BRAIN

1 - Altered glutathione redox state in schizophrenia.

Yao JK, Leonard S, Reddy R.

Source; http://www.ncbi.nlm.nih.gov/pubmed/16410648 VA Pittsburgh Healthcare System, 7180 Highland Drive, Pittsburgh, PA 15206, USA.
jkyao@pitt.edu

Abstract

Altered antioxidant status has been reported in schizophrenia. The glutathione (GSH) redox system is important for reducing oxidative stress. GSH, a radical scavenger, is converted to oxidized glutathione (GSSG) through glutathione peroxidase (GPx), and converted back to GSH by glutathione reductase (GR). Measurements of GSH, GSSG and its related enzymatic reactions are thus important for evaluating the redox and antioxidant status.

In the present study, levels of GSH, GSSG, GPx and GR were assessed in the caudate region of postmortem brains from schizophrenic patients and control subjects (with and without other psychiatric disorders). Significantly lower levels of GSH, GPx, and GR were found in schizophrenic group than in control groups without any psychiatric disorders.

Concomitantly, a decreased GSH:GSSG ratio was also found in schizophrenic group. Moreover, both GSSG and GR levels were significantly and inversely correlated to age of schizophrenic patients, but not control subjects. No significant differences were found in any GSH redox measures between control subjects and individuals with other types of psychiatric disorders.

There were, however, positive correlations between GSH and GPx, GSH and GR, as well as GPx and GR levels in control subjects without psychiatric disorders. These positive correlations suggest a dynamic state is kept in check during the redox coupling under normal conditions.

By contrast, lack of such correlations in schizophrenia point to a disturbance of redox coupling mechanisms in the antioxidant defense system, possibly resulting from a decreased level of GSH as well as age-related decreases of GSSG and GR activities.

PMID:
16410648
[PubMed - indexed for MEDLINE]

2 - Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders.

Gawryluk JW, Wang JF, Andreazza AC, Shao L, Young LT.

Source: http://www.ncbi.nlm.nih.gov/pubmed/20633320 Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada.

Abstract
Accruing data suggest that oxidative stress may be a factor underlying the pathophysiology of bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ).

Glutathione (GSH) is the major free radical scavenger in the brain. Diminished GSH levels elevate cellular vulnerability towards oxidative stress; characterized by accumulating reactive oxygen species.

The aim of this study was to determine if mood disorders and SCZ are associated with abnormal GSH and its functionally related enzymes. Post-mortem prefrontal cortex from patients with BD, MDD, SCZ, and from non-psychiatric comparison controls were provided by the Stanley Foundation Neuropathology Consortium. Spectrophotometric analysis was utilized for the quantitative determination of GSH, while immunoblotting analyses were used to examine expression of glutamyl-cysteine ligase (GCL), GSH reductase (GR), and GSH peroxidase (GPx).

We found that the levels of reduced, oxidized, and total GSH were significantly decreased in all psychiatric conditions compared to the control group. Although GCL and GR levels did not differ between groups, the levels of GPx were reduced in MDD and SCZ compared to control subjects.

Since oxidative damage has been demonstrated in MDD, BD, and SCZ, our finding that GSH levels are reduced in post-mortem prefrontal cortex suggests that these patient groups may be more susceptible to oxidative stress.

**PMID:
20633320
[PubMed - indexed for MEDLINE]**

3 - Glutathione--a review on its role and significance in Parkinson's disease.
Martin HL, Teismann P.
Source: http://www.ncbi.nlm.nih.gov/pubmed/19542204 School of Medical Sciences, College of Life Sciences and Medicine, University of Aberdeen, Aberdeen, AB25 2ZD, Scotland, UK.

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting over a million people in the United States alone, and is characterized by rigidity, bradykinesia, resting tremor, and postural instability. Its main neuropathological feature is the loss of dopaminergic neurons of the substantia nigra pars compacta. However, the pathogenesis of this loss is not understood fully.

One of the earliest biochemical changes seen in PD is a reduction in the levels of total glutathione, a key cellular antioxidant.

Traditionally, it has been thought that this decrease in GSH levels is the consequence of increased oxidative stress, a process heavily implicated in PD pathogenesis. However, emerging evidence suggests that GSH depletion may itself play an active role in PD pathogenesis.

This review aims to explore the contribution of GSH depletion to PD pathogenesis.

**PMID:
19542204**

[PubMed - indexed for MEDLINE]

4 - N-acetyl cysteine restores brain glutathione loss in combined 2-cyclohexene-1-one and d-amphetamine-treated rats: Relevance to schizophrenia and bipolar disorder.
Dean OM, van den Buuse M, Berk M, Copolov DL, Mavros C, Bush AI.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21621586 The Mental Health Research Institute of Victoria, Parkville, Victoria, Australia; The University of Melbourne, Parkville, Victoria, Australia; Deakin University, Geelong, Victoria, Australia.

Abstract

Oxidative stress and reduced brain levels of glutathione have been implicated in schizophrenia and bipolar disorder. N-acetyl cysteine (NAC) is a precursor of glutathione and has additional effects on glutamate neurotransmission, neurogenesis and inflammation.

While NAC treatment has shown benefits in both schizophrenia and bipolar disorder, the mechanisms of action are largely unknown. Similarly, the interaction between oxidative stress and altered dopaminergic activities in psychiatric illness is not yet characterized.

This study investigated the capacity of NAC in restoring brain glutathione depletion in rats that received 2-cyclohexene-1-one (CHX, 75mg/kg), d-amphetamine (2.5mg/kg) or both. CHX, but not amphetamine, induced significant depletion of glutathione levels in the striatum and frontal cortex.

Glutathione depletion was reversed by NAC (1000mg/kg) in saline-treated and amphetamine-treated (frontal cortex only) rats. While NAC was shown to be beneficial in this model, the lack of additional glutathione depletion by amphetamine in combination with CHX does not support a summative interaction between oxidative stress and altered dopamine transmission.

5 - N-Acetylcysteine reduces early- and late-stage cocaine seeking without affecting cocaine taking in rats.
Murray JE, Everitt BJ, Belin D.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21521427 Department of Experimental Psychology, University of Cambridge, UKINSERM AVENIR team, Psychobiology of Compulsive Disorders, Institut de Physiologie et de Biologie Cellulaires, & Université de Poitiers, France.

Abstract

N-acetylcysteine (NAC) has been suggested to have therapeutic potential in the treatment of drug addiction through its effects on brain glutamate homeostasis.

Here we show that NAC treatment resulted in dose-dependent reductions in cocaine seeking at both early and late stages of acquisition

and maintenance of cocaine-seeking behavior, while confirming it had no effect on cocaine reinforcement.

The results indicate that NAC is able to significantly diminish the propensity to seek cocaine early and late in the development of addiction
and, taken together with previous work, indicates significant potential in relapse prevention.

6 - The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels.
Adams JB, Baral M, Geis E, Mitchell J, Ingram J, Hensley A, Zappia I, Newmark S, Gehn E, Rubin RA, Mitchell K, Bradstreet J, El-Dahr JM.

Source: http://www.ncbi.nlm.nih.gov/pubmed/20107587 Division of Basic Medical Sciences, Southwest College of Naturopathic Medicine,
Tempe, AZ 85282, USA.

Abstract

This study investigated the relationship of children's autism symptoms with their toxic metal body burden and red blood cell (RBC)
glutathione levels. In children ages 3-8 years, the severity of autism was assessed using four tools: ADOS, PDD-BI, ATEC, and SAS.

Toxic metal body burden was assessed by measuring urinary excretion of toxic metals, both before and after oral dimercaptosuccinic acid
(DMSA). Multiple positive correlations were found between the severity of autism and the urinary excretion of toxic metals.

Variations in the severity of autism measurements could be explained, in part, by regression analyses of urinary excretion of toxic metals
before and after DMSA and the level of RBC glutathione (adjusted R(2) of 0.22-0.45, P < .005 in all cases).

This study demonstrates a significant positive association between the severity of autism and the relative body burden of toxic metals.
PMID:
20107587

7 - Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism.
FASEB J. 2009 Aug;23(8):2374-83. Epub 2009 Mar 23.

James SJ, Rose S, Melnyk S, Jernigan S, Blossom S, Pavliv O, Gaylor DW.

Source: http://www.ncbi.nlm.nih.gov/pubmed/19307255 Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas
Children's Hospital Research Institute, 1120 Marshall St., Little Rock, AR 72202, USA.
jamesjill@uams.edu

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.
PMID:
19307255

PMID:
20921235 [PubMed - in process]

8 - Glutathione pathway gene variation and risk of autism spectrum disorders.
Bowers K, Li Q, Bressler J, Avramopoulos D, Newschaffer C, Fallin MD.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21484198 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615
N. Wolfe St. room W6509, Baltimore, MD, 21205, USA.

Abstract

Despite evidence that autism is highly heritable with estimates of 15 or more genes involved, few studies have directly examined
associations of multiple gene interactions.

Since inability to effectively combat oxidative stress has been suggested as a mechanism of autism, we examined genetic variation 42
genes (308 single-nucleotide polymorphisms (SNPs)) related to glutathione, the most important antioxidant in the brain, for both marginal
association and multi-gene interaction among 318 case-parent trios from The Autism Genetic Resource Exchange.

Models of multi-SNP interactions were estimated using the trio Logic Regression method. A three-SNP joint effect was observed for
genotype combinations of SNPs in glutaredoxin, glutaredoxin 3 (GLRX3), and cystathione gamma lyase (CTH); OR = 3.78, 95% CI: 2.36, 6.04.
Marginal associations were observed for four genes including two involved in the three-way interaction: CTH, alcohol dehydrogenase 5,
gamma-glutamylcysteine synthetase, catalytic subunit and GLRX3.

These results suggest that variation in genes involved in counterbalancing oxidative stress may contribute to autism, though replication is

necessary.

9 - Abstract

Oxidative stress has been implicated in several psychiatric illnesses, including schizophrenia.

Glutathione is the brain's primary antioxidant and decreased levels of brain glutathione are reported in schizophrenia. Prepulse inhibition
(PPI) is a measure of sensory gating, and PPI is reduced in schizophrenia.

This study aimed to investigate the effects of brain glutathione depletion on PPI regulation. Rats and mice were treated with the
glutathione-depleting agent, 2-cyclohexene-1-one (CHX), and tested for baseline PPI and its disruption by treatment with amphetamine and
MK-801. Treatment with CHX caused significant depletion of GSH in frontal cortex and striatum of rats and mice. Baseline PPI and startle
were not altered. However, the disruption of PPI after treatment with amphetamine was absent in CHX-treated rats. In contrast, the effect of
MK-801 was not altered by CHX-treatment, nor was there any effect of CHX treatment in mice.

These data show an interaction of glutathione depletion with the effects of amphetamine treatment on PPI in rats. This effect could reflect
loss of plasticity in PPI regulation caused by the additive effects of CHX-induced glutathione depletion and additional oxidative stress
caused by amphetamine-induced dopamine release. The significance of these results for schizophrenia is discussed.

PMID:20816888
[PubMed - indexed for MEDLINE]

Behav Brain Res. 2009 Mar 2;198(1):258-62. Epub 2008 Nov 18.

10 - Glutathione depletion in the brain disrupts short-term spatial memory in the Y-maze in rats and mice. Dean O, Bush AI, Berk M,
Copolov DL, van den Buuse M.

Source: http://www.ncbi.nlm.nih.gov/pubmed/19061918 Mental Health Research Institute, 155 Oak Street, Parkville, Victoria 3052, Australia.
oliviad@barwonhealth.org.au

Abstract

Oxidative stress and reduced brain glutathione (GSH) levels have been reported in psychiatric illnesses including schizophrenia and
bipolar disorder. However the role of GSH in cognitive impairment in the illness remains unclear.

Treatment of Sprague-Dawley rats and C57Bl/6 mice with 2-cyclohexene-1-one (CHX) dose-dependently reduced striatal and frontal cortical
GSH levels similar to those in schizophrenia.

In both species, GSH depletion resulted in disruption of short-term spatial recognition memory in a Y-maze test. In conclusion, GSH
depletion induces cognitive impairment, which may be relevant to the role of GSH in psychiatric illnesses.

PMID:19061918
[PubMed - indexed for MEDLINE]

11 - Free Radic Biol Med. 1998 May;24(7-8):1149-58.
(32) Spatial learning and memory deficits induced by dopamine administration with decreased glutathione. Shukitt-Hale B, Erat SA, Joseph
JA.

Source: http://www.ncbi.nlm.nih.gov/pubmed/9626569 USDA-ARS, Human Nutrition Research Center on Aging, Tufts University, Boston, MA
02111, USA. hale_ne@hnrc.tufts.edu

Abstract Administration of buthionine sulfoximine (BSO) selectively inhibits glutathione (GSH) biosynthesis and induces a GSH deficiency.
Decreased GSH levels in the brain may result in less oxidative stress (OS) protection, because GSH contributes substantially to
intracellular antioxidant defense.

Under these conditions, administration of the pro-oxidant, dopamine (DA), which rapidly oxidizes to form reactive oxygen species, may
increase OS. To test the cognitive behavioral consequences of decreased GSH, BSO (3.2 mg in 30 microliters, intracerebroventricularly)
was administered to male Fischer 344 rats every other day for 4 days. In addition, DA (15 microliters of 500 microM) was administered every
day [either 1 h after BSO (BSO + DA group) or 1 h before BSO (DA + BSO group), when given on the same day as BSO] and spatial learning
and memory assessed (Morris water maze, six trials/day). BSO + DA rats, but not DA + BSO rats, demonstrated cognitive impairment
compared to a vehicle group, as evidenced by increased latencies to find the hidden platform, particularly on the first trial each day. Also,
the BSO + DA group utilized non-spatial strategies during the probe trials (swim with no platform): i.e., less time spent in the platform
quadrant, fewer crossings and longer latencies to the previous platform location, and more time spent in the platform quadrant, fewer
crossings and longer latencies to the previous platform location, and more time spent around the edge of the pool rather than in the
platform zone.

Therefore, the cognitive behavioral consequences of decreasing GSH brain levels with BSO in conjunction with DA administration depends
on the order of administration.

These findings are similar to those seen previously on rod and plank walking performance, as well as to those seen in aged rats,
suggesting that the oxidation of DA coupled with a reduced capacity to respond to oxidative stress may be responsible for the induction of
age-related cognitive deficits.

PMID:9626569

[PubMed - indexed for MEDLINE]

12 - Source: http://www.ncbi.nlm.nih.gov/pubmed/20868666 Mental Health Research Institute, Parkville,

Victoria, Australia.

Abstract

Glutathione (GSH) is the primary antioxidant in the body and is present in high levels in the brain. Levels of GSH and other antioxidants are
significantly altered in major psychiatric illnesses, such as schizophrenia.

