



Research Concerning Mitochondrial Dysfunction as Implicated in the Pathophysiology of Chronic Health Conditions

Autism Spectrum Disorders/ADHD

Altern Med Rev. 2010 Mar;15(1):15-32.

Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder.

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Abstract

Autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) are common and complex neurodevelopmental conditions. Diagnostic criteria for these conditions have traditionally relied solely on behavioral criteria without consideration for potential biomedical underpinnings. Newer evidence, however, reveals that ASDs are associated with: oxidative stress; decreased methylation capacity; limited production of glutathione; mitochondrial dysfunction; intestinal dysbiosis; increased toxic metal burden; immune dysregulation, characterized by a unique inflammatory bowel disease and immune activation of neuroglial cells; and ongoing brain hypoperfusion. Many of these same problems are common features in children with ADHD. These medical conditions, whether co-morbidities or etiopathogenic, would be expected to have synergistically negative effects on the development, cognition, focus, and attention of affected children. It is likely these biological abnormalities contribute significantly to the behavioral symptoms intrinsic in these diagnoses. However, treatment for these underlying medical disorders is clinically justified, even if no clear immediate behavioral improvements are observed. This article reviews the medical literature and discusses the authors clinical experience using various biomarkers for measuring oxidative stress, methylation capacity and transsulfuration, immune function, gastrointestinal problems, and toxic metal burden. These biomarkers provide useful guides for selection, efficacy, and sufficiency of biomedical interventions. The use of these biomarkers is of great importance in young children with ADHD or individuals of any age with ASD, because typically they cannot adequately communicate regarding their symptoms.

Biochim Biophys Acta. 2010 June - July;1797(6-7):1130-1137. Epub 2010 May 9.

Mitochondrial dysfunction in autism spectrum disorders: Cause or effect?

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Abstract

Autism Spectrum Disorders encompass severe developmental disorders characterized by variable degrees of impairment in language, communication and social skills, as well as by repetitive and stereotypic patterns of behaviour. Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as (a) elevated lactate, pyruvate, and alanine levels in blood, urine and/or cerebrospinal fluid, (b) serum carnitine deficiency, and/or (c) enhanced oxidative stress. These biochemical abnormalities are accompanied by highly heterogeneous clinical



presentations, which generally (but by no means always) encompass neurological and systemic symptoms relatively unusual in idiopathic autistic disorder. In some patients, these abnormalities have been successfully explained by the presence of specific mutations or rearrangements in their mitochondrial or nuclear DNA. However, in the majority of cases, abnormal energy metabolism cannot be immediately linked to specific genetic or genomic defects. Recent evidence from post-mortem studies of autistic brains points toward abnormalities in mitochondrial function as possible downstream consequences of dysreactive immunity and altered calcium (Ca²⁺) signalling. Copyright © 2010 Elsevier B.V. All rights reserved.

Curr Opin Neurol. 2010 Apr;23(2):103-10.

Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders.

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Abstract

PURPOSE OF REVIEW: This review presents a rationale and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASDs). **RECENT FINDINGS:** Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150, only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also suggest a role for environment. Systemic and central nervous system pathophysiology, including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be consistent with a role for environmental influence (e.g. from air pollution, organophosphates, heavy metals) in ASD, and some of the underlying biochemical disturbances (such as abnormalities in glutathione, a critical antioxidant and detoxifier) can be reversed by targeted nutritional interventions. Dietary factors and food contaminants may contribute risk. Improvement and loss of diagnosis in some with ASD suggest brain circuitry amenable to environmental modulation. **SUMMARY:** Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

Prostaglandins Leukot Essent Fatty Acids. 2009 Oct;81(4):253-64. Epub 2009 Jul 15.

Novel plasma phospholipid biomarkers of autism: mitochondrial dysfunction as a putative causative mechanism.

Pastural E, Ritchie S, Lu Y, Jin W, Kavianpour A, Khine Su-Myat K, Heath D, Wood PL, Fisk M, Goodenowe DB.

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Abstract

Autism is a neurological disorder that manifests as noticeable behavioral and developmental abnormalities predominantly in males between the ages of 2 and 10. Although the genetics, biochemistry and neuropathology of this disease have been extensively studied, underlying causal factors to this disease have remained elusive. Using a longitudinal trial design in which three plasma samples were collected from 15 autistic and 12 non-autistic age-matched controls over the course of 1 year, universal and unambiguous alterations in lipid metabolism were observed. Biomarkers of fatty acid elongation and desaturation (poly-unsaturated long chain fatty acids (PUFA) and/or saturated very long chain fatty acids (VLCFA)-containing ethanolamine phospholipids) were statistically elevated in all autistic subjects. In all 8 of the affected/non-affected sibling pairs, the affected sibling had higher levels of these biomarkers than the unaffected sibling. Exposure of neurons, astrocytes and hepatocytes in vitro to elevated extracellular glutamate levels resulted in lipid biomarker changes indistinguishable from those observed in autistic subjects. Glutamate stress also resulted in in vitro decreased levels of reduced glutathione (GSH), methionine and cysteine, in a similar way to the decreases we observed in autism plasma. Impaired mitochondrial fatty acid oxidation, elevated plasma VLCFAs, and glutamate toxicity as putative causal factors in the biochemistry, neuropathology, and gender bias in autism are discussed.



EPIDEMIC ANSWERS

FASEB J. 2009 Aug;23(8):2374-83. Epub 2009 Mar 23.

Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism.

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Abstract

Research into the metabolic phenotype of autism has been relatively unexplored despite the fact that metabolic abnormalities have been implicated in the pathophysiology of several other neurobehavioral disorders. Plasma biomarkers of oxidative stress have been reported in autistic children; however, intracellular redox status has not yet been evaluated. Lymphoblastoid cells (LCLs) derived from autistic children and unaffected controls were used to assess relative concentrations of reduced glutathione (GSH) and oxidized disulfide glutathione (GSSG) in cell extracts and isolated mitochondria as a measure of intracellular redox capacity. The results indicated that the GSH/GSSG redox ratio was decreased and percentage oxidized glutathione increased in both cytosol and mitochondria in the autism LCLs. Exposure to oxidative stress via the sulfhydryl reagent thimerosal resulted in a greater decrease in the GSH/GSSG ratio and increase in free radical generation in autism compared to control cells. Acute exposure to physiological levels of nitric oxide decreased mitochondrial membrane potential to a greater extent in the autism LCLs, although GSH/GSSG and ATP concentrations were similarly decreased in both cell lines. These results suggest that the autism LCLs exhibit a reduced glutathione reserve capacity in both cytosol and mitochondria that may compromise antioxidant defense and detoxification capacity under prooxidant conditions.

