed children to investigate the remineralization processes of enamel by transverse microradiography and X-ray micro analyzer (XMA).

**METHODS:** Mineral loss, lesion depth, maximum mineral value, minimum mineral value, depth of maximum mineral value, and depth of minimum mineral value were used to analyze transverse microradiography (TMR). In addition, we calculated the percentage of enamel remineralization. **RESULTS:** All the parameters in the 2 groups showed marked recovery. The
results indicated that the Down syndrome group was significantly remineralized the same way as the control group. According to the comparison of mineral content distribution by XMA, the content distribution of magnesium was different between the 2 groups. CONCLUSION: While recovery through remineralization of primary teeth was similar between Down syndrome children and normally developed children, the mechanism of remineralization process may be different between the 2 groups; consequently, magnesium may be considered as one of the factors affecting recovery.