Recent clinical trials have demonstrated that chronic treatment with N-acetyl-l-cysteine (NAC), a GSH precursor, improved symptoms in
individuals with this illness.

We previously showed in rats and mice that depletion of GSH by treatment with 2-cyclohexene-1-one (CHX) induced short-term spatial
memory deficits in the Y-maze test.

The aim of present study was to characterise the effect of NAC in this CHX-induced glutathione depletion model. Consistent with our
previous studies, CHX treatment induced approximately 50% reduction of GSH levels in striatum, hippocampus and frontal cortex tissue.
GSH depletion was significantly rescued by either 1.2 g/kg or 1.6 g/kg of NAC administration, with a full recovery observed in the frontal
cortex after the high dose of NAC.

CHX treatment also induced a disruption in short-term spatial recognition memory in Y-maze test, as measured by the duration of time
spent in the novel arm. This disruption was reversed by treatment with 1.6 g/kg of NAC. In conclusion, this study suggests that rescue of
depleted levels of GSH in the brain restores cognitive deficits, as measured by the Y-maze. These effects appear to be dose-dependent
and region-specific. These results may be relevant to the understanding and management of the cognitive symptoms of schizophrenia and
bipolar disorder.

PMID: 20868666

[PubMed - indexed for MEDLINE]

13 - Ann Neurol. 2011 Mar;69(3):509-20. doi: 10.1002/ana.22162. Epub 2010 Nov 23.

N-acetylcysteine prevents loss of dopaminergic neurons in the EAAC1-/- mouse. Berman AE, Chan WY, Brennan AM, Reyes RC, Adler BL,
Suh SW, Kauppinen TM, Edling Y, Swanson RA.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21446024 Department of Neurology, University of California, San Francisco, San Francisco
Veterans Affairs Medical Center, USA.

Abstract

OBJECTIVE:

Dopaminergic neuronal death in Parkinson's disease (PD) is accompanied by oxidative stress and preceded

by glutathione depletion. The
development of disease-modifying therapies for PD has been hindered by a paucity of animal models that mimic these features and
demonstrate an age-related progression. The EAAC1(-/-) mouse may be useful in this regard, because EAAC1(-/-) mouse neurons have
impaired neuronal cysteine uptake, resulting in reduced neuronal glutathione content and chronic oxidative stress. Here we aimed to (1)
characterize the age-related changes in nigral dopaminergic neurons in the EAAC1(-/-) mouse, and (2) use the EAAC1(-/-) mouse to evaluate
N-acetylcysteine, a membrane-permeable cysteine pro-drug, as a potential disease-modifying intervention for PD.

METHODS:

Wild-type mice, EAAC1(-/-) mice, and EAAC1(-/-) mice chronically treated with N-acetylcysteine were evaluated at serial time points for
evidence of oxidative stress, dopaminergic cell death, and motor abnormalities.

RESULTS:

EAAC1(-/-) mice showed age-dependent loss of dopaminergic neurons in the substantia nigra pars compacta, with more than 40% of these
neurons lost by age 12 months. This neuronal loss was accompanied by increased nitrotyrosine formation, nitrosylated α-synuclein, and
microglial activation. These changes were substantially reduced in mice that received N-acetylcysteine.

INTERPRETATION:

These findings suggest that the EAAC1(-/-) mouse may be a useful model of the chronic neuronal oxidative stress that occurs in PD. The
salutary effects of N-acetylcysteine in this mouse model provide an impetus for clinical evaluation of glutathione repletion in PD.

14 - Neurochem Res. 2011 Apr 12. [Epub ahead of print]

Evaluation of Markers of Oxidative Stress, Antioxidant Function and Astrocytic Proliferation in the Striatum and Frontal Cortex of
Parkinson's Disease Brains. Mythri RB, Venkateshappa C, Harish G, Mahadevan A, Muthane UB, Yasha TC, Srinivas Bharath MM, Shankar SK.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21484266 Department of Neurochemistry, National Institute of Mental Health and
Neurosciences, # 2900, Hosur Road, Bangalore, 560029, Karnataka, India.

Abstract

Dopaminergic neurons die in Parkinson's disease (PD) due to oxidative stress and mitochondrial dysfunction in the substantia nigra (SN).
We evaluated if oxidative stress occurs in other brain regions like the caudate nucleus (CD), putamen (Put) and frontal cortex (FC) in
human postmortem PD brains (n = 6). While protein oxidation was elevated only in CD ($P < 0.05$), lipid peroxidation was increased only in FC
($P < 0.05$) and protein nitration was unchanged in PD compared to controls.

Interestingly, mitochondrial complex I (CI) activity was unaffected in PD compared to controls. There was

a 3-5 fold increase in the total
glutathione (GSH) levels in the three regions ($P < 0.01$ in FC and CD; $P < 0.05$ in Put) but activities of antioxidant enzymes catalase,
superoxide dismutase, glutathione reductase and glutathione-s-tranferase were not increased.

Total GSH levels were elevated in these areas because of decreased activity of gamma glutamyl transpeptidase (γ-GT) ($P < 0.05$) activity
suggesting a decreased breakdown of GSH. There was an increase in expression of glial fibrillary acidic protein (GFAP) ($P < 0.001$ in FC; $P <$
0.05 in CD) and glutathione peroxidase ($P < 0.05$ in CD and Put) activity due to proliferation of astrocytes.

We suggest that increased GSH and astrocytic proliferation protects non-SN brain regions from oxidative and mitochondrial damage in PD.

PMID: 21484266 [PubMed - as supplied by publisher]

15 - Mol Neurodegener. 2011 Jan 21;6(1):8.

Glutathione Peroxidase 4 is associated with Neuromelanin in Substantia Nigra and Dystrophic Axons in Putamen of Parkinson's brain.

Bellinger FP, Bellinger MT, Seale LA, Takemoto AS, Raman AV, Miki T, Manning-Boğ AB, Berry MJ, White LR, Ross GW.

Source: http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%2021255396

Cell and Molecular Biology Department, John A, Burns School of Medicine, University of Hawaii, Honolulu, HI 96813 USA. fb@hawaii.edu.

ABSTRACT:

BACKGROUND:

Parkinson's disease is a neurodegenerative disorder characterized pathologically by the loss of nigrostriatal dopamine neurons that
project from the substantia nigra in the midbrain to the putamen and caudate nuclei, leading to the clinical features of bradykinesia, rigidity,
and rest tremor. Oxidative stress from oxidized dopamine and related compounds may contribute to the degeneration characteristic of this
disease.

RESULTS:

To investigate a possible role of the phospholipid hydroperoxidase glutathione peroxidase 4 (GPX4) in protection from oxidative stress, we
investigated GPX4 expression in postmortem human brain tissue from individuals with and without Parkinson's disease. In both control and
Parkinson's samples, GPX4 was found in dopaminergic nigral neurons colocalized with neuromelanin. Overall GPX4 was significantly
reduced in substantia nigra in Parkinson's vs. control subjects, but was increased relative to the cell density of surviving nigral cells. In
putamen, GPX4 was concentrated within dystrophic dopaminergic axons in Parkinson's subjects, although overall levels of GPX4 were not

significantly different compared to control putamen.

CONCLUSIONS:

This study demonstrates an up-regulation of GPX4 in neurons of substantia nigra and association of this protein with dystrophic axons in
striatum of Parkinson's brain, indicating a possible neuroprotective role. Additionally, our findings suggest this enzyme may contribute to
the production of neuromelanin.

PMID: 21255396

16 - Acta Neuropathol. 2011 Apr;121(4):475-85. Epub 2010 Dec 30.

Glutathione depletion and overproduction both initiate degeneration of nigral dopaminergic neurons.
Garrido M, Tereshchenko Y,
Zhevtsova Z, Taschenberger G, Bähr M, Kügler S.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21191602 Department of Neurology, Center of Molecular Physiology of the Brain (CMPB) at
University Medicine Göttingen, Waldweg 33, 37073 Göttingen, Germany.

Abstract Parkinson's disease is a neurodegenerative disorder characterized by severe motor deficits mainly due to degeneration of
dopaminergic neurons in the substantia nigra. Decreased levels of the cell's most important anti-oxidant, glutathione, have been detected
in nigral neurons of Parkinson patients, but it is unknown if they are the cause or merely the consequence of the disease. To elucidate if
glutathione depletion causes selective degeneration of nigral dopaminergic neurons, we down-regulated glutathione synthesis in different
brain areas of adult rats by a viral vector-based RNAi approach. Decreased glutathione synthesis resulted in progressive degeneration of
nigral dopaminergic neurons, while extra-nigral and striatal neurons were significantly less vulnerable. Degeneration of dopaminergic
neurons was accompanied by progressive protein aggregate formation and functional motor deficits and was partially rescued by α-
synuclein. That the survival of nigral dopaminergic neurons depends on the precise control of glutathione levels was further
demonstrated by significant degeneration induced through moderate overproduction of glutathione. Over-expression of either of the two
subunits of glutamate-cysteine ligase induced aberrant glutathiolation of cellular proteins and significant degeneration of dopaminergic
neurons. Thus, while glutathione depletion was demonstrated to be a selective trigger for dopaminergic neuron degeneration, a
glutathione replacement approach as a potential treatment option for Parkinson's patients must be considered with great care. In
conclusion, our data demonstrate that survival of nigral dopaminergic neurons crucially depends on a tight regulation of their glutathione
levels and that the depleted glutathione content detected in the brains of Parkinson's disease patients can be a causative insult for
neuronal degeneration.

PMID: 21191602

17 - Neurosci Lett. 1985 Aug 5;58(3):343-6.

Glutathione peroxidase activity in Parkinson's disease brain. Kish SJ, Morito C, Hornykiewicz O.

Source: http://www.ncbi.nlm.nih.gov/pubmed/4047494 Abstract

Glutathione peroxidase is an enzyme of major importance in the detoxification of peroxides in brain. Using the spectrophotometric procedure of Paglia and Valentine [8] and Beutler [2] we measured the activity of this enzyme in autopsied brain from 12 patients dying with idiopathic Parkinson's disease and 11 neurologically normal adults matched with respect to age and postmortem interval.

In the Parkinson's disease patients glutathione peroxidase activity was slightly but significantly reduced in several brain areas including substantia nigra.

Although the magnitude of the glutathione peroxidase deficiency in Parkinson's disease substantia nigra was small (19% reduction), coupled with the reported marked deficiency of reduced glutathione [9] it may represent one of the contributing factors leading to nigral dopamine neurone loss.

PMID:4047494

18 - An in vivo and in vitro study on the protective effects of N-acetylcysteine on mitochondrial dysfunction in isoproterenol treated myocardial infarcted rats . Basha RH, Priscilla DH.

Source : http://www.ncbi.nlm.nih.gov/pubmed/21641783 Department of Biochemistry and Biotechnology, Annamalai University, Annamalai Nagar 608002, Tamil Nadu, India.

Abstract

Altered mitochondrial function plays an important role in the pathology of myocardial infarction. We investigated the protective effects of N-acetylcysteine on mitochondrial dysfunction in isoproterenol induced myocardial infarcted rats.

Rats were pretreated with N-acetylcysteine (10mg/kg) orally daily for 14days. After pretreatment, rats were induced myocardial infarction by isoproterenol (100mg/kg) at an interval of 24h for 2 days. Lipid peroxidation products, antioxidants, lipids, mitochondrial marker enzymes and calcium in the mitochondrial heart were determined. Transmission electron microscopic and in vitro studies were also done.
Isoproterenol treatment caused significant increase in mitochondrial lipid peroxides and lipids except phospholipids with significant decrease in mitochondrial antioxidants. Significant decreased activities of marker enzymes and significant

**increased calcium were
observed in mitochondria of myocardial infarcted rats.**

**Pretreatment with N-acetylcysteine showed significant protective effects on all the biochemical parameters and preserved the integrity of
heart tissue and restored normal mitochondrial function in myocardial infarcted rats. Transmission electron microscopic findings on the
structure of the heart mitochondria confirmed the protective effects and in vitro study also confirmed the antioxidant potential of NAC.**

**The possible mechanism for the improved cardiac mitochondrial function might be due to scavenging free radicals, improving the
antioxidant and mitochondrial marker enzymes, maintaining GSH levels, lipids and Ca(2+) levels by its antioxidant effect. Thus, N-
acetylcysteine protected the mitochondrial heart from ISO treated mitochondrial damage. A diet containing N-acetylcysteine may be
beneficial to myocardial infarcted heart.**

**19 - Therapeutic potential of N-acetylcysteine as an antiplatelet agent in patients with type-2 diabetes.Gibson KR, Winterburn TJ, Barrett F,
Sharma S, Macrury SM, Megson IL.**

Source: http://www.ncbi.nlm.nih.gov/pubmed/21600014 ABSTRACT:

BACKGROUND:

**- Platelet hyperaggregability is a pro-thrombotic feature of type-2 diabetes, associated with low levels of the antioxidant glutathione (GSH).
Clinical delivery of N-acetylcysteine (NAC), a biosynthetic precursor of GSH, may help redress a GSH shortfall in platelets, thereby reducing
thrombotic risk in type-2 diabetes patients. We investigated the effect of NAC in vitro, at concentrations attainable with tolerable oral
dosing, on platelet GSH concentrations and aggregation propensity in blood from patients with type-2 diabetes.**

METHOD:

**S - Blood samples (n=13) were incubated (2 h, 37degreesC) with NAC (10-100 micromolar) in vitro. Platelet aggregation in response to
thrombin and ADP (whole blood aggregometry) was assessed, together with platelet GSH concentration (reduced and oxidized), antioxidant
status, reactive oxygen species (ROS) generation, and plasma NOx (a surrogate measure of platelet-derived nitric oxide; NO).**

RESULTS:

**- At therapeutically relevant concentrations (10-100 micromolar), NAC increased intraplatelet GSH levels, enhanced the antioxidant effects
of platelets, and reduced ROS generation in blood from type-2 diabetes patients. Critically, NAC inhibited thrombin- and ADP-induced
platelet aggregation in vitro. Plasma NOx was enhanced by 30 micromolar NAC.**

CONCLUSIONS:

- Our results suggest that NAC reduces thrombotic propensity in type-2 diabetes patients by increasing platelet antioxidant status as a result of elevated GSH synthesis, thereby lowering platelet-derived ROS. This may increase bioavailability of protective NO in a narrow therapeutic range.

Therefore, NAC might represent an alternative or additional therapy to aspirin that could reduce thrombotic risk in type-2 diabetes.
PMID:
21600014
[PubMed - as supplied by publisher]

20 - Different effects of low- and high-dose insulin on ROS production and VEGF expression in bovine retinal microvascular endothelial cells in the presence of high glucose.
Wu H, Jiang C, Gan D, Liao Y, Ren H, Sun Z, Zhang M, Xu G.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21494874 Department of Ophthalmology, Eye Ear Nose and Throat Hospital of Fudan University, #83 Fenyang Road, Shanghai, 200031, China.