Insulin Resistance, Diabetes, Metabolic Syndrome

J Hepatol. 2010 Mar 4. [Epub ahead of print]

Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model.

Rector RS, Thyfault JP, Uptergrove GM, Morris EM, Naples SP, Borengasser SJ, Mikus CR, Laye MJ, Laughlin MH, Booth FW, Ibdah JA.

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Abstract

BACKGROUND & AIMS: In this study, we sought to determine the temporal relationship between hepatic mitochondrial dysfunction, hepatic steatosis and insulin resistance, and to examine their potential role in the natural progression of non-alcoholic fatty liver disease (NAFLD) utilising a sedentary, hyperphagic, obese, Otsuka Long-Evans Tokushima Fatty (OLETF) rat model. **METHODS:** OLETF rats and their non-hyperphagic control Long-Evans Tokushima Otsuka (LETO) rats were sacrificed at 5, 8, 13, 20, and 40 weeks of age (n=6-8 per group). **RESULTS:** At 5 weeks of age, serum insulin and glucose and hepatic triglyceride (TG) concentrations did not differ between animal groups; however, OLETF animals displayed significant ($p < 0.01$) hepatic mitochondrial dysfunction as measured by reduced hepatic carnitine palmitoyl-CoA transferase-1 activity, fatty acid oxidation, and cytochrome c protein content compared with LETO rats. Hepatic TG levels were significantly elevated by 8 weeks of age, and insulin resistance developed by 13 weeks in the OLETF rats. NAFLD progressively worsened to include hepatocyte ballooning, perivenular fibrosis, 2.5-fold increase in serum ALT, hepatic mitochondrial ultrastructural abnormalities, and increased hepatic oxidative stress in the OLETF animals at later ages. Measures of hepatic mitochondrial content and function including beta-hydroxyacyl-CoA dehydrogenase activity, citrate synthase activity, and immunofluorescence staining for mitochondrial carbamoyl phosphate synthetase-1, progressively worsened and were significantly reduced at 40 weeks in OLETF rats compared to LETO animals. **CONCLUSIONS:** Our study documents that hepatic mitochondrial dysfunction precedes the development of NAFLD and insulin resistance in the

OETF rats. This evidence suggests that progressive mitochondrial dysfunction contributes to the natural history of obesity-associated NAFLD

Protective effects of R-alpha-lipoic acid and acetyl-L-carnitine in MIN6 and isolated rat islet cells chronically exposed to oleic acid.

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Abstract

Mitochondrial dysfunction due to oxidative stress and concomitant impaired beta-cell function may play a key role in type 2 diabetes. Preventing and/or ameliorating oxidative mitochondrial dysfunction with mitochondria-specific nutrients may have preventive or therapeutic potential. In the present study, the oxidative mechanism of mitochondrial dysfunction in pancreatic beta-cells exposed to sublethal levels of oleic acid (OA) and the protective effects of mitochondrial nutrients [R-alpha-lipoic acid (LA) and acetyl-L-carnitine (ALC)] were investigated. Chronic exposure (72 h) of insulinoma MIN6 cells to OA (0.2-0.8 mM) increased intracellular oxidant formation, decreased mitochondrial membrane potential (MMP), enhanced uncoupling protein-2 (UCP-2) mRNA and protein expression, and consequently, decreased glucose-induced ATP production and suppressed glucose-stimulated insulin secretion. Pretreatment with LA and/or ALC reduced oxidant formation, increased MMP, regulated UCP-2 mRNA and protein expression, increased glucose-induced ATP production, and restored glucose-stimulated insulin secretion. The key findings on ATP production and insulin secretion were verified with isolated rat islets. These results suggest that mitochondrial dysfunction is involved in OA-induced pancreatic beta-cell dysfunction and that pretreatment with mitochondrial protective nutrients could be an effective strategy to prevent beta-cell dysfunction.

Carnitine: Therapeutic Role in Diabetes

Diabetologia. 2007 Apr;50(4):824-32. Epub 2007 Feb 20.

Carnitine revisited: potential use as adjunctive treatment in diabetes.

Power RA, Hulver MW, Zhang JY, Dubois J, Marchand RM, Ilkayeva O, Muoio DM, Mynatt RL.

Division of Nutrition and Chronic Disease, Pennington Biomedical Research Center, Baton Rouge, LA, USA.

Abstract

AIMS/HYPOTHESIS: This study examined the efficacy of supplemental L: -carnitine as an adjunctive diabetes therapy in mouse models of metabolic disease. We hypothesised that carnitine would facilitate fatty acid export from tissues in the form of acyl-carnitines, thereby alleviating lipid-induced insulin resistance. MATERIALS AND METHODS: Obese mice with genetic or diet-induced forms of insulin resistance were fed rodent chow +/- 0.5% L: -carnitine for a period of 1-8 weeks. Metabolic outcomes included insulin tolerance tests, indirect calorimetry and mass spectrometry-based profiling of acyl-carnitine esters in tissues and plasma. RESULTS: Carnitine supplementation improved insulin-stimulated glucose disposal in genetically diabetic mice and wild-type mice fed a high-fat diet, without altering body weight or food intake. In severely diabetic mice, carnitine supplementation increased average daily respiratory exchange ratio from 0.886 +/- 0.01 to 0.914 +/- 0.01 (p < 0.01), reflecting a marked increase in systemic carbohydrate oxidation. Similarly, under insulin-stimulated conditions, carbohydrate oxidation was higher and total energy expenditure increased from 172 +/- 10 to 210 +/- 9 kJ kg fat-free mass(-1) h(-1) in the carnitine-supplemented compared with control animals. These metabolic improvements corresponded with a 2.3-fold rise in circulating levels of acetyl-carnitine, which accounts for 86 and 88% of the total acyl-carnitine pool in plasma and skeletal muscle, respectively. Carnitine supplementation also increased several medium- and long-chain acyl-carnitine species in both plasma and tissues. CONCLUSIONS/INTERPRETATION: These findings suggest that carnitine supplementation relieves lipid overload and glucose intolerance in obese rodents by enhancing mitochondrial efflux of excess acyl groups from insulin-responsive tissues. Carefully controlled clinical trials should be considered.



Mitochondrial Dysfunction and Type 2 Diabetes

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Maintenance of normal blood glucose levels depends on a complex interplay between the insulin responsiveness of skeletal muscle and liver and glucose-stimulated insulin secretion by pancreatic β cells. Defects in the former are responsible for insulin resistance, and defects in the latter are responsible for progression to hyperglycemia. Emerging evidence supports the potentially unifying hypothesis that both of these prominent features of type 2 diabetes are caused by mitochondrial dysfunction.

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Indian J Med Res. 2007 Mar;125(3):399-410.

Skeletal muscle mitochondrial dysfunction & diabetes.

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Abstract

Skeletal muscle insulin resistance is a key contributor to the pathophysiology of type 2 diabetes. Recent studies have shown that insulin resistance in a variety of conditions including type 2 diabetes, ageing and in offspring of type 2 diabetes is associated with muscle mitochondrial dysfunction. The important question is whether insulin resistance results from muscle mitochondrial dysfunction or vice versa. Gene array studies from muscle biopsy samples showed that transcript levels of several genes, especially OXPHOS genes are altered in type 2 diabetic patients during poor glycaemic control but many of these alterations are normalized by insulin treatment suggesting that reduced insulin action is a factor involved in muscle mitochondrial dysfunction. Moreover, insulin infusion while maintaining glucose and amino acid levels results in increase in muscle mitochondrial gene transcript levels and ATP production indicating that insulin is a key regulator of muscle mitochondrial biogenesis. At a similar post-absorptive insulin levels both type 2 diabetic patients and non diabetic controls have similar muscle mitochondrial ATP production but increasing insulin from low to high levels stimulate ATP production only in non diabetic people but not in the diabetic people. The lack of muscle mitochondrial response to insulin in type 2 diabetic patients is likely to be related to insulin resistance and reduced substrate utilization.

Additional Information on Diabetes

INSULIN RESISTANCE AND MITOCHONDRIAL DYSFUNCTION

It has been known for many years that severe mitochondrial dysfunction can result in diabetes that is typically associated with severe β -cell dysfunction and neurological abnormalities (78–80). More recent MRS studies, measuring rates of mitochondrial oxidative phosphorylation activity in skeletal muscle, have found that more subtle defects in mitochondrial function may play an important role in the pathogenesis of type 2 diabetes. Using ¹³C/³¹P MRS, we directly assessed mitochondrial oxidative and phosphorylation activity in the healthy lean elderly volunteers with severe muscle insulin resistance and found that they have an ~40% reduction in rates of oxidative phosphorylation activity associated with increased intramyocellular and intrahepatic lipid content compared with BMI activity-matched young control subjects (19). This study suggests that an acquired loss of mitochondrial function associated with aging predisposes elderly subjects to intramyocellular lipid accumulation, which results in insulin resistance through the mechanisms described earlier (Fig. 1). Using a similar approach, we used ³¹P MRS to examine mitochondrial function in young lean insulin-resistant offspring of parents with type 2 diabetes (20). Insulin resistance in these individuals could be attributed to severe defects in insulin-stimulated muscle glucose metabolism, which were associated with an ~80% increase in intramyocellular lipid content assessed by ¹H MRS. Furthermore, these changes were associated with a 30% reduction in rates of mitochondrial ATP production compared with age-, weight-, and activity-matched insulin-sensitive control subjects (20). To further examine the mechanism responsible for reduced mitochondrial activity in these subjects, we recently assessed mitochondrial



density by electron microscopy and found that mitochondrial density was reduced by 38% in the insulin-resistant offspring (17). Taken together, these data suggest that the reduced mitochondrial function observed in the insulin-resistant offspring may be secondary to reduced mitochondrial content and is consistent with previous studies demonstrating lower mitochondrial density in patients with type 2 diabetes (81). Ritov et al. (82) also reported the subsarcolemmal fraction was especially impaired in obese and type 2 diabetic subjects. In agreement with the finding of decreased mitochondrial density using electron microscopy, we also measured the expression of several mitochondrial proteins and found mitochondrial cytochrome-c oxidase I to be reduced by ~50% in insulin-resistant offspring and a tendency for succinate dehydrogenase and pyruvate dehydrogenase to be reduced by a similar amount (17). Taken together, these data suggest that insulin-resistant offspring of patients with type 2 diabetes may have an inherited condition that causes a reduction in mitochondrial content in skeletal muscle, which in turn may be responsible for the reduced rates of mitochondrial oxidative phosphorylation predisposing them to intramyocellular lipid accumulation.

Excerpted from:

http://diabetes.diabetesjournals.org/content/55/Supplement_2/S9.full

Chronic Fatigue Syndrome

Neuro Endocrinol Lett. 2009;30(4):470-6.

Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder.

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E.