Abstract

BACKGROUND:

Clinical trials have demonstrated that acute intensive insulin therapy may cause transient worsening of retinopathy in type 1 and type 2 diabetes patients. However, the related mechanism still remains controversial. The purpose of the present study was to investigate the effect of insulin on the mitochondrial membrane potential ($\Delta\Psi m$), reactive oxygen species (ROS) production, UCP-2 and VEGF expression in bovine retinal microvascular endothelial cells (BRECs) in the presence of normal or high glucose and the related mechanisms.

METHODS:

BRECs were isolated as primary cultures and identified by immunostaining. Passage BRECs were initially exposed to normal (5 mM) or high glucose (30 mM) for 3 days, with equimolar L: -glucose supplemented for osmotic equation. Then the cells were treated with 1 nM, 10 nM, or 100 nM insulin for 24 h: $\Delta\Psi m$ and ROS production were determined by JC-1 and CM-H2DCFDA, respectively. Expression of UCP-2 and VEGF mRNA was determined by real-time RT-PCR; expression UCP-2 and VEGF protein was determined by Western-blotting analysis. A general ROS scavenger N-acetylcysteine (NAC, 10 mM) and an NADPH oxidase inhibitor apocynin (1 mmol/l) were added 1 h before treatment with 100 nM insulin.

RESULTS:

Insulin increased $\Delta\Psi m$, ROS production, and expression of UCP-2 and VEGF in BRECs at normal glucose (5 mM) in a dose-dependent

manner. Low-dose insulin (1 nM) decreased $\Delta\Psi m$, ROS production, and UCP-2, VEGF expression in BRECs at high glucose (30 mM); and
high-dose insulin (10 nM, 100nM) recovered $\Delta\Psi m$, ROS production, and UCP-2, VEGF expression. Pretreatment of cells with NADPH
oxidase inhibitor apocynin significantly suppressed 100 nM insulin-induced ROS production ($p < 0.01$, one-way ANOVA). Pretreatment of
cells with ROS scavenger N-acetylcysteine completely blocked insulin-induced UCP-2 expression ($p < 0.01$, one-way ANOVA) and
significantly suppressed VEGF expression ($p < 0.01$, one-way ANOVA).

CONCLUSIONS:

High-dose insulin-induced ROS production and VEGF expression in BRECs in the presence of high glucose might be one of the reasons for
the transient worsening of diabetic retinopathy during intensive insulin treatment.

21 - N-Acetylcysteine promotes long-term survival of cones in a model of retinitis pigmentosa.
Lee SY, Usui S, Zafar AB, Oveson BC, Jo YJ, Lu L, Masoudi S, Campochiaro PA.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21506115 Department of Ophthalmology, Johns Hopkins University School of Medicine,
Baltimore, Maryland 21287-9277, USA.

Abstract

Retinitis pigmentosa (RP) is a major source of blindness caused by a large variety of mutations that lead to the death of rod
photoreceptors. After rods die, cones gradually die from progressive oxidative damage. Several types of antioxidant formulations have
been shown to reduce cone cell death over a relatively short-time frame, but in order for this strategy to be translated into a new treatment
for patients with RP, prolonged effects will be needed.

In this study, we determined that orally administered N-acetylcysteine (NAC) reduced cone cell death and preserved cone function by
reducing oxidative damage in two models of RP, rd1(+/+) and rd10(+/+) mice. In rd10(+/+) mice, supplementation of drinking water with NAC
promoted partial maintenance of cone structure and function for at least 6 months. Topical application of NAC to the cornea also reduced
superoxide radicals in the retina and promoted survival and functioning of cones.

Since oral and/or topical administration of NAC is feasible for long-term treatment in humans, and NAC has a good safety profile, it is
reasonable to consider clinical trials to evaluate the effects of prolonged treatment with NAC in patients with RP.

22 - Lower levels of glutathione in the brains of secondary progressive multiple sclerosis patients measured by 1H magnetic resonance
chemical shift imaging at 3 T. Choi IY, Lee SP, Denney DR, Lynch SG.

Source: http://www.ncbi.nlm.nih.gov/pubmed/20921235 Hoglund Brain Imaging Center, Department of

Neurology, University of Kansas
Medical Center, Kansas City, KS 66160, USA. ichoi@kumc.edu

Abstract

BACKGROUND:

Disability levels for patients with secondary progressive multiple sclerosis (SPMS) often worsen despite a stable MRI T(2) lesion burden.
The presence of oxidative stress in the absence of measurable inflammation could help explain this phenomenon.

In this study, the assessment of an in vivo marker of oxidative stress, cerebral glutathione (GSH), using magnetic resonance chemical shift
imaging (CSI) is described, and GSH levels were compared in patients with SPMS and healthy controls.

OBJECTIVE:

To assess whether GSH, a key antioxidant in the brain, is lower in the SPMS patients compared to matched controls.

METHODS:

Seventeen patients with SPMS (Expanded Disability Status Scale=4.0-7.0; length of MS diagnosis=19.4 ± 7 years) and 17 age- and gender-
matched healthy controls were studied. GSH levels were measured in the fronto-parietal regions of the brain using a specially designed
magnetic resonance spectroscopy technique, CSI of GSH, at 3T.

RESULTS:

The levels of GSH were lower for SPMS patients than for controls, the largest reduction (18.5%) being in the frontal region (p=0.001).

CONCLUSION:

The lower GSH levels in these patients indicate the presence of oxidative stress in SPMS. This process could be at least partially
responsible for ongoing functional decline in SPMS.

23 - Diabetic retinal neurodegeneration is associated with mitochondrial oxidative stress and is improved by an angiotensin receptor
blocker in a model combining hypertension and diabetes.
Silva KC, Rosales MA, Biswas SK, Lopes de Faria JB, Lopes de Faria JM.

Source: http://www.ncbi.nlm.nih.gov/pubmed/19289456 Renal Pathophysiology Laboratory, Investigation on Complications of Diabetes,
Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas, Campinas, São Paulo, Brazil.

Abstract

OBJECTIVE:

Diabetic retinopathy displays the features of a neurodegenerative disease. Oxidative stress is involved in the

pathogenesis of diabetic
retinopathy. This investigation sought to determine whether hypertension exacerbates the oxidative stress, neurodegeneration, and
mitochondrial dysfunction that exists in diabetic retinopathy and whether these changes could be minimized by the angiotensin II type 1 (AT
(1)) receptor blocker (ARB) losartan.

RESEARCH DESIGN AND METHODS:

Diabetes was induced in spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto (WKY) rats. The diabetic SHRs were
assigned to receive or not receive losartan.

RESULTS:

The level of apoptosis in the retina was higher in diabetic WKY rats than in the control group, and higher levels were found in diabetic
SHRs. The apoptotic cells expressed neural and glial markers. The retinal glial reaction was more evident in diabetic WKY rats and was
markedly accentuated in diabetic SHRs. Superoxide production in retinal tissue increased in diabetic WKY rats, and a greater increase
occurred in diabetic SHRs. Glutathione levels decreased only in diabetic SHRs. As a consequence, the levels of nitrotyrosine and 8-hydroxy
2'-deoxyguanosine, markers of oxidative stress, were elevated in diabetic groups, mainly in diabetic SHRs. Mitochondrial integrity was
dramatically affected in the diabetic groups. The ARB treatment reestablished all of the above-mentioned parameters.

CONCLUSIONS:

These findings suggest that concomitance of hypertension and diabetes exacerbates oxidative stress, neurodegeneration, and
mitochondrial dysfunction in the retinal cells. These data provide the first evidence of AT(1)blockage as a neuroprotective treatment of
diabetic retinopathy by reestablishing oxidative redox and the mitochondrial function.

PMID:

19289456 [PubMed - indexed for MEDLINE] PMCID: PMC2682683Free PMC Article

24 - Glutathione and catalase suppress TGFbeta-induced cataract-related changes in cultured rat lenses and lens epithelial explants.
Chamberlain CG, Mansfield KJ, Cerra A.

Source: http://www.ncbi.nlm.nih.gov/pubmed/19421408 School of Medical Sciences (Anatomy and Histology) and Bosch Institute, University
of Sydney, Sydney, NSW, Australia. coralcha@anatomy.usyd.edu.au

Abstract

PURPOSE:

The damaging effects of oxidative stress and transforming growth factor-beta (TGFbeta)-induced transdifferentiation of lens epithelial cells

have both been implicated independently in the etiology of cataract. The aim of this study was to investigate whether the presence of
antioxidant systems in the lens influences the ability of lens epithelial cells to respond to TGFbeta.

METHODS:

Whole lenses from young rats were cultured with or without TGFbeta in the presence or absence of reduced glutathione (GSH). Lens
epithelial explants from weanling rats were used to investigate the effects of GSH and catalase on TGFbeta-induced cataract-related
changes. Lenses were monitored for opacification for three to four days, photographed, and then processed for routine histology. Explants
were assessed by phase contrast microscopy, enzyme-linked immunosorbent assay (ELISA) of alpha-smooth muscle actin (alphaSMA),
and/or immunolocalization of alphaSMA and Pax6, markers for transdifferentiation and normal lens epithelial phenotype, respectively.

RESULTS:

In cultured lenses, GSH strongly suppressed TGFbeta-induced opacification and subcapsular plaque formation. In explants, both GSH and
catalase suppressed changes typically associated with TGFbeta-induced transdifferentiation including wrinkling of the lens capsule, cell-
surface blebbing, apoptotic cell loss, induction of alphaSMA, and loss of Pax6 expression.

CONCLUSIONS:

This study suggests that antioxidant systems present in the normal lens, which protect the epithelium against the damaging effects of
reactive oxygen species, may also serve to protect it against the potentially cataractogenic effects of TGFbeta. Taken together with other
recent studies, it also raises the possibility that TGFbeta may induce cataract-related changes in lens epithelial cells via release of
hydrogen peroxide.

PMID:
19421408
[PubMed - indexed for MEDLINE]
PMCID: PMC2676196
Free PMC Article

Clin Dev Immunol. 2012;2012:734125. Epub 2011 Dec 29.

25 - Unveiling the Mechanisms for Decreased Glutathione in Individuals with HIV Infection.Morris D, Guerra C, Donohue C, Oh H, Khurasany
M, Venketaraman V.SourceGraduate College of Biomedical Sciences, Western University of Health Sciences, Pomona, CA 91766, USA.

Abstract: We examined the causes for decreased glutathione (GSH) in individuals with HIV infection. We observed lower levels of
intracellular GSH in macrophages from individuals with HIV compared to healthy subjects. Further, the GSH composition found in
macrophages from HIV(+) subjects heavily favors oxidized glutathione (GSSG) which lacks antioxidant activity, over free GSH which is

responsible for GSH's antioxidant activity. This decrease correlated with an increase in the growth of Mycobacterium tuberculosis (M. tb) in
macrophages from HIV(+) individuals. In addition, we observed increased levels of free radicals, interleukin-1 (IL-1), interleukin-17 (IL-17)
and transforming growth factor-β (TGF-β) in plasma samples derived from HIV(+) individuals compared to healthy subjects. We observed
decreased expression of the genes coding for enzymes responsible for de novo synthesis of GSH in macrophages derived from HIV(+)
subjects using quantitative PCR (qPCR). Our results indicate that overproduction of proinflammatory cytokines in HIV(+) individuals lead to
increased production of free radicals. This combined with the decreased expression of GSH synthesis enzymes leads to a depletion of free
GSH and may lead in part to the loss of immune function observed in HIV patients.

PMID: 22242038 [PubMed - in process] PMCID: PMC3254057 Free PMC Article

Nutrition. 2012 Jan 18. [Epub ahead of print]

26 - Plasma glutathione of HIV(+) patients responded positively and differently to dietary supplementation with cysteine or glutamine.
Borges-Santos MD, Moreto F, Pereira PC, Ming-Yu Y, Burini RC.SourceDepartment of Public Health, Botucatu Medical School, UNESP-São
Paulo State University, Botucatu, São Paulo, Brazil.
AbstractOBJECTIVE: Patients with positivity for the human immunodeficiency virus (HIV(+)) present low concentrations of antioxidant
nutrients, including total glutathione (GSH) and its precursors. We investigated the responses of the sulfur-containing amino acid pathway
to cysteine and glutamine (Gln) dietary supplements in patients with HIV(+) compared with healthy controls.

METHODS: Twelve treated patients (six men and six women, 22-45 y old) and 20 healthy controls (10 men and 10 women, 20-59 y old) were
randomly assigned to 7-d dietary supplements containing N-acetylcysteine (NAC; 1 g/d) or Gln (20 g/d), with a 7-d washout period ingesting
their usual diet. Blood samples were drawn after an overnight fast. High-performance liquid chromatographic plasma analysis of sulfur-
containing amino acids (methionine, homocysteine, cysteine, and taurine), GSH, oxidized GSH, and serine, glycine, glutamic acid, and Gln
was carried out moments before and after 7-d supplementations. Statistical comparisons were undertaken between groups and between
dietary supplements ($P < 0.05$).

RESULTS: Patients with HIV(+) showed higher oxidized GSH and lower concentrations of GSH and all amino acids except homocysteine. The
HIV(+) group responded to the NAC by increased levels of sulfur-containing amino acids and GSH and equalized taurine and GSH levels in
the control group. The Gln supplements also equalized the levels of GSH, Gln, and glycine in the control group.

CONCLUSION: An increase in GSH may be attained by NAC or Gln supplementation, with NAC acting by increasing cysteine levels and Gln
likely acting by replenishing the glycine pool (trial registered at http://www.clinicaltrials.gov, identifier NCT00910442).

PMID: 22261571 [PubMed - as supplied by publisher]
(19) Enhanced expression of glutathione-S-transferase A1-1 protects against oxidative stress in human retinal pigment epithelial cells.
Liang FQ, Alssadi R, Morehead P, Awasthi YC, Godley BF.

Source: http://www.ncbi.nlm.nih.gov/pubmed/15652532 Retina Foundation of the Southwest, 9900 N. Central Expressway, Suite 400, Dallas,
TX 75231, USA.

27 - Abstract

Glutathione-S-transferases (GSTs) play an important role in protection mechanisms against oxidative stress. We sought to determine
whether over-expression of human GSTA1-1 in RPE cells is able to attenuate H(2)O(2)-induced oxidative stress. SV40-transformed human
fetal RPE cells were stably transfected with pRC/hGSTA1-1 vector which carries a full-length of human GSTA1-1 cDNA. The control RPE cells
were either non-transfected or transfected with control vector pRC. Expression of hGSTA1-1 protein in these cells was confirmed by
Western blot and immunocytochemical analyses. The protective effects of hGSTA1-1 on cell viability and mitochondrial DNA (mtDNA)
damage caused by H(2)O(2) were examined with MTT assay and quantitative PCR (QPCR), respectively. The hGSTA1-1 transfected RPE cells
exhibited a similar morphology and growth rate as control RPE cells. Immunocytochemical analysis showed robust expression hGSTA1-1 in
hGSTA1-1 transfected cells versus background staining in control cells. Western blotting of protein extracts from cells transfected with
hGSTA1-1 revealed a 26 kDa protein band which corresponds to the size of recombinant mature hGSTA1-1. The active GST present in the
hGSTA1-1 transfected cells was approximately three times higher than in control cells. The MTT assay showed a significantly greater
viability of hGSTA1-1 cells in response to H(2)O(2) (100 and 200 microm) compared to control cells ($p<0.05$). QPCR indicated that mtDNA
damage was significantly decreased in hGSTA1-1 cells than in control cells ($p<0.05$). Human GSTA1-1 transfection protect against RPE cell
death and mtDNA damage caused by H(2)O(2), suggesting an important role of GST in protection against oxidative stress in RPE cells.

(20) Vitamin C and vitamin E restore the resistance of GSH-depleted lens cells to H2O2. Shang F, Lu M, Dudek E, Reddan J, Taylor A.

Source: http://www.ncbi.nlm.nih.gov/pubmed/12614841 JM USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA
02111, USA. fu.shang@tufts.edu

28 - Abstract

A decline in reduced glutathione (GSH) levels is associated with aging and many age-related diseases. The objective of this study was to
determine whether other antioxidants can compensate for GSH depletion in protection against oxidative insults.

Rabbit lens epithelial cells were depleted of > 75% of intracellular GSH by 25-200 microM buthionine sulfoximine (BSO). Depletion of GSH by
BSO alone had little direct effect on cell viability, but resulted in an approximately 30-fold increase in

susceptibility to H(2)O(2)-induced cell
death. Experimentally enhanced levels of nonprotein sulfhydryls other than GSH (i.e., N-acetylcysteine) did not protect GSH-depleted cells
from H(2)O(2)-induced cell death. In contrast, pretreatment of cells with vitamin C (25-50 microM) or vitamin E (5-40 microM), restored the
resistance of GSH-depleted cells to H(2)O(2). However, concentrations of vitamin C > 400 microM and vitamin E > 80 microM enhanced the
toxic effect of H(2)O(2). Although levels of GSH actually decreased by 10-20% in cells supplemented with vitamin C or vitamin E, the
protective effects of vitamin C and vitamin E on BSO-treated cells were associated with significant (approximately 70%) decreases in
oxidized glutathione (GSSG) and concomitant restoration of the cellular redox status (as indicated by GSH:GSSG ratio) to levels detected in
cells not treated with BSO.

These results demonstrate a role for vitamin C and vitamin E in maintaining glutathione in its reduced form. The ability of vitamin C and
vitamin E in compensations for GSH depletion to protect against H(2)O(2)-induced cell death suggests that GSH, vitamin C, and vitamin E
have common targets in their actions against oxidative damage, and supports the preventive or therapeutic use of vitamin C and E to
combat age- and pathology-associated declines in GSH. Moreover, levels of these nutrients must be optimized to achieve the maximal
benefit.

Glutathione and NADH, but not ascorbate, protect lens proteins from modification by UV filters. Taylor LM, Andrew Aquilina J, Jamie JF,
Truscott RJ.

Source: http://www.ncbi.nlm.nih.gov/pubmed/12076094 Australian Cataract Research Foundation, University of Wollongong, Wollongong,
NSW, Australia 2522.

29 - Abstract

Age-dependent human lens colouration and fluorescence may stem primarily from the covalent binding of UV filters to crystallins. The
tendency of the kynurenine (Kyn) UV filters to deaminate at neutral pH, with the generation of reactive alpha,beta-ketoalkenes, underlies
this phenomenon. In this study the authors examined the ability of small molecular weight antioxidants, which are known to be present in
the lens, to inhibit this process. Crystallins were incubated with Kyn at pH 7 in the presence of glutathione (GSH), ascorbate or NADH.
Ascorbate, even at high (15 m M) levels, was not found to significantly retard the time-dependent covalent binding of Kyn to the proteins.

GSH, and to a lesser extent NADH, however, had a major impact in preventing this modification. The increase in protein UV absorbance and
fluorescence was inhibited by GSH intercepting the reactive ketone intermediate, to form a GSH-Kyn adduct. NADH seemed to protect by
both reduction of the reactive ketone intermediate and by competing with Kyn for presumably hydrophobic sites on the crystallins. This
may indicate that the covalent attachment of aromatic Kyn molecules could be facilitated by initial hydrophobic interactions.

Since GSH is present at far greater concentrations than NADH, these results show that in primate lenses, GSH is the key agent responsible for protecting the crystallins from covalent modification.

(22) Curcumin prevents experimental diabetic retinopathy in rats through its hypoglycemic, antioxidant, and anti-inflammatory mechanisms.
Gupta SK, Kumar B, Nag TC, Agrawal SS, Agrawal R, Agrawal P, Saxena R, Srivastava S.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21314438 Department of Pharmacology, Delhi Institute of Pharmaceutical Sciences and Research, University of Delhi, Pushp Vihar Sec-3, New Delhi, India. skgup@hotmail.com

30 - Source: http://www.ncbi.nlm.nih.gov/pubmed/17437639 Abstract

BACKGROUND:

Oxidative stress and inflammation are implicated in the pathogenesis of retinopathy in diabetes. The aim of this study is to examine the effect of curcumin, a polyphenol with antioxidant and anti-inflammatory properties, on diabetes-induced oxidative stress and inflammation in the retina of rats.

METHODS: A group of streptozotocin-induced diabetic rats received powdered diet supplemented with 0.05% curcumin (w/w), and another group received diet without curcumin. The diets were initiated soon after induction of diabetes, and the rats were sacrificed 6 weeks after induction of diabetes. The retina was used to quantify oxidative stress and pro-inflammatory markers.

RESULTS: Antioxidant capacity and the levels of intracellular antioxidant, GSH (reduced form of glutathione) levels were decreased by about 30-35%, and oxidatively modified DNA (8-OHdG) and nitrotyrosine were increased by 60-70% in the retina of diabetic rats. The levels of interleukin-1beta (IL-1beta) and vascular endothelial growth factor (VEGF) were elevated by 30% and 110% respectively, and the nuclear transcription factor (NF-kB) was activated by 2 fold. Curcumin administration prevented diabetes-induced decrease in the antioxidant capacity, and increase in 8-OHdG and nitrotyrosine; however, it had only partial beneficial effect on retinal GSH. Curcumin also inhibited diabetes-induced elevation in the levels of IL-1beta, VEGF and NF-kB. The effects of curcumin were achieved without amelioration of the severity of hyperglycemia.

CONCLUSION: Thus, the beneficial effects of curcumin on the metabolic abnormalities postulated to be important in the development of diabetic retinopathy suggest that curcumin could have potential benefits in inhibiting the development of retinopathy in diabetic patients.
PMID: 17437639 [PubMed] PMCID: PMC1868028 Free PMC Article

31 - Effect of ribose cysteine pretreatment on hepatic and renal acetaminophen metabolite formation and glutathione depletion.
Slitt AM, Dominick PK, Roberts JC, Cohen SD.

Source: http://www.ncbi.nlm.nih.gov/pubmed/15910414 Toxicology Program, Department of Pharmaceutical Sciences, University of

Connecticut, Storrs, CT, USA.

32 - Abstract

Ribose cysteine (2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)thiazolidine-4(R)-carboxylic acid) protects against acetaminophen-induced
hepatic and renal toxicity. The mechanism for this protection is not known, but may involve inactivation of the toxic electrophile via
enhancement of glutathione (GSH) biosynthesis.

Therefore, the goal of this study was to determine if GSH biosynthesis was required for the ribose cysteine protection. Male CD-1 mice
were injected with either acetaminophen or acetaminophen and ribose cysteine. The ribose cysteine cotreatment antagonized the
acetaminophen-induced depletion of non-protein sulfhydryls in liver as well as GSH in kidney. Moreover, ribose cysteine cotreatment
significantly increased the concentration of acetaminophen-cysteine, hepatic acetaminophen-mercapturate in liver and renal
acetaminophen-GSH metabolites in kidney 4 hr after acetaminophen.

To determine whether protection against acetaminophen-induced liver and kidney damage involved ribose cysteine dependent GSH
biosynthesis, buthionine sulfoximine was used to selectively block gamma-glutamylcysteine synthetase (gamma-GCS). Plasma sorbitol
dehydrogenase (SDH) activity and blood urea nitrogen from mice pretreated with buthionine sulfoximine and challenged with
acetaminophen indicated that both liver and kidney injury had occurred. While co-treatment with ribose cysteine had previously protected
against acetaminophen-induced liver and kidney injury, it did not diminish the acetaminophen-induced damage to either organ in the
buthionine sulfoximine-treated mice.

In Conclusion, ribose cysteine serves as a cysteine prodrug that facilitates GSH biosynthesis and protects against acetaminophen-induced
target organ toxicity.

33 - Abstract

Ribose-cysteine (RibCys) is a prodrug of L-cysteine that stimulates glutathione biosynthesis. Increased glutathione levels have been
shown to have a protective effect against radiation-induced injury and oxidative stress. Surface oximetry has previously been used
successfully to predict anastomotic leakage.

PURPOSE: The following study was done to evaluate the protective effect of RibCys and the predictive value of PtO2 determinations in a
swine model.

METHODS: Domestic swine were divided into three groups: Group A served as a nonradiated control; Group B received 6,000 to 6,500 rad
to the rectosigmoid; and Group C received RibCys (1 g/kg) prior to receiving 6,000 to 6,500 rad. Radiated animals and controls underwent
rectosigmoid resection after a three-week rest period. Intraoperative anastomotic PtO2 was checked with a modified Clark electrode.

Anastomoses were evaluated radiographically at three and seven days; animals were sacrificed, and bursting strength was recorded at 10 days.

RESULTS: Mean bursting pressures were 243.8 +/- 59.4, 199.5 +/- 37.8, and 209.5 +/- 54.9 mmHg (NS) for Groups A, B, and C, respectively. Anastomotic PtO2 ranged from 19 to 98 mmHg and could not be correlated with anastomotic leaks or bursting pressure. There were 11/15 radiation-related deaths and leaks (eight deaths and three leaks) in the radiated group and 4/12 radiation-related deaths and leaks (three deaths and one leak) in the group receiving radiation and RibCys ($P < 0.04$).

CONCLUSIONS: RibCys protected animals against radiation-related deaths and anastomotic leaks following high doses of pelvic irradiation; 2) anastomotic PtO2 levels did not correlate with anastomotic healing in this model.
PMID: 8348853 [PubMed - indexed for MEDLINE]

Basic Clin Pharmacol Toxicol. 2005 Jun;96(6):487-94.
(26) Effect of ribose cysteine pretreatment on hepatic and renal acetaminophen metabolite formation and glutathione depletion. Slitt AM, Dominick PK, Roberts JC, Cohen SD.

Source: http://www.ncbi.nlm.nih.gov/pubmed/15910414 Toxicology Program, Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, USA.

34 - Abstract

Ribose cysteine (2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)thiazolidine-4(R)-carboxylic acid) protects against acetaminophen-induced hepatic and renal toxicity.

The mechanism for this protection is not known, but may involve inactivation of the toxic electrophile via enhancement of glutathione (GSH) biosynthesis. Therefore, the goal of this study was to determine if GSH biosynthesis was required for the ribose cysteine protection. Male CD-1 mice were injected with either acetaminophen or acetaminophen and ribose cysteine. The ribose cysteine cotreatment antagonized the acetaminophen-induced depletion of non-protein sulfhydryls in liver as well as GSH in kidney.

Moreover, ribose cysteine cotreatment significantly increased the concentration of acetaminophen-cysteine, hepatic acetaminophen-mercapturate in liver and renal acetaminophen-GSH metabolites in kidney 4 hr after acetaminophen. To determine whether protection against acetaminophen-induced liver and kidney damage involved ribose cysteine dependent GSH biosynthesis, buthionine sulfoximine was used to selectively block gamma-glutamylcysteine synthetase (gamma-GCS). Plasma sorbitol dehydrogenase (SDH) activity and blood urea nitrogen from mice pretreated with buthionine sulfoximine and challenged with acetaminophen indicated that both liver and kidney injury had occurred. While co-treatment with ribose cysteine had previously protected against acetaminophen-induced liver and kidney injury, it did not diminish the acetaminophen-induced damage to either organ in the buthionine

sulfoximine-treated mice. In conclusion,
ribose cysteine serves as a cysteine prodrug that facilitates GSH biosynthesis and protects against acetaminophen-induced target organ
toxicity.

PMID:15910414
[PubMed - indexed for MEDLINE]

PLoS One. 2011;6(5):e20676. Epub 2011 May 31.
(27) Glutathione restores the mechanism of synaptic plasticity in aged mice to that of the adult. Robillard JM, Gordon GR, Choi HB, Christie
BR, Macvicar BA.
Source: http://www.ncbi.nlm.nih.gov/pubmed?term=21655192 Department of Psychiatry, Brain Research Centre, University of British
Columbia, Vancouver, Canada.

35 - Abstract

Glutathione (GSH), the major endogenous antioxidant produced by cells, can modulate the activity of N-methyl-D-aspartate receptors
(NMDARs) through its reducing functions.

During aging, an increase in oxidative stress leads to decreased levels of GSH in the brain. Concurrently, aging is characterized by calcium
dysregulation, thought to underlie impairments in hippocampal NMDAR-dependent long-term potentiation (LTP), a form of synaptic plasticity
thought to represent a cellular model for memory.

Here we show that orally supplementing aged mice with N-acetylcysteine, a precursor for the formation of glutathione, reverses the L-type
calcium channel-dependent LTP seen in aged animals to NMDAR-dependent LTP.

In addition, introducing glutathione in the intrapipette solution during whole-cell recordings restores LTP obtained in whole-cell conditions
in the aged hippocampus.

We conclude that aging leads to a reduced redox potential in hippocampal neurons, triggering impairments in LTP.

PMID:21655192
Click here for Images: http://www.ncbi.nlm.nih.gov/pmc?term=21655192[PMID]&report=imagesdocsum
[PubMed - in process]
Free PMC Article

36 - An in vivo and in vitro study on the protective effects of N-acetylcysteine on mitochondrial dysfunction in isoproterenol treated
myocardial infarcted rats. Basha RH, Priscilla DH.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21641783 Department of Biochemistry and Biotechnology, Annamalai University, Annamalai
Nagar 608002, Tamil Nadu, India.