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Abstract

INTRODUCTION: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a medical illness characterized by disorders in inflammatory and oxidative and nitrosative (IO&NS) pathways. **METHODS:** This paper examines the role of Coenzyme Q10 (CoQ10), a mitochondrial nutrient which acts as an essential cofactor for the production of ATP in mitochondria and which displays significant antioxidant activities. Plasma CoQ10 has been assayed in 58 patients with ME/CFS and in 22 normal controls; the relationships between CoQ10 and the severity of ME/CFS as measured by means of the FibroFatigue (FF) scale were measured. **RESULTS:** Plasma CoQ10 was significantly ($p=0.00001$) lower in ME/CFS patients than in normal controls. Up to 44.8% of patients with ME/CFS had values beneath the lowest plasma CoQ10 value detected in the normal controls, i.e. 490 microg/L. In ME/CFS, there were significant and inverse relationships between CoQ10 and the total score on the FF scale, fatigue and autonomic symptoms. Patients with very low CoQ10 (<390 microg/L) suffered significantly more from concentration and memory disturbances. **DISCUSSION:** The results show that lowered levels of CoQ10 play a role in the pathophysiology of ME/CFS and that symptoms, such as fatigue, and autonomic and neurocognitive symptoms may be caused by CoQ10 depletion. Our results suggest that patients with ME/CFS would benefit from CoQ10 supplementation in order to normalize the low CoQ10 syndrome and the IO&NS disorders. The findings that lower CoQ10 is an independent predictor of chronic heart failure (CHF) and mortality due to CHF may explain previous reports that the mean age of ME/CFS patients dying from CHF is 25 years younger than the age of those dying from CHF in the general population. Since statins significantly decrease plasma CoQ10, ME/CFS should be regarded as a relative contraindication for treatment with statins without CoQ10 supplementation.

Depression

Neuro Endocrinol Lett. 2009;30(4):462-9.

Lower plasma Coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness.

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E.

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Abstract



INTRODUCTION: There is now evidence that major depression is accompanied by an induction of inflammatory and oxidative and nitrosative stress (IO&NS) pathways and by a lowered antioxidant status. Coenzyme Q10 (CoQ10) is a strong antioxidant that has anti-inflammatory effects. **METHODS:** This paper examines the plasma concentrations of CoQ10 in 35 depressed patients and 22 normal volunteers and the relationships between plasma CoQ10 and treatment resistant depression (TRD), the severity of illness as measured by means of the Hamilton Depression Rating Scale (HDRS) and the presence of chronic fatigue syndrome (CFS). **RESULTS:** We found that plasma CoQ10 was significantly ($p=0.0002$) lower in depressed patients than in normal controls. 51.4% of the depressed patients had plasma CoQ10 values that were lower than the lowest plasma CoQ10 value detected in the controls. Plasma CoQ10 was significantly lower in patients with TRD and with CFS than in the other depressed patients. There were no significant correlations between plasma CoQ10 and the HDRS. **DISCUSSION:** The results show that lower CoQ10 plays a role in the pathophysiology of depression and in particular in TRD and CFS accompanying depression. It is suggested that depressed patients may benefit from CoQ10 supplementation. The findings that lower CoQ10 is a risk factor to coronary artery disease and chronic heart failure (CHF) and mortality due to CHF suggest that low CoQ10 is another factor explaining the risk to cardiovascular disorder in depression. Since statins significantly lower plasma CoQ10, depressed patients and in particular those with TRD and CFS represent populations at risk to statin treatment.

Obesity, Diabetes and Insulin Resistance

J Biol Chem. 2009 Aug 21;284(34):22840-52. Epub 2009 Jun 24.

Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control.

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Abstract

In addition to its essential role in permitting mitochondrial import and oxidation of long chain fatty acids, carnitine also functions as an acyl group acceptor that facilitates mitochondrial export of excess carbons in the form of acylcarnitines. Recent evidence suggests carnitine requirements increase under conditions of sustained metabolic stress. Accordingly, we hypothesized that carnitine insufficiency might contribute to mitochondrial dysfunction and obesity-related impairments in glucose tolerance. Consistent with this prediction whole body carnitine diminution was identified as a common feature of insulin-resistant states such as advanced age, genetic diabetes, and diet-induced obesity. In rodents fed a lifelong (12 month) high fat diet, compromised carnitine status corresponded with increased skeletal muscle accumulation of acylcarnitine esters and diminished hepatic expression of carnitine biosynthetic genes. Diminished carnitine reserves in muscle of obese rats was accompanied by marked perturbations in mitochondrial fuel metabolism, including low rates of complete fatty acid oxidation, elevated incomplete beta-oxidation, and impaired substrate switching from fatty acid to pyruvate. These mitochondrial abnormalities were reversed by 8 weeks of oral carnitine supplementation, in concert with increased tissue efflux and urinary excretion of acetylcarnitine and improvement of whole body glucose tolerance. Acetylcarnitine is produced by the mitochondrial matrix enzyme, carnitine acetyltransferase (CrAT). A role for this enzyme in combating glucose intolerance was further supported by the finding that CrAT overexpression in primary human skeletal myocytes increased glucose uptake and attenuated lipid-induced suppression of glucose oxidation. These results implicate carnitine insufficiency and reduced CrAT activity as reversible components of the metabolic syndrome.

Diabetologia. 2007 Apr;50(4):824-32. Epub 2007 Feb 20.

Carnitine revisited: potential use as adjunctive treatment in diabetes.

Power RA, Hulver MW, Zhang JY, Dubois J, Marchand RM, Ilkayeva O, Muoio DM, Mynatt RL.

Division of Nutrition and Chronic Disease, Pennington Biomedical Research Center, Baton Rouge, LA, USA.

Abstract

AIMS/HYPOTHESIS: This study examined the efficacy of supplemental L: -carnitine as an adjunctive diabetes therapy in mouse models of metabolic disease. We hypothesized that carnitine would facilitate fatty acid export from tissues in the form of acyl-carnitines, thereby alleviating lipid-induced insulin resistance. **MATERIALS AND METHODS:** Obese mice with genetic or diet-induced forms of insulin resistance were fed rodent chow +/- 0.5% L: -carnitine for a period of 1-8



weeks. Metabolic outcomes included insulin tolerance tests, indirect calorimetry and mass spectrometry-based profiling of acyl-carnitine esters in tissues and plasma. RESULTS: Carnitine supplementation improved insulin-stimulated glucose disposal in genetically diabetic mice and wild-type mice fed a high-fat diet, without altering body weight or food intake. In severely diabetic mice, carnitine supplementation increased average daily respiratory exchange ratio from 0.886 +/- 0.01 to 0.914 +/- 0.01 ($p < 0.01$), reflecting a marked increase in systemic carbohydrate oxidation. Similarly, under insulin-stimulated conditions, carbohydrate oxidation was higher and total energy expenditure increased from 172 +/- 10 to 210 +/- 9 kJ kg fat-free mass(-1) h(-1) in the carnitine-supplemented compared with control animals. These metabolic improvements corresponded with a 2.3-fold rise in circulating levels of acetyl-carnitine, which accounts for 86 and 88% of the total acyl-carnitine pool in plasma and skeletal muscle, respectively. Carnitine supplementation also increased several medium- and long-chain acyl-carnitine species in both plasma and tissues. CONCLUSIONS/INTERPRETATION: These findings suggest that carnitine supplementation relieves lipid overload and glucose intolerance in obese rodents by enhancing mitochondrial efflux of excess acyl groups from insulin-responsive tissues. Carefully controlled clinical trials should be considered.