Abstract Altered mitochondrial function plays an important role in the pathology of myocardial infarction. We investigated the protective
effects of N-acetylcysteine on mitochondrial dysfunction in isoproterenol induced myocardial infarcted

rats.

Rats were pretreated with N-acetylcysteine (10mg/kg) orally daily for 14days. After pretreatment, rats were induced myocardial infarction by
isoproterenol (100mg/kg) at an interval of 24h for 2 days. Lipid peroxidation products, antioxidants, lipids, mitochondrial marker enzymes
and calcium in the mitochondrial heart were determined. Transmission electron microscopic and in vitro studies were also done.
Isoproterenol treatment caused significant increase in mitochondrial lipid peroxides and lipids except phospholipids with significant
decrease in mitochondrial antioxidants. Significant decreased activities of marker enzymes and significant increased calcium were
observed in mitochondria of myocardial infarcted rats. Pretreatment with N-acetylcysteine showed significant protective effects on all the
biochemical parameters and preserved the integrity of heart tissue and restored normal mitochondrial function in myocardial infarcted rats.
Transmission electron microscopic findings on the structure of the heart mitochondria confirmed the protective effects and in vitro study
also confirmed the antioxidant potential of NAC.

The possible mechanism for the improved cardiac mitochondrial function might be due to scavenging free radicals, improving the
antioxidant and mitochondrial marker enzymes, maintaining GSH levels, lipids and Ca(2+) levels by its antioxidant effect.

Thus, N-acetylcysteine protected the mitochondrial heart from ISO treated mitochondrial damage. A diet containing N-acetylcysteine may be
beneficial to myocardial infarcted heart.

PMID: 21641783

Eur J Pharmacol. 2011 Jun 1;659(2-3):95-101. Epub 2011 Mar 17.

37 - Effects of glutathione, Trolox and desferrioxamine on hemoglobin-induced protein oxidative damage: Anti-oxidant or pro-oxidant? Lu
N, Chen W, Peng YY.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21419762 Key Laboratory of Functional Small Organic Molecule, Ministry of Education and
College of Life Science, Jiangxi Normal University, 99 Ziyang Road, Nanchang, Jiangxi 330022, China.

Abstract

Evidence to support the role of heme proteins as major inducers of oxidative damage is increasingly present. Antioxidants have been
widely used to ameliorate oxidative damage in vivo and in vitro, where the mechanism of this therapeutic action was usually dependent on
their anti-oxidant effects. In this study, we chose three classic antioxidants, i.e. glutathione (GSH, an important intracellular antioxidant), 6-
hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylic acid (Trolox, a phenolic antioxidant without chelating effect) and desferrioxamine (DFO, a
good iron chelator), to study their efficiencies on hemoglobin-induced protein oxidative damage. It was found that all of these antioxidants
had the capacities to act as free radical scavengers and reducing agents to remove cytotoxic ferryl

hemoglobin, demonstrating apparent
anti-oxidant activities. However, the effects on hemoglobin-H(2)O(2)-induced protein oxidation depended on the categories and
concentrations of antioxidants.

GSH efficiently inhibited protein (bovine serum albumin or rat heart homogenate) carbonyl formation in a dose-dependent manner. In
contrast to their protective effects at high concentrations, both Trolox and DFO could significantly aggravate protein oxidation at low
concentrations. The pro-oxidant effects of Trolox and DFO on hemoglobin-mediated oxidative damage were probably related to their
abilities in producing additional free radicals, such as superoxide (O(2)(.-)) and hydroxyl radical ((.)OH). The dual effects on hemoglobin
redox reactions may provide new insights into the physiological implications of Trolox and DFO with cellular heme proteins.

PMID: 21419762

Pharmacol Biochem Behav. 2010 Dec;97(2):293-300. Epub 2010 Sep 9.
(30) Interaction of glutathione depletion and psychotropic drug treatment in prepulse inhibition in rats and mice. Dean O, Bush AI, Berk M,
Copolov DL, van den Buuse M.
Source: http://www.ncbi.nlm.nih.gov/pubmed/20816888 Mental Health Research Institute, 155 Oak Street, Parkville, Victoria 3052, Australia.
oliviad@barwonhealth.org.au

38 - Hippocampus. 2008;18(6):602-9.Late

N-acetylcysteine treatment prevents the deficits induced in the offspring of dams exposed to an immune stress during gestation. Lanté F,
Meunier J, Guiramand J, De Jesus Ferreira MC, Cambonie G, Aimar R, Cohen-Solal C, Maurice T, Vignes M, Barbanel G.

Source: http://www.ncbi.nlm.nih.gov/pubmed/18306297 Oxidative Stress and Neuroprotection, IBMM, CNRS UMR-5247, UM-1 and UM-2,
Place E. Bataillon, 34095 Montpellier Cedex 5, France.

Abstract

Prenatal infection is a major stressful experience leading to enhanced susceptibility for mental illnesses in humans. We recently reported
in rats, that oxidative stress and glutathione (GSH) shortage occurred in fetal male brain after lipopolysaccharide (LPS) to the dams and that
these responses might be involved in the neurodevelopmental deficits observed in adolescent offspring.

Furthermore, pretreatment with N-acetylcysteine (NAC) before LPS avoided both delayed synaptic plasticity and mnesic performance
deficits.

Since NAC is one of the few medications permitted in pregnant women, this study evaluated the ability of NAC to serve as a protective
therapy even after the LPS challenge. Pregnant rats received a single ip injection of E. coli LPS, two days before delivery, and were given

NAC in their tap water after the LPS. GSH was evaluated at the time of its expected drop in the hippocampus of male fetuses, whereas long-
term potentiation (LTP) in the CA1 area of the hippocampus and spatial memory in the water-maze were recorded in 28-day-old male
offspring.

Post-treatment with NAC, four hours after the LPS challenge fully prevented the drop in the GSH hippocampal content. LTP, as well as
spatial learning were completely protected. NAC administration at delivery also partially restored the LTP whereas post-treatment two days
later was inefficient. Another set of dams were supplemented with alpha-tocopherol prior to LPS exposure, enhancing the alpha-tocopherol
levels in fetal hippocampus. This treatment did not prevent the LPS-induced synaptic plasticity impairment. These results point to fetal
hippocampal GSH as a major target of the detrimental effects of in utero LPS challenge.

The therapeutic window of NAC extends up to birth, suggesting that this drug might be clinically useful even after an immuno-inflammatory
episode.

PMID:18306297

39 - Am J Obstet Gynecol. 2003 Jan;188(1):203-8.

Protective effect of N-acetylcysteine against fetal death and preterm labor induced by maternal inflammation. Buhimschi IA, Buhimschi CS,
Weiner CP.

Source: http://www.ncbi.nlm.nih.gov/pubmed/12548218 Department of Obstetrics, Gynecology and Reproductive Sciences, University of
Maryland School of Medicine, Baltimore, MD, USA. ibuhimsc@med.wayne.edu

OBJECTIVE: Intrauterine and maternal systemic infections are proposed causes of preterm labor. The resulting prematurity is associated
with 75% of infant mortality and 50% of long-term neurologic handicaps.

We hypothesize that free radicals generated in large quantities during an inflammatory response shift the fetomaternal redox balance to an
oxidative state, compromising the fetus. Thus, if our working hypothesis is correct, selective inactivation of free radicals with N-
acetylcysteine (NAC), an antioxidant and glutathione (GSH) precursor, would improve the outcome of preterm deliveries associated with
inflammation. We tested aspects of this hypothesis in an animal model of preterm labor and fetal damage (death).

STUDY DESIGN: NAC (1 g/kg) was administered orally to C57Bl/6 mice injected intraperitoneally with either 10 microg lipopolysaccharide
(LPS) or saline solution (CRL) on day 16 of gestation. The latency period (time from injection to delivery of the first pup) and fetal viability
were recorded. To discriminate between an effect of prematurity from an effect of inflammation, and to document any improvement in
survival, mice were killed at 3, 6, and 16 hours after injection. Maternal and fetal redox states were approximated by measuring hepatic

GSH.

RESULTS: Each C57Bl/6 LPS-treated mouse delivered prematurely after a significantly shorter latency period (LPS: 16.8 hours [95% CI 15.9-17.6] vs CRL: 54.7 hours [95% CI 43.8-65.5]). NAC doubled the latency interval of LPS-treated animals to 35.2 hours (95% CI 21.0-49.2). LPS alone resulted in a 100% rate of stillbirth. Fifty-eight percent of fetuses were already dead 16 hours after LPS. In contrast, only 33% of fetuses were dead 16 hours after LPS (P =.001) when NAC was given. LPS was followed by a reduction in maternal (LPS: 26.3 nmol/mg [95% CI 19.9-32.8] vs CRL: 41.3 nmol/mg [95% CI 34.7-47.9, P <.01]) and fetal GSH (LPS: 19.7 nmol/mg [95% CI 11.7-27.8] vs CRL: 34.5 nmol/mg [95% CI 32.0-37.0, P <.001]). This decline was reversed by NAC (NAC/LPS maternal GSH: 37.0 nmol/mg [95% CI 22.5-51.5] and fetal GSH: 28.4 nmol/mg [95% CI 22.8-33.9]).

Importantly, maternal liver GSH impacted on fetal survival. NAC/LPS mothers with living pups 16 hours after LPS had significantly higher liver GSH compared with NAC/LPS mothers whose pups died in utero. In fact, all NAC-treated mice whose hepatic GSH exceeded 20 nmol/mg had living fetuses at 16 hours.

CONCLUSION: Maternal inflammation in C57Bl/6 mice results in oxidative stress associated with maternal and fetal GSH depletion. Oxidative stress damages the fetus independent of prematurity. Restoration of maternal and fetal oxidative balance by NAC protects the fetus and reduces the rate of preterm birth.

PMID:12548218

40 - nt J Gen Med. 2011 Jan 25;4:105-13.

Role of glutathione in immunity and inflammation in the lung. Ghezzi P.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21403800 Brighton and Sussex Medical School, Trafford Centre, Falmer, Brighton, UK. p.ghezzi@bsms.ac.uk

Abstract

Reactive oxygen species and thiol antioxidants, including glutathione (GSH), regulate innate immunity at various levels. This review outlines the redox-sensitive steps of the cellular mechanisms implicated in inflammation and host defense against infection, and describes how GSH is not only important as an antioxidant but also as a signaling molecule. There is an extensive literature of the role of GSH in immunity.

Most reviews are biased by an oversimplified picture where "bad" free radicals cause all sorts of diseases and "good" antioxidants protect from them and prevent oxidative stress. While this may be the case in certain fields (eg, toxicology), the role of thiols (the topic of this review) in immunity certainly requires wearing scientist's goggles and being prepared to accept a more

complex picture. This review aims
at describing the role of GSH in the lung in the context of immunity and inflammation.

The first part summarizes the history and basic concepts of this picture. The second part focuses on GSH metabolism/levels in pathology,
the third on the role of GSH in innate immunity and inflammation, and the fourth gives 4 examples describing the importance of GSH in the
response to infections.

PMID:21403800

[PubMed]

PMCID: PMC3048347

Free PMC Article; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3048347/

Very informative Article!

41 - Arthritis Res Ther. 2010;12(6):R213. Epub 2010 Nov 18.

Anticitrullinated protein antibody (ACPA) in rheumatoid arthritis: influence of an interaction between HLA-DRB1 shared epitope and a
deletion polymorphism in glutathione s-transferase in a cross-sectional study. Mikuls TR, Gould KA, Bynoté KK, Yu F, Levan TD, Thiele GM,
Michaud KD, O'Dell JR, Reimold AM, Hooker R, Caplan L, Johnson DS, Kerr G, Richards JS, Cannon GW, Criswell LA, Noble JA, Bridges SL Jr,
Hughes L, Gregersen PK.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21087494 Omaha Veterans Affairs Medical Center and Nebraska Arthritis Outcomes Research
Center, University of Nebraska Medical Center, 986270 Nebraska Medical Center, Omaha, NE 68198-6270, USA. tmikuls@unmc.edu

Abstract

INTRODUCTION: A deletion polymorphism in glutathione S-transferase Mu-1 (GSTM1-null) has previously been implicated to play a role in
rheumatoid arthritis (RA) risk and progression, although no prior investigations have examined its associations with anticitrullinated
protein antibody (ACPA) positivity. The purpose of this study was to examine the associations of GSTM1-null with ACPA positivity in RA and
to assess for evidence of interaction between GSTM1 and HLA-DRB1 shared epitope (SE).

METHODS: Associations of GSTM1-null with ACPA positivity were examined separately in two RA cohorts, the Veterans Affairs Rheumatoid
Arthritis (VARA) registry (n = 703) and the Study of New-Onset RA (SONORA; n = 610). Interactions were examined by calculating an
attributable proportion (AP) due to interaction.

RESULTS: A majority of patients in the VARA registry (76%) and SONORA (69%) were positive for ACPA with a similar frequency of GSTM1-null
(53% and 52%, respectively) and HLA-DRB1 SE positivity (76% and 71%, respectively). The parameter of patients who had ever smoked was
more common in the VARA registry (80%) than in SONORA (65%). GSTM1-null was significantly

associated with ACPA positivity in the VARA
registry (odds ratio (OR), 1.45; 95% confidence interval (CI), 1.02 to 2.05), but not in SONORA (OR, 1.00; 95% CI, 0.71 to 1.42). There were
significant additive interactions between GSTM1 and HLA-DRB1 SE in the VARA registry (AP, 0.49; 95% CI, 0.21 to 0.77; P < 0.001) in ACPA
positivity, an interaction replicated in SONORA (AP, 0.38; 95% CI, 0.00 to 0.76; P = 0.050).

CONCLUSIONS:This study is the first to show that the GSTM1-null genotype, a common genetic variant, exerts significant additive
interaction with HLA-DRB1 SE on the risk of ACPA positivity in RA. Since GSTM1 has known antioxidant functions, these data suggest that
oxidative stress may be important in the development of RA-specific autoimmunity in genetically susceptible individuals.

PMID:21087494

42 - J Dent Res. 2011 Mar;90(3):353-9. Epub 2010 Nov 18.

N-acetyl cysteine protects TMJ chondrocytes from oxidative stress. Ueno T, Yamada M, Sugita Y, Ogawa T.

Source: http://www.ncbi.nlm.nih.gov/pubmed/21088145 Laboratory for Bone and Implant Sciences, The Jane and Jerry Weintraub Center for
Reconstructive Biotechnology, Division of Advanced Prosthodontics, Biomaterials and Hospital Dentistry, UCLA School of Dentistry, 10833
Le Conte Avenue, CHS B3-088H, Los Angeles, CA 90095-1668, USA. takepr01@tmd.ac.jp

Abstract Temporomandibular joint (TMJ) inflammation is closely associated with oxidative stress. This study tested the potential of N-acetyl
cysteine (NAC), an anti-oxidant amino-acid derivative, in alleviating oxidative stress-related damage in TMJ chondrocytes.

The inflammatory condition was simulated by the addition of hydrogen peroxide (H_2O_2) to TMJ-derived chondrocyte cultures. Exposure to
H_2O_2 decreased the cell population by half within 2 days as a result of induced apoptosis and reduced proliferation. Gene expression of
aggrecan and collagen II, as well as glycosaminoglycan production, were reduced by more than 70%. These compromised chondrocyte
viability and function were fully restored by the addition of NAC to the cultures.

NAC reduced the H_2O_2-elevated intracellular reactive oxygen species to the normal level and increased cellular glutathione reserves.
These results indicate that NAC restores oxidative stress-induced cell death and severe functional impairment in TMJ chondrocytes, and
warrant in vivo testing to explore its therapeutic potential as an anti-inflammatory agent.

PMID: 21088145

43 - Dent Mater. 2009 Dec;25(12):1532-40. Epub 2009 Aug 12.

N-Acetyl cysteine (NAC) inhibits proliferation, collagen gene transcription, and redox stress in rat palatal mucosal cells. Sato N, Ueno T,
Kubo K, Suzuki T, Tsukimura N, Att W, Yamada M, Hori N, Maeda H, Ogawa T.

Source: http://www.ncbi.nlm.nih.gov/pubmed/19679343 Laboratory of Bone and Implant Sciences (LBIS),

Weintraub Center for
Reconstructive Biotechnology, Division of Advanced Prosthodontics, Biomaterials and Hospital Dentistry, UCLA School of Dentistry, Los
Angeles, CA, USA.

Abstract OBJECTIVES: Control of hyperplastic and invasively growing gingival tissue is crucial for maintaining normal oral function and for
successful bone regenerative therapy. We tested the hypothesis that materials containing N-acetyl cysteine (NAC), an antioxidant cysteine
derivative, can control proliferation and function of oral mucosal cells.

METHODS: Oral mucosal cells derived from the rat palatal tissue were cultured with or without NAC at different concentrations (2.5-10.0
mM). To simulate inflammatory conditions, cultures were treated with hydrogen peroxide. NAC was also applied via collagen materials in
membrane and sponge forms to explore the clinical applicability. The redox balance inside the cells was evaluated by measuring the
concentration of intracellular glutathione (GSH).

RESULTS: Adding NAC into cultures of oral mucosal cells reduced their proliferation, transcriptional expression, and collagen production in
an NAC-concentration-dependent manner without cytotoxic effects. Furthermore, NAC substantially reduced the hydrogen peroxide-
induced elevation of cellular proliferation and collagen production. The controlling effects of NAC were also demonstrated in cells cultured
on NAC-containing collagen materials and were associated with an increase in intracellular glutathione (GSH) reserves and a decrease in
the oxidized form of glutathione (GSSG).

SIGNIFICANCE: These results indicate that NAC may abrogate inflammation- or oxidative-stress-induced hyperfunction of oral mucosal cells
and that it can be delivered effectively via biodegradable materials. This study provides a basis to explore NAC-containing biomaterials that
are functionalized to control oral soft tissue growth and function without cytotoxicity.

PMID:19679343

44 - Arthritis Res Ther. 2010;12(3):210. Epub 2010 Jun 28.

Central role of nitric oxide in the pathogenesis of rheumatoid arthritis and systemic lupus erythematosus. Nagy G, Koncz A, Telarico T,
Fernandez D, Ersek B, Buzás E, Perl A.

Source: http://www.ncbi.nlm.nih.gov/pubmed/20609263 Department of Rheumatology, Semmelweis University, Medical School, Budapest,
Hungary. gyorgyngy@gmail.com

Abstract Nitric oxide (NO) has been shown to regulate T cell functions under physiological conditions, but overproduction of NO may
contribute to T lymphocyte dysfunction. NO-dependent tissue injury has been implicated in a variety of rheumatic diseases, including
systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Several studies reported increased endogenous NO synthesis in both
SLE and RA, and recent evidence suggests that NO contributes to T cell dysfunction in both autoimmune diseases.

**The depletion of intracellular glutathione may be a key factor predisposing patients with SLE to mitochondrial dysfunction, characterized by
mitochondrial hyperpolarization, ATP depletion and predisposition to death by necrosis. Thus, changes in glutathione metabolism may
influence the effect of increased NO production in the pathogenesis of autoimmunity.**

PMID:20609263

[PubMed - indexed for MEDLINE]

PMCID: PMC2911902

Free PMC Article

45 - Arthritis Rheum. 2002 Jan;46(1):175-90.

Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus.
**Gergely P Jr, Grossman C, Niland B,
Puskas F, Neupane H, Allam F, Banki K, Phillips PE, Perl A.**

Source: http://www.ncbi.nlm.nih.gov/pubmed/11817589 State University of New York, College of Medicine, Syracuse 13210, USA.

Abstract

OBJECTIVE:

**Peripheral blood lymphocytes (PBLs) from systemic lupus erythematosus (SLE) patients exhibit increased spontaneous and diminished
activation-induced apoptosis. We tested the hypothesis that key biochemical checkpoints, the mitochondrial transmembrane potential
(deltapsim) and production of reactive oxygen intermediates (ROIs), mediate the imbalance of apoptosis in SLE.**

METHODS:

**We assessed the deltapsim with potentiometric dyes, measured ROI production with oxidation-sensitive fluorochromes, and monitored cell
death by annexin V and propidium iodide staining of lymphocytes, using flow cytometry. Intracellular glutathione levels were measured by
high-performance liquid chromatography, while ATP and ADP levels were assessed by the luciferin-luciferase assay.**

RESULTS:

**Both deltapsim and ROI production were elevated in the 25 SLE patients compared with the 25 healthy subjects and the 10 rheumatoid
arthritis patients. Intracellular glutathione contents were diminished, suggesting increased utilization of reducing equivalents in SLE.
H2O2, a precursor of ROIs, increased deltapsim and caused apoptosis in normal PBLs. In contrast, H2O2-induced apoptosis and deltapsim
elevation were diminished, particularly in T cells, and the rate of necrotic cell death was increased in patients with SLE. The intracellular
ATP content and the ATP:ADP ratio were reduced and correlated with the deltapsim elevation in lupus.**

CD3:CD28 costimulation led to
transient elevation of the deltapsim, followed by ATP depletion, and sensitization of normal PBLs to H2O2-induced necrosis. Depletion of
ATP by oligomycin, an inhibitor of F0F1-ATPase, had similar effects.

CONCLUSION:

T cell activation and apoptosis are mediated by deltapsim elevation and increased ROI production. Mitochondrial hyperpolarization and the
resultant ATP depletion sensitize T cells for necrosis, which may significantly contribute to inflammation in patients with SLE.

PMID: 11817589 [PubMed - indexed for MEDLINE]

Free full text

46 - J Orthop Res. 2010 Feb;28(2):156-63.

N-acetylcysteine prevents nitric oxide-induced chondrocyte apoptosis and cartilage degeneration in an experimental model of
osteoarthritis. Nakagawa S, Arai Y, Mazda O, Kishida T, Takahashi KA, Sakao K, Saito M, Honjo K, Imanishi J, Kubo T.

Source: http://www.ncbi.nlm.nih.gov/pubmed/19725096 Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural
University of Medicine, Kamigyo-ku, Kyoto 602-8566, Japan.

Abstract

We investigated whether N-acetylcysteine (NAC), a precursor of glutathione, could protect rabbit articular chondrocytes against nitric oxide
(NO)-induced apoptosis and could prevent cartilage destruction in an experimental model of osteoarthritis (OA) in rats. Isolated
chondrocytes were treated with various concentrations of NAC (0-2 mM). Apoptosis was induced by 0.75 mM sodium nitroprusside (SNP)
dehydrate, which produces NO.

Cell viability was assessed by MTT assay, while apoptosis was evaluated by Hoechst 33342 and TUNEL staining. Intracellular reactive
oxygen species (ROS) and glutathione levels were measured, and expression of p53 and caspase-3 were determined by Western blotting.
To determine whether intraarticular injection of NAC prevents cartilage destruction in vivo, cartilage samples of an OA model were
subjected to H&E, Safranin O, and TUNEL staining. NAC prevented NO-induced apoptosis, ROS overproduction, p53 up-regulation, and
caspase-3 activation.

The protective effects of NAC were significantly blocked by buthionine sulfoximine, a glutathione synthetase inhibitor, indicating that the
apoptosis-preventing activity of NAC was mediated by glutathione.

Using a rat model of experimentally induced OA, we found that NAC also significantly prevented cartilage destruction and chondrocyte
apoptosis in vivo. These results indicate that NAC inhibits NO-induced apoptosis of chondrocytes through glutathione in vitro, and inhibits

chondrocyte apoptosis and articular cartilage degeneration in vivo.

(c) 2009 Orthopaedic Research Society.

PMID: 19725096

[PubMed - indexed for MEDLINE]

47 - Clin Rheumatol. 2008 Feb;27(2):141-5. Epub 2007 Oct 3.

The interrelation of glutathione reductase, catalase, glutathione peroxidase, superoxide dismutase, and glucose-6-phosphate in the
pathogenesis of rheumatoid arthritis. Kalpakcioglu B, Senel K.

Source: http://www.ncbi.nlm.nih.gov/pubmed/17912575 Physical Therapy and Rehabilitation, Haydarpasa Numune Training and Research
Hospital, Istanbul, Turkey. banubolay@superonline.com

Abstract

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis, a systemic autoimmune disease characterized by chronic
inflammation of the synovial joints, ultimately leading to joint destruction and permanent disability, affecting 1% of the world population.

Oxidative stress in rheumatoid inflammation, due to the fact that antioxidant systems are impaired in RA and caused by fee radicals, might
have an essential role in etiology of RA. This review includes the interrelation of antioxidants against free radicals in RA patients.

There is much evidence that antioxidant team that covers glutathione reductase, catalase, glutathione peroxidase, superoxide dismutase,
and glucose-6-phopshate destroy reactive oxygen species and other free radicals through enzymatic as well as nonenzymatic means. The
change in relative levels of antioxidants vis-à-vis free radical formation and level could be used as indicators for effective and earlier
diagnosis of RA.

PMID: 17912575

[PubMed - indexed for MEDLINE]

48 - Clin Exp Rheumatol. 2006 May-Jun;24(3):268-73.

Glutathione S-transferase gene polymorphisms in Japanese patients with rheumatoid arthritis. Morinobu S, Morinobu A, Kanagawa S,
Hayashi N, Nishimura K, Kumagai S.

Source: http://www.ncbi.nlm.nih.gov/pubmed/16870093 Department of Clinical Pathology and Immunology, Kobe, Japan.

Abstract

OBJECTIVE:

To investigate the role of polymorphisms of the glutathione S-transferase M1 (GSTM1), GSTT1, and GSTP1 genes in determining
susceptibility to rheumatoid arthritis (RA) and association with the clinical features.

METHODS:

Polymorphisms of the GSTM1, GSTT1, and GSTP1 genes in 108 Japanese patients with RA and in 143 healthy controls were analyzed by
polymerase chain reaction (PCR) or PCR-restriction fragment length polymorphism.

RESULTS:

The frequency of the GSTM1 null genotype was significantly higher among RA patients than among control subjects (60.2% and 44.1%,
respectively. P = 0.011). Moreover, the female patients with GSTM1 homozygous null genotype showed significantly higher serum MMP-3
level than the female patients with non-null genotype (P = 0.030). Frequencies of the GSTT1 and GSTP1 gene polymorphism were not
different between RA patients and controls.

CONCLUSION:

The GSTM1 homozygous null genotype could be a genetic factor that determines susceptibility to RA and may have influence on the
disease process.

PMID:16870093

[PubMed - indexed for MEDLINE]

49 - Diabetes Care. 2011 Jan;34(1):162-7. Epub 2010 Oct 7.

Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and
glycine. Sekhar RV, McKay SV, Patel SG, Guthikonda AP, Reddy VT, Balasubramanyam A, Jahoor F.
Source: http://www.ncbi.nlm.nih.
gov/pubmed/20929994

Translational Metabolism Unit, Baylor College of Medicine, Houston, Texas, USA. rsekhar@bcm.edu

Abstract

OBJECTIVE:

Sustained hyperglycemia is associated with low cellular levels of the antioxidant glutathione (GSH), which leads to tissue damage attributed
to oxidative stress. We tested the hypothesis that diminished GSH in adult patients with uncontrolled type 2 diabetes is attributed to
decreased synthesis and measured the effect of dietary supplementation with its precursors cysteine and glycine on GSH synthesis rate
and oxidative stress.

RESEARCH DESIGN AND METHODS:

We infused 12 diabetic patients and 12 nondiabetic control subjects with [$^{2}H_{2}$]-glycine to measure GSH

synthesis. We also measured
intracellular GSH concentrations, reactive oxygen metabolites, and lipid peroxides. Diabetic patients were restudied after 2 weeks of
dietary supplementation with the GSH precursors cysteine and glycine.

RESULTS:

Compared with control subjects, diabetic subjects had significantly higher fasting glucose (5.0 ± 0.1 vs. 10.7 ± 0.5 mmol/l; P < 0.001), lower
erythrocyte concentrations of glycine (514.7 ± 33.1 vs. 403.2 ± 18.2 µmol/l; P < 0.01), and cysteine (25.2 ± 1.5 vs. 17.8 ± 1.5 µmol/l; P < 0.01);
lower concentrations of GSH (6.75 ± 0.47 vs. 1.65 ± 0.16 µmol/g Hb; P < 0.001); diminished fractional (79.21 ± 5.75 vs. 44.86 ± 2.87%/day; P <
0.001) and absolute (5.26 ± 0.61 vs. 0.74 ± 0.10 µmol/g Hb/day; P < 0.001) GSH synthesis rates; and higher reactive oxygen metabolites (286 ±
10 vs. 403 ± 11 Carratelli units [UCarr]; P < 0.001) and lipid peroxides (2.6 ± 0.4 vs. 10.8 ± 1.2 pg/ml; P < 0.001). Following dietary
supplementation in diabetic subjects, GSH synthesis and concentrations increased significantly and plasma oxidative stress and lipid
peroxides decreased significantly.

CONCLUSIONS:

Patients with uncontrolled type 2 diabetes have severely deficient synthesis of glutathione attributed to limited precursor availability.
Dietary supplementation with GSH precursor amino acids can restore GSH synthesis and lower oxidative stress and oxidant damage in the
face of persistent hyperglycemia.