Mitochondrial nutrients improve immune dysfunction in the type 2 diabetic Goto-Kakizaki rats.

Hao J, Shen W, Tian C, Liu Z, Ren J, Luo C, Long J, Sharman E, Liu J.

Institute for Nutritional Science, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, China.

Abstract

The development of type 2 diabetes is accompanied by decreased immune function and the mechanisms are unclear. We hypothesize that oxidative damage and mitochondrial dysfunction may play an important role in the immune dysfunction in diabetes. In the present study, we investigated this hypothesis in diabetic Goto-Kakizaki rats by treatment with a combination of four mitochondrial-targeting nutrients, namely, R-alpha-lipoic acid, acetyl-L-carnitine, nicotinamide and biotin. We first studied the effects of the combination of these four nutrients on immune function by examining cell proliferation in immune organs (spleen and thymus) and immunomodulating factors in the plasma. We then examined, in the plasma and thymus, oxidative damage biomarkers, including lipid peroxidation, protein oxidation, reactive oxygen species, calcium and antioxidant defence systems, mitochondrial potential and apoptosis-inducing factors (caspase 3, p53 and p21). We found that immune dysfunction in these animals is associated with increased oxidative damage and mitochondrial dysfunction and that the nutrient treatment effectively elevated immune function, decreased oxidative damage, enhanced mitochondrial function and inhibited the elevation of apoptosis factors. These effects are comparable to, or greater than, those of the anti-diabetic drug pioglitazone. These data suggest that a rational combination of mitochondrial-targeting nutrients may be effective in improving immune function in type 2 diabetes through enhancement of mitochondrial function, decreased oxidative damage, and delayed cell death in the immune organs and blood.

Neurodegenerative Disease (e.g., Alzheimer's)

Neuropsychiatr Dis Treat. 2009;5:597-610. Epub 2009 Nov 16.

Coenzyme Q10 effects in neurodegenerative disease.

Spindler M, Beal MF, Henchcliffe C.

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Abstract

Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain, and as a dietary supplement it has recently gained attention for its potential role in the treatment of neurodegenerative disease. Evidence for mitochondrial dysfunction in neurodegenerative disorders derives from animal models, studies of mitochondria from patients, identification of genetic defects in patients with neurodegenerative disease, and measurements of markers of oxidative stress. Studies of in vitro models of neuronal toxicity and animal models of neurodegenerative disorders have demonstrated potential neuroprotective effects of CoQ10. With this data in mind, several clinical trials of CoQ10 have been performed in Parkinson's disease and atypical Parkinson's syndromes, Huntington's disease, Alzheimer disease,



Friedreich's ataxia, and amyotrophic lateral sclerosis, with equivocal findings. CoQ10 is widely available in multiple formulations and is very well tolerated with minimal adverse effects, making it an attractive potential therapy. Phase III trials of high-dose CoQ10 in large sample sizes are needed to further ascertain the effects of CoQ10 in neurodegenerative diseases.

Expert Opin Ther Targets. 2010 May;14(5):497-511.

Targeting mitochondrial dysfunction in neurodegenerative disease: Part II.

Burchell VS, Gandhi S, Deas E, Wood NW, Abramov AY, Plun-Favreau H.

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Abstract

IMPORTANCE OF THE FIELD: With improvements in life expectancy over the past decades, the incidence of neurodegenerative disease has dramatically increased and new therapeutic strategies are urgently needed. One possible approach is to target mitochondrial dysfunction, which has been implicated in the pathogenesis of numerous neurodegenerative disorders. **AREAS COVERED IN THIS REVIEW:** This review examines the role of mitochondrial dysfunction in neurodegeneration, drawing examples from common diseases such as Alzheimer's disease and rarer familial disorders such as Charcot-Marie-Tooth. The review is provided in two parts. In part I we discussed the mitochondrial defects which have been most extensively researched (oxidative stress, bioenergetic dysfunction, calcium mishandling). We focus now on those defects which have more recently been implicated in neurodegeneration; in mitochondrial fusion/fission, protein import, protein quality control, kinase signalling and opening of the permeability transition pore. **WHAT THE READER WILL GAIN:** An examination of mitochondrial defects observed in neurodegeneration, and existing and possible future therapies to target these defects. **TAKE HOME MESSAGE:** The mitochondrially-targeted therapeutics that have reached clinical trials so far have produced encouraging but largely inconclusive results. Increasing understanding of mitochondrial dysfunction has, however, led to preclinical work focusing on novel approaches, which has generated exciting preliminary data.

Biopolar and Schizophrenia

Arch Gen Psychiatry. 2010 Apr;67(4):360-8.

Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder.

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Abstract

CONTEXT: Accumulating evidence suggests that mitochondrial dysfunction and oxidative stress contribute to the pathogenesis of bipolar disorder and schizophrenia. It remains unclear whether mitochondrial dysfunction, specifically complex I impairment, is associated with increased oxidative damage and, if so, whether this relationship is specific to bipolar disorder. **OBJECTIVE:** To evaluate whether decreased levels of the electron transport chain complex I subunit NDUFS7 are associated with complex I activity and increased oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder, schizophrenia, or major depressive disorder. **DESIGN:** Postmortem prefrontal cortex from patients and controls were assessed using immunoblotting, spectrophotometric, competitive enzyme immunoassay to identify group differences in expression and activity of complex I, and in oxidative damage in mitochondria. **SETTING:** University of British Columbia, Vancouver, Canada. **Patients** Forty-five patients with a psychiatric disorder (15 each with bipolar disorder, schizophrenia, and major depressive disorder) and 15 nonpsychiatric control subjects were studied. **MAIN OUTCOME MEASURES:** Oxidative damage to proteins and mitochondrial complex I activity. **RESULTS:** Levels of NDUFS7 and complex I activity were decreased significantly in patients with bipolar disorder but



were unchanged in those with depression and schizophrenia compared with controls. Protein oxidation, as measured by protein carbonylation, was increased significantly in the bipolar group but not in the depressed or schizophrenic groups compared with controls. We observed increased levels of 3-nitrotyrosine in the bipolar disorder and schizophrenia groups. CONCLUSIONS: Impairment of complex I may be associated with increased protein oxidation and nitration in the prefrontal cortex of patients with bipolar disorder. Therefore, complex I activity and mitochondrial dysfunction may be potential therapeutic targets for bipolar disorder.

Drug News Perspect. 2006 Dec;19(10):597-602.

The role of mitochondrial dysfunction in bipolar disorder.

Kato T.

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Abstract

Altered energy metabolism and accumulated mitochondrial DNA (mtDNA) mutations in the brain, associated mtDNA polymorphisms/mutations or nuclear encoded mitochondrial genes, effects of mood stabilizers on mitochondria and comorbidity of mood disorders with mitochondrial disorders, together suggest the role of mitochondrial dysfunction in the pathophysiology of bipolar disorder. Mitochondrial dysfunction may be involved in the calcium signaling abnormality found in bipolar disorder. We recently produced mice accumulating neuron-specific mtDNA deletions. Bipolar disorder-like behavioral phenotypes of these mice supported this hypothesis. Thus, development of new mood stabilizers acting on mitochondrial function might be warranted.

Arch Gen Psychiatry. 2004;61:300-308.

Molecular Evidence for Mitochondrial Dysfunction in Bipolar Disorder

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Background The disease mechanism of bipolar disorder remains unknown. Recent studies have provided evidence for abnormal gene expression in bipolar disorder. **Objective** To determine the expression of 12 558 nuclear genes in the human hippocampus in healthy control subjects and those with bipolar disorder or schizophrenia. **Design** We used gene arrays to study messenger RNA expression. Data were verified with a real-time quantitative polymerase chain reaction assay. **Subjects** We studied 10 healthy control subjects, 9 subjects with bipolar disorder, and 8 subjects with schizophrenia. **Results** The expression of nuclear messenger RNA coding for mitochondrial proteins was significantly decreased in the hippocampus in subjects with bipolar disorder but not in those with schizophrenia. Subjects with bipolar disorder were characterized by a pronounced and extensive decrease in the expression of genes regulating oxidative phosphorylation and the adenosine triphosphate-dependent process of proteasome degradation. **Conclusions** These findings point toward a widespread dysregulation of mitochondrial energy metabolism and downstream deficits of adenosine triphosphate-dependent processes in bipolar disorder.

Eur Child Adolesc Psychiatry. 2010 May;19(5):441-8. Epub 2009 Nov 6.

Expression analyses of the mitochondrial complex I 75-kDa subunit in early onset schizophrenia and autism spectrum disorder: increased levels as a potential biomarker for early onset schizophrenia.

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Abstract

Searching for a peripheral biological marker for schizophrenia, we previously reported on elevated mitochondrial complex I 75-kDa subunit mRNA-blood concentrations in early onset schizophrenia (EOS). The aim of this study was to further evaluate the utility of this gene as a potential marker for schizophrenia. Both-schizophrenia and autism-are suggested to be neuronal maldevelopmental disorders with reports of mitochondrial dysfunction and increased oxidative stress. Therefore we have investigated the expression levels of mitochondrial complex I 75-kDa subunit mRNA in whole blood of children with autistic spectrum disorder (ASD) and a group of adolescent acute first-episode EOS patients in comparison to matched controls. We have found that compared to the respective controls only the group of EOS patients-and not the ASD group-showed a significantly altered expression of the complex I 75-kDa subunit mRNA. Although further studies are necessary to test for the specificity of this marker, our findings point to the potential use of the mitochondrial complex I as a biomarker for schizophrenia.

Parkinson's Disease

J Cell Mol Med. 2010 Jan;14(1-2):215-25.

Combined R-alpha-lipoic acid and acetyl-L-carnitine exerts efficient preventative effects in a cellular model of Parkinson's disease.

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Abstract

Mitochondrial dysfunction and oxidative damage are highly involved in the pathogenesis of Parkinson's disease (PD). Some mitochondrial antioxidants/nutrients that can improve mitochondrial function and/or attenuate oxidative damage have been implicated in PD therapy. However, few studies have evaluated the preventative effects of a combination of mitochondrial antioxidants/nutrients against PD, and even fewer have sought to optimize the doses of the combined agents. The present study examined the preventative effects of two mitochondrial antioxidant/nutrients, R-alpha-lipoic acid (LA) and acetyl-L-carnitine (ALC), in a chronic rotenone-induced cellular model of PD. We demonstrated that 4-week pretreatment with LA and/or ALC effectively protected SK-N-MC human neuroblastoma cells against rotenone-induced mitochondrial dysfunction, oxidative damage, and accumulation of alpha-synuclein and ubiquitin. Most notably, we found that when combined, LA and ALC worked at 100 to 1000 fold lower concentrations than they did individually. We also found that pretreatment with combined LA and ALC increased mitochondrial biogenesis and decreased production of reactive oxygen species through the upregulation of the peroxisome proliferator-activated receptor-gamma coactivator 1alpha as a possible underlying mechanism. This study provides important evidence that combining mitochondrial antioxidant/nutrients at optimal doses might be an effective and safe prevention strategy for PD.

Early involvement of the cerebral cortex in Parkinson's disease: convergence of multiple metabolic defects.