PMID:20929994

Free full text

50 - Biomed Khim. 2010 Sep-Oct;56(5):545-51.

[L-cysteine influx in diabetic erythrocytes]. Source: http://www.ncbi.nlm.nih.gov/pubmed/21254624
[Article in Russian]

Rizvi SI, Srivastava N.

Abstract

Erythrocyte oxidative stress has been implicated in the pathogenesis of diabetes mellitus, and the deficiency of antioxidant defense by the
glutathione (GSH) pathway is thought to be one of the factors responsible for development of complications in diabetes. Erythrocytes
require L-cysteine for the synthesis of GSH and the rate of synthesis is determined only by L-cysteine availability. In the present study we
have found that the L-cysteine influx in erythrocytes from type 2 diabetic patients was significantly lower compared to age-matched
controls. The decreased influx may be one of the factors leading to low GSH concentration observed in type 2 diabetes. Since L-cysteine is
the limiting amino acid in GSH synthesis, any strategy aimed to increase L-cysteine influx in erythrocytes may be beneficial for type 2
diabetic patients.

PMID: 21254624

[PubMed - indexed for MEDLINE]

- J Neurol. 2007 Dec;254(12):1676-83. Epub 2007 Nov 9.

Oxidative stress parameters in plasma of Huntington's disease patients, asymptomatic Huntington's disease gene carriers and healthy subjects : a cross-sectional study.

Klepac N, Relja M, Klepac R, Hećimović S, Babić T, Trkulja V.

Source: http://www.ncbi.nlm.nih.gov/pubmed/17990062 Dept. of Neurology, University Clinical Hospital Center Zagreb, Zagreb University School of Medicine, Kispatićeva, Zagreb, Croatia. natasa.klepac@zg.htnet.hr

Abstract

BACKGROUND:

Animal data and postmortem studies suggest a role of oxidative stress in the Huntington's disease (HD), but in vivo human studies have been scarce.

AIM:

To assess the presence of oxidative stress in HD patients and its occurrence relative to clinical symptoms.

METHODS:

Oxidative stress markers were determined in plasma of HD patients (n = 19), asymptomatic HD gene carriers (with > 38 CAG repeats) (n = 11) and their respective sex and age matched healthy controls (n = 47 and n = 22) in a cross-sectional study.

RESULTS:

With adjustment for age and sex, HD patients had higher plasma lipid peroxidation (LP) levels (ratio 1.20, 95% CI 1.09 to 1.32, p < 0.001) and lower reduced glutathione (GSH) levels (ratio 0.72, CI 0.55 to 0.94, p = 0.011) than their age and sex-matched controls. Although considerably younger, HD gene carriers did not differ from HD patients regarding LP and GSH levels, and had higher plasma LP (ratio 1.16, CI 1.02 to 1.32, p = 0.016) and lower GSH than their matched controls (ratio 0.73, CI 0.5 to 1.05). They had higher LP (ratio 1.18, CI 1.02 to 1.34, p = 0.019) and lower GSH (ratio 0.75, CI 0.51 to 1.11) than the healthy subjects matched to HD patients.

CONCLUSIONS:

Oxidative stress is more pronounced in HD patients and asymptomatic HD gene carriers than in healthy subjects. Differences in plasma LP and GSH are in line with the brain findings in animal models of HD. Data suggest that oxidative stress occurs before the onset of the HD symptoms.

PMID: 17990062

- Aberrant Rab11-dependent trafficking of the neuronal glutamate transporter EAAC1 causes oxidative stress and cell death in Huntington's disease. Li X, Valencia A, Sapp E, Masso N, Alexander J, Reeves P, Kegel KB, Aronin N, Difiglia M.

Source: http://www.ncbi.nlm.nih.gov/pubmed/20357106 Cellular Neurobiology Laboratory and Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA. xli12@partners.org

Abstract

Oxidative stress contributes to neurodegeneration in Huntington's disease (HD). However, the origins of oxidative stress in HD remain unclear. Studies in HD transgenic models suggest involvement of mitochondrial dysfunction, which would lead to overproduction of reactive oxygen species (ROS). Impaired mitochondria complexes occur in late stages of HD but not in presymptomatic or early-stage HD patients. Thus, other mechanisms may account for the earliest source of oxidative stress caused by endogenous mutant huntingtin.

Here, we report that decreased levels of a major intracellular antioxidant glutathione coincide with accumulation of ROS in primary HD neurons prepared from embryos of HD knock-in mice (HD(140Q/140Q)), which have human huntingtin exon 1 with 140 CAG repeats inserted into the endogenous mouse huntingtin gene.

Uptake of extracellular cysteine through the glutamate/cysteine transporter EAAC1 is required for de novo synthesis of glutathione in neurons. We found that, compared with wild-type neurons, HD neurons had lower cell surface levels of EAAC1 and were deficient in taking up cysteine. Constitutive trafficking of EAAC1 from recycling endosomes relies on Rab11 activity, which is defective in the brain of HD (140Q/140Q) mice.

Enhancement of Rab11 activity by expression of a dominant-active Rab11 mutant in primary HD neurons ameliorated the deficit in cysteine uptake, increased levels of intracellular glutathione, normalized clearance of ROS, and improved neuronal survival. Our data support a novel mechanism for oxidative stress in HD: Rab11 dysfunction slows trafficking of EAAC1 to the cell surface and impairs cysteine uptake, thereby leading to deficient synthesis of glutathione.

- PMID:20357106

Neurosci Lett. 2005 Sep 23;386(1):63-8.

Increased glutathione levels in cortical and striatal mitochondria of the R6/2 Huntington's disease mouse model. Choo YS, Mao Z, Johnson

GV, Lesort M.

Source: http://www.ncbi.nlm.nih.gov/pubmed/15993538 Department of Cell Biology, University of Alabama at Birmingham, Birmingham, AL
35294-0017, USA.

Abstract Huntington's disease (HD) is a progressive neurodegenerative disease characterized by a severe neuronal loss that occurs
primarily in the neostriatum. It has been postulated that mitochondria dysfunction and oxidative stress may play significant roles in the
etiology of the disease. Indeed, markers of oxidative stress damage have been detected in the brains of HD patients and in mouse models
of HD. In this study, we evaluate the changes in the levels of the potent, endogenous antioxidant glutathione and enzymes involved in its
metabolism or recycling in the cortex and striatum of an extensively studied HD mouse model (R6/2). In both cortex and striatum, the levels
of cellular glutathione were not significantly different in the R6/2 mice when compared with littermate wild type controls. Remarkably, the
levels of glutathione were significantly increased in mitochondria isolated from the cortex and striatum of R6/2 mice when compared with
wild type control mice. This specific increase in the levels of glutathione in mitochondria suggests that a compensatory mechanism is
induced in the R6/2 mice to protect against an increase in oxidative stress in mitochondria.

PMID:15993538

- J Neurochem. 2004 Oct;91(2):413-22.

Cystamine increases L-cysteine levels in Huntington's disease transgenic mouse brain and in a PC12 model of polyglutamine aggregation.
Fox JH, Barber DS, Singh B, Zucker B, Swindell MK, Norflus F, Buzescu R, Chopra R, Ferrante RJ, Kazantsev A, Hersch SM.

Source: http://www.ncbi.nlm.nih.gov/pubmed/15447674 MassGeneral Institute for Neurodegenerative Disease, Department of Neurology,
Massachusetts General Hospital, Charlestown, Massachusetts, USA.

Abstract

Cystamine, a small disulfide-containing chemical, is neuroprotective in a transgenic mouse and a Drosophila model of Huntington's disease
(HD) and decreases huntingtin aggregates in an in vitro model of HD. The mechanism of action of cystamine in these models is widely
thought to involve inhibition of transglutaminase mediated cross-linking of mutant huntingtin in the process of aggregate
formation/stabilization. In this study we show that cystamine, both in vitro and in a transgenic mouse model of HD (R6/2), increases levels of
the cellular antioxidant L-cysteine. Several oxidative stress markers increase in HD brain. We provide further evidence of oxidative stress
in mouse HD by demonstrating compensatory responses in R6/2 HD brains.

We found age-dependent increases in forebrain glutathione (GSH), and increased levels of transcripts coding for proteins involved in GSH synthesis and detoxification pathways, as revealed by quantitative PCR analysis. Given the general importance of oxidative stress as a mediator of neurodegeneration we propose that an increase in brain L-cysteine levels could be protective in HD. Furthermore, cystamine was dramatically protective against 3-nitropropionic acid-induced striatal injury in mice. We suggest that cystamine's neuroprotective effect in HD transgenic mice results from pleiotropic effects that include transglutaminase inhibition and antioxidant activity.

PMID: 15447674

- Neuro Endocrinol Lett. 2011 Apr 9;32(2). [Epub ahead of print]

Lower whole blood glutathione peroxidase (GPX) activity in depression, but not in myalgic encephalomyelitis / chronic fatigue syndrome: another pathway that may be associated with coronary artery disease and neuroprogression in depression.
Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E.

Source : http://www.ncbi.nlm.nih.gov/pubmed/21552194

Piyavate Hospital, Bangkok, Thailand, Thailand.

Abstract

BACKGROUND: Major depression and myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) are two disorders accompanied by an upregulation of the inflammatory and oxidative and nitrosative (IO&NS) pathways and a decreased antioxidant status. Moreover, depression is accompanied by disorders in inflammatory and neuroprogressive (IN-PRO) pathways.

METHODS:

This study examines whole blood glutathione peroxidase (GPX) in depression and in ME/CFS; GPX is an enzyme that reduces hydroperoxides by oxidizing glutathione and consequently protects the cells from oxidative damage. Blood was sampled in 39 patients with depression, 40 patients with ME/CFS and 24 normal volunteers. Whole blood was analysed for GPX activity using the Ransel assay (Randox). Severity of illness was measured by means of the Hamilton Depression Rating Scale (HDRS) and the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF scale).

RESULTS:

We found that whole blood GPX activity was significantly (p=0.001) lower in depressed patients than in normal controls and that there were no significant differences between ME/CFS and controls. In depression and ME/CFS, there were significant and inverse relationships between GPX activity and the FF items, depressed mood and autonomic symptoms. In depression, there were significant and negative

correlations between whole blood GPX and the HDRS score and autonomic symptoms.

DISCUSSION:

The results show that lowered whole blood GPX activity contributes to the lowered antioxidant status in depression. Since GPX activity is a predictor of neuroprogression and coronary artery disease (CAD), lowered GPX activity in depression contributes to the IN-PRO pathways and the comorbidity between depression and CAD.

Our results suggest that patients with depression would benefit from Ebselen or a supplementation with glutathione, N-Acetyl-l-Cysteine and selenium.

PMID: 21552194

- Pflugers Arch. 2010 Jun;460(1):55-68. Epub 2010 Mar 20.

Glutathione peroxidase 1 protects mitochondria against hypoxia/reoxygenation damage in mouse hearts.
Thu VT, Kim HK, Ha SH, Yoo JY, Park WS, Kim N, Oh GT, Han J.

Source: http://www.ncbi.nlm.nih.gov/pubmed/20306076 National Research Laboratory for Mitochondrial Signaling, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, FIRST Mitochondrial Research Group, Inje University, 633-165 Gaegeum-Dong, Busanjin-Gu, Busan, 613-735, Korea.

Abstract

Glutathione peroxidase 1 (GPx1) plays an important role in preventing cardiac dysfunction following ischemia-reperfusion injury. However, its role in protecting cardiac mitochondria against reoxygenation-induced reactive oxygen species (ROS) generation in vivo is unclear.

We examined the role of GPx1 in protecting cardiac mitochondria against hypoxia-reoxygenation (HR) damage by testing for alterations in cardiac mitochondrial function. We used a two-dimensional gel electrophoresis proteomics analysis to examine the effects of reoxygenation on cardiac protein in wild-type (GPx1(+/+)) and GPx1 knockout (GPx1(-/-)) mouse hearts. We identified 42 protein spots showing differential expression in the two groups. Sixteen of the proteins identified were located in mitochondria and were involved in a number of key metabolic pathways.

To verify our proteomics findings functionally, we performed NADH autofluorescence measurements and ATP production assays. The reduced expression of oxidative phosphorylation proteins in GPx1(-/-) mice following HR treatment resulted in loss of the mitochondrial membrane potential and decreased mitochondrial respiration. Mitochondrial ROS production and oxidative mtDNA damage were increased markedly during reoxygenation in GPx1(-/-) hearts. We also found morphological abnormalities in cardiac mitochondria and myocytes in HR-treated GPx1(-/-).

This is the first report of the role of GPx1 in protecting cardiac mitochondria against reoxygenation damage in vivo. These findings will help
clarify the mechanisms of HR injury and will aid in the development of antioxidant therapies to prevent cardiac mitochondrial dysfunction
associated with reoxygenation.

PMID:20306076

- Eur J Clin Invest. 1996 Jan;26(1):38-44.

Decreased release of glutathione into the systemic circulation of patients with HIV infection. Helbling B, von Overbeck J, Lauterburg BH.

Source: http://www.ncbi.nlm.nih.gov/pubmed/8682153 Department of Clinical Pharmacology, University of Bern, Switzerland.

Abstract Low glutathione (GSH) in patients with HIV infection could contribute to their immune deficiency since GSH plays an important role
in the function of lymphocytes and sulphydryls decrease the expression of HIV in vitro.

In order to gain more insight into the mechanisms responsible for the deranged sulphydryl homeostasis in HIV infection, the release of
GSH into the circulation, an estimate of the systemic production of GSH, was determined using a pharmacokinetic approach. The basal
plasma concentrations of free GSH (3.3 +/- 1.3 vs. 5.3 +/- 1.9 mumol L(-1)) and cysteine (7.7 +/- 2.6 vs. 13.4 +/- 4.9 mumol L(-1)) were
significantly lower in eight HIV-infected patients than in eight controls. Upon infusion of GSH at a constant rate of 1 mumol min-1 kg-1, GSH
in plasma reached a new plateau. The increment in plasma GSH was significantly larger in the HIV-infected patients than in the controls. The
input of GSH into the circulation (12.9 +/- 5.7 vs. 30.1 +/- 11.7 mumol min-1; P < 0.01) and the clearance of GSH (25 +/- 7 vs. 35 +/- 7 mL min-1
kg-1) were significantly lower in patients with HIV-infection. During infusion of GSH the concentration of cysteine in peripheral blood
mononuclear cells of the HIV-infected patients increased significantly. Nevertheless, intracellular GSH did not increase.

Thus, the consumption of GSH is not increased in HIV infection. Rather, the present data suggest that GSH in patients with HIV infection is
low because of a decreased systemic synthesis of GSH.

PMID: 8682153

[PubMed - indexed for MEDLINE]

Pharmacol Toxicol. 1994 Dec;75(6):343-7.