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Abstract

Parkinson's disease (PD) has been considered a paradigm of degenerative diseases of the nervous system characterized by motor impairment (parkinsonism) due to malfunction and loss of dopaminergic neurons of the substantia nigra pars compacta. However, PD is a systemic disease of the nervous system with variegated clinical symptoms appearing before parkinsonism and due to the involvement of selected nuclei of the medulla oblongata, pons, autonomic nervous system and olfactory structures, among others. Furthermore, recent clinical data have shown modifications in behavior, personality changes and cognitive impairment leading to dementia. Lewy pathology, hallmark of PD, in the cerebral cortex does not correlate with cognitive impairment. However, recent studies have shown abnormal mitochondria content and function, and increased oxidative stress and oxidative responses in the cerebral cortex in PD. Furthermore, several key PD-related proteins are oxidatively damaged, including alpha-synuclein, beta-synuclein, superoxide dismutases, parkin,



DJ1, UCHL1 and enzymes involved in glycolysis and energy metabolism. DNA and RNA are also targets of oxidative damage. Furthermore, abnormal phosphorylation of alpha-synuclein and tau occurs at the cortical synapses. Finally, abnormal cortical metabolism has been revealed with neuroimaging methods. These data demonstrate early involvement of the cerebral cortex in PD due to the convergence of multiple metabolic defects. Lewy pathology is a relative late event, geared to isolate unremoved damaged protein, with little significance on cortical neurological deficits.

Parkinsonism Relat Disord. 2009 Dec;15 Suppl 3:S189-94.

Therapeutic approaches to mitochondrial dysfunction in Parkinson's disease.

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Abstract

A large body of evidence from postmortem brain tissue and genetic analysis in humans, as well as biochemical and pathological studies in animal models of neurodegeneration suggest that mitochondrial dysfunction is a key pathological mechanism in Parkinson's Disease (PD). Mitochondrial dysfunction leads to oxidative stress, damage to mitochondrial DNA, mitochondrial DNA deletions, altered mitochondrial morphology, alterations in mitochondrial fission and fusion and ultimately neuronal demise. Therapeutic approaches targeting mitochondrial dysfunction and oxidative damage, therefore, hold great promise in PD. A number of agents, which target energy metabolism, are presently in therapeutic trials in PD. Both creatine and Coenzyme Q10 (CoQ10) are being tested in phase III clinical trials. In addition, preclinical studies in animal models have shown efficacy of mitochondrial-targeted antioxidants and the SS peptides. A promising approach for increasing antioxidant defenses is to transcriptionally increase the activity of the Nrf2/ARE pathway, which activates transcription of anti-inflammatory and antioxidant genes. A number of agents including sulforaphane, curcumin and triterpenoids have been shown to activate this pathway and to produce neuroprotective effects. Lastly, newly identified therapeutic targets include peroxisomal proliferator activated receptor gamma-coactivator (PGC-1alpha) and sirtuins. These pathways provide promise for future therapeutic developments in the treatment of PD.

Aging

Neurochem Res. 2009 Apr;34(4):755-63. Epub 2008 Oct 10.

Mitochondrial decay in the brains of old rats: ameliorating effect of alpha-lipoic acid and acetyl-L-carnitine.

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Abstract

To investigate the mitochondrial decay and oxidative damage resulting from aging, the activities/kinetics of the mitochondrial complexes were examined in the brains of young and old rats as well as in old rats fed R-alpha-lipoic acid plus acetyl-L-carnitine (LA/ALC). The brain mitochondria of old rats, compared with young rats, had significantly decreased endogenous antioxidants and superoxide dismutase activity; more oxidative damage to lipids and proteins; and decreased activities of complex I, IV and V. Complex I showed a decrease in binding affinity (increase in $K(m)$) for substrates. Feeding LA/ALC to old rats partially restored age-associated mitochondrial dysfunction to the levels of the young rats. These results indicate that oxidative mitochondrial decay plays an important role in brain aging and that a combination of nutrients targeting mitochondria, such as LA/ALC, could ameliorate mitochondrial decay through preventing mitochondrial oxidative damage.



EPIDEMIC ANSWERS

Neurochem Res. 2008 Jan;33(1):194-203. Epub 2007 Jun 29.

The effects and mechanisms of mitochondrial nutrient alpha-lipoic acid on improving age-associated mitochondrial and cognitive dysfunction: an overview.

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Abstract

We have identified a group of nutrients that can directly or indirectly protect mitochondria from oxidative damage and improve mitochondrial function and named them "mitochondrial nutrients". The direct protection includes preventing the generation of oxidants, scavenging free radicals or inhibiting oxidant reactivity, and elevating cofactors of defective mitochondrial enzymes with increased Michaelis-Menten constant to stimulate enzyme activity, and also protect enzymes from further oxidation, and the indirect protection includes repairing oxidative damage by enhancing antioxidant defense systems either through activation of phase 2 enzymes or through increase in mitochondrial biogenesis. In this review, we take alpha-lipoic acid (LA) as an example of mitochondrial nutrients by summarizing the protective effects and possible mechanisms of LA and its derivatives on age-associated cognitive and mitochondrial dysfunction of the brain. LA and its derivatives improve the age-associated decline of memory, improve mitochondrial structure and function, inhibit the age-associated increase of oxidative damage, elevate the levels of antioxidants, and restore the activity of key enzymes. In addition, co-administration of LA with other mitochondrial nutrients, such as acetyl-L: -carnitine and coenzyme Q10, appears more effective in improving cognitive dysfunction and reducing oxidative mitochondrial dysfunction. Therefore, administering mitochondrial nutrients, such as LA and its derivatives in combination with other mitochondrial nutrients to aged people and patients suffering from neurodegenerative diseases, may be an effective strategy for improving mitochondrial and cognitive dysfunction.

Gastrointestinal Disorders (e.g., Colitis)

Mol Genet Metab. 2007 Dec;92(4):315-24. Epub 2007 Sep 19.

Spontaneous development of intestinal and colonic atrophy and inflammation in the carnitine-deficient jvs (OCTN2^{-/-}) mice.