Effect of oral glutathione monoethyl ester and glutathione on circulating and hepatic sulfhydrils in the rat. Grattagliano I, Wieland P,
Schranz C, Lauterburg BH.

Source: http://www.ncbi.nlm.nih.gov/pubmed/7899255 Department of Clinical Pharmacology, University of Bern, Schweiz.

Abstract Glutathione (GSH) plays an important role in the detoxification of reactive metabolites of oxygen and xenobiotics and as a source of cysteine. Since several clinical situations characterized by low circulating and intracellular GSH have been identified, there is a growing interest in pharmacological interventions to correct a deranged sulfhydril status. Therefore, the systemic bioavailability of orally administered GSH and glutathione monoethyl ester (GSHE) was examined in the rat.

Following the intraduodenal administration of 0.5 mmol/kg of GSH and GSHE there was no significant increase in the concentrations of cysteine and GSH in plasma, but hepatic cysteine and GSH increased significantly, albeit transiently. Five mmol/kg of GSH and GSHE significantly increased circulating and hepatic cysteine and GSH. Following the administration of 0.5 and 5 mmol/kg of GSHE low concentrations of the ester were found in plasma and the liver, indicating that GSHE is not readily absorbed from the gastrointestinal tract, although it is not a substrate for gamma-glutamyl-transferase. GSHE resulted in a delayed release of cysteine and GSH compared to GSH, such that the concentrations of GSH and cysteine in liver and plasma were significantly higher 2 h after administration of GSHE than after GSH.

The data indicate that the bioavailability of GSH and GSHE is low in the rat. Orally administered GSH and GSHE do not affect the circulating concentrations of GSH and cysteine unless very high doses are administered, but increase hepatic cysteine and GSH at lower doses because of the efficient extraction by the liver of cysteine originating from the breakdown of GSH and GSHE in the gut.

PMID: 7899255

[PubMed - indexed for MEDLINE]

AIDS. 1992 Aug;6(8):815-9.

Glutathione depletion in HIV-infected patients: role of cysteine deficiency and effect of oral N-acetylcysteine. de Quay B, Malinverni R, Lauterburg BH.

Source: http://www.ncbi.nlm.nih.gov/pubmed/1418777 Department of Clinical Pharmacology and Medizinische Poliklinik, University of Bern, Switzerland.

Abstract OBJECTIVE: To determine whether a single oral dose of N-acetylcysteine corrects the deficiency of cysteine and glutathione in plasma and mononuclear cells of HIV-infected patients.

DESIGN: Pharmacokinetic and pharmacodynamic study.

METHODS: Cysteine and glutathione were measured in plasma and peripheral blood mononuclear cells of patients at different stages of HIV infection before and after a single oral dose of N-acetylcysteine.

RESULTS: At baseline, the plasma concentrations of glutathione and cysteine were significantly lower in

HIV-infected patients than in
healthy controls. The intracellular concentration of glutathione correlated with the absolute CD4 lymphocyte counts: the concentration of
glutathione in mononuclear cells was significantly lower in patients with more advanced immunodeficiency. A single oral dose of N-
acetylcysteine increased the concentration of cysteine in plasma and mononuclear cells of HIV-infected patients. Four hours after N-
acetylcysteine administration, intracellular glutathione concentrations in the patients were moderately higher than at baseline and at 2 h.

CONCLUSIONS: Oral N-acetylcysteine transiently increases the concentrations of cysteine and glutathione in mononuclear cells of patients
with HIV infection. A sustained increase in intracellular cysteine may be necessary to normalize intracellular glutathione. This may be
accomplished by repeat administration of N-acetylcysteine.

PMID: 1418777

[PubMed - indexed for MEDLINE]

Eur J Clin Invest. 2001 Feb;31(2):171-8.

Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients.
Micke P, Beeh KM, Schlaak JF, Buhl
R.

Source: http://www.ncbi.nlm.nih.gov/pubmed/11168457 Pulmonary Division, III. Medical Department, Mainz University Hospital, D-455101
Mainz, Germany. p.micke@3-med.klinik.uni-mainz.de

Abstract HIV infection is characterized by an enhanced oxidant burden and a systemic deficiency of the tripeptide glutathione (GSH), a
major antioxidant. The semi-essential amino acid cysteine is the main source of the free sulfhydryl group of GSH and limits its synthesis.

Therefore, different strategies to supplement cysteine supply have been suggested to increase glutathione levels in HIV-infected
individuals. The aim of this study was to evaluate the effect of oral supplementation with two different cysteine-rich whey protein formulas
on plasma GSH levels and parameters of oxidative stress and immune status in HIV-infected patients.

In a prospective double blind clinical trial, 30 patients (25 male, 5 female; mean age (+/- SD) 42 +/- 9.8 years) with stable HIV infection (221 +/-
102 CD4 + lymphocytes L-1) were randomized to a supplemental diet with a daily dose of 45 g whey proteins of either Protectamin
(Fresenius Kabi, Bad Hamburg, Germany) or Immunocal (Immunotec, Vandreuil, Canada) for two weeks. Plasma concentrations of total,
reduced and oxidized GSH, superoxide anion (O2-) release by blood mononuclear cells, plasma levels of TNF-alpha and interleukins 2 and
12 were quantified with standard methods at baseline and after therapy. Pre-therapy, plasma GSH levels (Protectamin: 1.92 +/- 0.6 microM;
Immunocal: 1.98 +/- 0.9 microM) were less than normal (2.64 +/- 0.7 microM, P = 0.03). Following two weeks of oral supplementation with whey
proteins, plasma GSH levels increased in the Protectamin group by 44 +/- 56% (2.79 +/- 1.2 microM, P = 0.004) while the difference in the

Immunocal group did not reach significance (+ 24.5 +/- 59%, 2.51 +/- 1.48 microM, P = 0.43). Spontaneous O2- release by blood mononuclear cells was stable (20.1 +/- 14.2 vs. 22.6 +/- 16.1 nmol h-1 10-6 cells, P = 0.52) whereas PMA-induced O2- release decreased in the Protectamin group (53.7 +/- 19 vs. 39.8 +/- 18 nmol h-1 10-6 cells, P = 0.04). Plasma concentrations of TNF-alpha and interleukins 2 and 12 (P > 0.08, all comparisons) as well as routine clinical parameters remained unchanged. Therapy was well tolerated.

In glutathione-deficient patients with advanced HIV-infection, short-term oral supplementation with whey proteins increases plasma glutathione levels. A long-term clinical trial is clearly warranted to see if this "biochemical efficacy" of whey proteins translates into a more favourable course of the disease.

PMID:11168457 [PubMed - indexed for MEDLINE]

Thorax. 1991 Jan;46(1):39-42.

Cysteine and glutathione concentrations in plasma and bronchoalveolar lavage fluid after treatment with N-acetylcysteine. Bridgeman MM, Marsden M, MacNee W, Flenley DC, Ryle AP.

Source: http://www.ncbi.nlm.nih.gov/pubmed/1871695 Department of Biochemistry, University of Edinburgh Medical School.

Abstract N-acetylcysteine (600 mg/day) was given to patients by mouth for five days before bronchoscopy and bronchoalveolar lavage to determine whether N-acetylcysteine could increase the concentrations of the antioxidant reduced glutathione in plasma and bronchoalveolar lavage fluid.

Bronchoalveolar lavage was performed 1-3 hours (group 2, n = 9) and 16-20 hours (group 3, n = 10) after the last dose of N-acetylcysteine and the values were compared with those in a control group receiving no N-acetylcysteine (group 1, n = 8). N-acetylcysteine was not detected in plasma or lavage fluid.

Plasma concentrations of cysteine, the main metabolite of N-acetylcysteine and a precursor of reduced glutathione, were greater in the groups receiving treatment (groups 2 and 3) than in group 1. Cysteine concentrations in lavage fluid were similar in the three groups. Concentrations of reduced glutathione were greater in both plasma and lavage fluid in group 2 than in group 1.

These data suggest that N-acetylcysteine given by mouth is rapidly deacetylated to cysteine, with resulting increases in the concentrations of cysteine in plasma and of reduced glutathione in plasma and the airways, which thus temporarily increase the antioxidant capacity of the lung.

PMID: 1871695

[PubMed - indexed for MEDLINE]

PMCID: PMC1020912

Free PMC Article

J Altern Complement Med. 2008 Nov;14(9):1159-64.

Cysteine, sulfite, and glutamate toxicity: a cause of ALS? Woolsey PB.

Source: http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%2018973429
pbwoolsey@NutritionConsultant.net

Abstract

BACKGROUND:

Amyotrophic lateral sclerosis (ALS) of nonmutant superoxide dismutase (SOD) type may be caused by toxicity of the reduced glutathione (GSH) precursors glutamate and cysteine, and sulfite (a metabolite of cysteine), which accumulate when one or more of the enzymes needed for GSH synthesis are defective.

OBJECTIVES:

A case is examined where the patient exhibited elevated sulfur on a hair mineral analysis, elevated blood cysteine, positive urine sulfite, elevated urine glutamate, and low whole blood GSH. During the time when strict dietary and supplement measures normalized the patient's whole blood GSH, blood cysteine, and urine sulfite, the patient did not experience additional physical decline. The possible causes of abnormalities of the patient's laboratory test results, as well as the nutrition measures used to normalize them, are discussed in relationship to the functions and importance of cysteine, sulfite, and glutamate in glutathione metabolism in ALS.

CONCLUSIONS:

Since elevated plasma cysteine has been reported in other ALS patients, sulfite and cysteine toxicity may be involved in other cases of ALS. Patients with ALS with nonmutant-SOD should be tested for sulfite toxicity, cysteine, glutamate and GSH levels, and whether they have low levels of GSH metabolism enzymes. Since glutamate metabolism appears to be inhibited by sulfite, research on the effect of sulfite on glutamate levels in patients with ALS should be pursued. Life might be prolonged in those patients with ALS with sulfite toxicity by closely monitoring the blood cysteine and urine sulfite levels and minimizing their dietary intake, as well as increasing GSH by using sublingual GSH. A long-term solution might be found through research to determine methods to increase GSH synthesis without using sulfur-containing supplements that may add to the cysteine and sulfite toxicity.

PMID: 18973429

[PubMed - indexed for MEDLINE]

Neuroscience. 2007 Feb 9;144(3):991-1003. Epub 2006 Dec 5.

Depletion of reduced glutathione enhances motor neuron degeneration in vitro and in vivo. Chi L, Ke Y, Luo C, Gozal D, Liu R.

Source: http://www.ncbi.nlm.nih.gov/pubmed/17150307 Department of Anatomy and Cell Biology, University of North Dakota School of Medicine, 501 North Columbia Road, Grand Forks, ND 58202, USA.

Abstract The mechanism of selective and age-dependent motor neuron degeneration in human amyotrophic lateral sclerosis (ALS) has not been defined and the role of glutathione (GSH) in association with motor neuron death remains largely unknown. A motor neuron-like cell culture system and a transgenic mouse model were used to study the effect of cellular GSH alteration on motor neuron cell death. Exposure of NSC34 motor neuron-like cells to ethacrynic acid (EA) or l-buthionine sulfoximine (BSO) dramatically reduced the cellular GSH levels, and was accompanied by increased production of reactive oxygen species (ROS) measured by the dichlorofluorescin (DCF) fluorescent oxidation assay. In addition, GSH depletion enhanced oxidative stress markers, AP-1 transcriptional activation, c-Jun, c-Fos and heme oxygenase-1 (HO-1) expression in NSC34 cells analyzed by a luciferase reporter, Western blotting and quantitative PCR assays respectively. Furthermore, depletion of GSH decreased mitochondrial function, facilitated apoptosis inducing factor (AIF) translocation, cytochrome c release, and caspase 3 activation, and consequently led to motor neuron-like cell apoptosis.

In an ALS-like transgenic mouse model overexpressing mutant G93A-Cu, Zn-superoxide dismutase (SOD1) gene, we showed that the reduction of GSH in the spinal cord and motor neuron cells is correlated with AIF translocation, caspase 3 activation, and motor neuron degeneration during ALS-like disease onset and progression.

Taken together, the in vitro and in vivo data presented in the current report demonstrated that decreased GSH promotes multiple apoptotic pathways contributing, at least partially, to motor neuron degeneration in ALS.

Click here for images from this publication: http://www.ncbi.nlm.nih.gov/pmc?term=17150307[PMID]&report=imagesdocsum

PMID: 17150307

[PubMed - indexed for MEDLINE]

- J Neurol Sci. 2003 Mar 15;207(1-2):51-8.

Mitochondrial dysfunction and death in motor neurons exposed to the glutathione-depleting agent ethacrynic acid. Rizzardini M, Lupi M, Bernasconi S, Mangolini A, Cantoni L.

Source: http://www.ncbi.nlm.nih.gov/pubmed/12614931 Istituto di Ricerche Farmacologiche Mario Negri, Via Eritrea 62, 20157 Milan, Italy.

Abstract

This study investigated the mechanisms of toxicity of glutathione (GSH) depletion in one cell type, the motor neuron. Ethacrynic acid (EA)

(100 microM) was added to immortalized mouse motor neurons (NSC-34) to deplete both cytosolic and mitochondrial glutathione rapidly.
This caused a drop in GSH to 25% of the initial level in 1 h and complete loss in 4 h. This effect was accompanied by enhanced generation of
reactive oxygen species (ROS) with a peak after 2 h of exposure, and by signs of mitochondrial dysfunction such as a decrease in 3-(4,5-
dimethyl-2-thiazoyl)-2,5-diphenyltetrazolium bromide (MTT) (30% less after 4 h). The increase in ROS and the MTT reduction were both EA
concentration-dependent. Expression of heme oxygenase-1 (HO-1), a marker of oxidative stress, also increased. The mitochondrial damage
was monitored by measuring the mitochondrial membrane potential (MMP) from the uptake of rhodamine 123 into mitochondria. MMP
dropped (20%) after only 1 h exposure to EA, and slowly continued to decline until 3 h, with a steep drop at 5 h (50% decrease), i.e. after the
complete GSH loss. Quantification of DNA fragmentation by the TUNEL technique showed that the proportion of cells with fragmented nuclei
rose from 10% after 5 h EA exposure to about 65% at 18 h.

These results indicate that EA-induced GSH depletion rapidly impairs the mitochondrial function of motor neurons, and this precedes cell
death. This experimental model of oxidative toxicity could be useful to study mechanisms of diseases like spinal cord injury (SCI) and
amyotrophic lateral sclerosis (ALS), where motor neurons are the vulnerable population and oxidative stress has a pathogenic role.

PMID: 12614931

[PubMed - indexed for MEDLINE]

GLUTATHIONE RESEARCH PUBMED STUDIES