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Abstract

Carnitine is essential for transport of long-chain fatty acids into mitochondria for their subsequent beta-oxidation, but its role in the gastrointestinal tract has not been well described. Recently several genetic epidemiologic studies have shown strong association between mutations in carnitine transporter genes OCTN1 and OCTN2 and a propensity to develop Crohn's disease. This study aims to investigate role of carnitine and beta-oxidation in the GI tract. We have studied the gastrointestinal tract effects of carnitine deficiency in a mouse model with loss-of-function mutation in the OCTN2 carnitine transporter. juvenile visceral steatosis (OCTN2^{-/-}) mouse spontaneously develops intestinal villous atrophy, breakdown and inflammation with intense lymphocytic and macrophage infiltration, leading to ulcer formation and gut perforation. There is increased apoptosis of jvs (OCTN2^{-/-}) gut epithelial cells. We observed an up-regulation of heat shock factor-1 (HSF-1) and several heat shock proteins (HSPs) which are known to regulate OCTN2 gene expression. Intestinal and colonic epithelial cells in wild type mice showed high expression and activity of the enzymes of beta-oxidation pathway. These studies provide evidence of an obligatory role for carnitine in the maintenance of normal intestinal and colonic structure and morphology. Fatty acid oxidation, a metabolic pathway regulated by carnitine-dependent entry of long-chain fatty acids into mitochondrial matrix, is likely essential for normal gut function. Our studies suggest that carnitine supplementation, as a means of boosting fatty acid oxidation, may be therapeutically beneficial in patients with inflammation of the intestinal tract.

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Mitochondrial respiratory chain in the colonic mucosal of patients with ulcerative colitis.

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory disease of the large bowel. Its pathogenesis remains unclear, but it appears to result from a deregulated immune response, with infiltration of leukocytes into the mucosal interstitium. Several studies link oxidative stress and mitochondrial dysfunction to the pathogenesis of UC. Thus, the aim of this study was to evaluate the activities of mitochondrial respiratory chain complexes in the colonic mucosal of UC patients. Colonic biopsies were obtained from UC patients (n = 13). The control specimens were taken from patients without any history of inflammatory bowel disease (n = 8). Colon mucosal was removed by colonoscopy and homogenized. Mitochondrial respiratory chain complexes activities were then measured. Our results showed that the activity of complex I was not altered in UC patients, when compared to the control group. On the other hand, complexes II, III, and IV were decreased around 50-60% in the colonic mucosal of UC patients. Based on the present findings, we hypothesize that mitochondrial dysfunction may play a role in pathogenesis of UC.

J Cell Physiol. 2010 May;223(2):442-50.

Exposure of Toll-like receptors 4 to bacterial lipopolysaccharide (LPS) impairs human colonic smooth muscle cell function.

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Abstract

Endotoxemia by bacterial lipopolysaccharide (LPS) has been reported to affect gut motility specifically depending on Toll-like receptor 4 activation (TLR4). However, the direct impact of LPS ligation to TLR4 on human smooth muscle cells (HSMC) activity still remains to be elucidated. The present study shows that TLR4, its associated molecule MD2, and TLR2 are constitutively expressed on cultured HSMC and that, once activated, they impair HSMC function. The stimulation of TLR4 by LPS induced a time- and dose-dependent contractile dysfunction, which was associated with a decrease of TLR2 messenger, a rearrangement of microfilament cytoskeleton and an oxidative imbalance, i.e., the formation of reactive oxygen species (ROS) together with the depletion of GSH content. An alteration of mitochondria, namely a hyperpolarization of their membrane potential, was also detected. Most of these effects were partially prevented by the NADPH oxidase inhibitor apocynin or the NFkappaB inhibitor MG132. Finally, a 24 h washout in LPS-free medium almost completely restored morphofunctional and biochemical HSMC resting parameters, even if GSH levels remained significantly lower and no recovery was observed in TLR2 expression. Thus, the exposure to bacterial endotoxin directly and persistently impaired gastrointestinal smooth muscle activity indicating that HSMC actively participate to dysmotility during infective burst. The knowledge of these interactions might provide novel information on the pathogenesis of infection-associated gut dysmotility and further clues for the development of new therapeutic strategies.

Asthma

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Effects of vitamin E on mitochondrial dysfunction and asthma features in an experimental allergic murine model.



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Abstract

We showed recently that IL-4 causes mitochondrial dysfunction in allergic asthma. IL-4 is also known to induce 12/15-lipoxygenase (12/15-LOX), a potent candidate molecule in asthma. Because vitamin E (Vit-E) reduces IL-4 and inhibits 12/15-LOX in vitro, here we tested the hypothesis that Vit-E may be effective in restoring key mitochondrial dysfunctions, thus alleviating asthma features in an experimental allergic murine model. Ovalbumin (OVA)-sensitized and challenged male BALB/c mice showed the characteristic features of asthma such as airway hyperresponsiveness (AHR), airway inflammation, and airway remodeling. In addition, these mice showed increase in the expression and metabolites of 12/15-LOX, reduction in the activity and expression of the third subunit of mitochondrial cytochrome-c oxidase, and increased cytochrome c in lung cytosol, which indicate that OVA sensitization and challenge causes mitochondrial dysfunction. Vit-E was administered orally to these mice, and 12/15-LOX expression, key mitochondrial functions, ultrastructural changes of mitochondria in bronchial epithelia, and asthmatic parameters were determined. Vit-E treatment reduced AHR, Th2 response including IL-4, IL-5, IL-13, and OVA-specific IgE, eotaxin, transforming growth factor-beta1, airway inflammation, expression and metabolites of 12/15-LOX in lung cytosol, lipid peroxidation, and nitric oxide metabolites in the lung, restored the activity and expression of the third subunit of cytochrome-c oxidase in lung mitochondria and bronchial epithelia, respectively, reduced the appearance of cytochrome c in lung cytosol, and also restored mitochondrial ultrastructural changes of bronchial epithelia. In summary, these findings show that Vit-E reduces key mitochondrial dysfunctions and alleviates asthmatic features.
