N-acetylcysteine Versus Placebo for Treating Nail Biting, A Double Blind Randomized Placebo Controlled Clinical Trial.

Ghanizadeh A, Derakhshan N, Berk M.

Abstract

N-acetylcysteine versus placebo for treating nail biting, a double blind randomized placebo controlled clinical trial. Nail biting is a common behavioral problem. While there are established behavioral interventions for management, they are of modest efficacy, and there is minimal evidence of effective pharmacotherapy. This study investigated the role of N-acetylcysteine (NAC) as a potent antioxidant substance for the treatment of pathological nail biting in children and adolescents. This randomized, double-blind, placebo-controlled clinical trial of NAC (800mg/day) or placebo enrolled 42 children and adolescents with chronic nail biting. Nail length was the objective outcome. Evaluations were carried out three times; before treatment, one month after enrollment in the study, and two months after enrollment. The duration (chronicity) of nail biting in the NAC and placebo groups was 3.63(2.45) and 5.09(3.74) years (P=0.14). The mean nail length gradually increased in both the NAC and placebo groups during this trial. However, there was a statistically significant difference between the two groups regarding increased nail length after the first month of trial [(5.21(5.75) and 1.18(3.02) millimeters]. No difference after two months was observed. Two patients in the NAC group discontinued medication due to adverse events. One patient experienced headache, agitation, and being withdrawn from other individuals. Another patient expressed severe aggression after taking medication and was withdrawn from the study. This study supports the hypothesis that NAC decreases nail biting behavior in children and adolescents for a very short term. Current results do not support its efficacy after one month. Further studies with longer durations that build on these preliminary data are recommended. This study is registered at the Iranian Registry of Clinical Trials (Irct registration number: IRCT201103023930N3).

The terminal oxidase cytochrome bd-I in Escherichia coli has lower susceptibility than cytochromes bd-II or bo' to inhibition by the carbon monoxide-releasing molecule, CORM-3: N-acetylcysteine reduces CO-RM uptake and inhibition of respiration.

Jesse HE, Nye TL, McLean S, Green J, Mann BE, Poole RK.

Abstract

Background: CO-releasing molecules (CO-RMs) are potential therapeutic agents, able to deliver CO - a critical gasotransmitter - in biological environments. CO-RMs are also effective antimicrobial agents; although the mechanisms of action are poorly defined, haem-containing terminal oxidases are primary targets. Nevertheless, it is clear from several studies that the effects of CO-RMs on biological systems are frequently not adequately explained by the release of CO: CO-RMs are generally more potent inhibitors than is CO gas and other effects of the molecules are evident. Methods: Because sensitivity to CO-RMs cannot
We present the first sensitive measurement of the oxygen affinity of cytochrome bd-II (K_m 0.24 µM) employing globin deoxygenation. Finally, we investigate the way(s) in which thiol compounds abolish the inhibitory effects of CORM-2 and CORM-3 on respiration, growth and viability, a phenomenon that is well documented, but poorly understood. Results: We show that a strain expressing cytochrome bd-I as the sole oxidase is least susceptible to inhibition by CORM-3 in its growth and respiration of both intact cells and membranes. Growth studies show that cytochrome bd-II has similar CORM-3 sensitivity to cytochrome bo'. Cytochromes bo' and bd-II also have considerably lower affinities for oxygen than bd-I. We show that the ability of N-acetylcysteine to abrogate the toxic effects of CO-RMs is not attributable to its antioxidant effects, or prevention of CO targeting to the oxidases, but may be largely due to the inhibition of CO-RM uptake by bacterial cells. Conclusions: A strain expressing cytochrome bd-I as the sole terminal oxidase is least susceptible to inhibition by CORM-3. N-acetylcysteine is a potent inhibitor of CO-RM uptake by E. coli. General significance: Rational design and exploitation of CO-RMs require a fundamental understanding of their activity. CO and CO-RMs have multifaceted effects on mammalian and microbial cells; here we show that the quinol oxidases of E. coli are differentially sensitive to CORM-3. This article is part of a Special Issue entitled: Oxygen Binding and Sensing Proteins


**The chemistry and biological activities of N-acetylcysteine.**

Samuni Y, Goldstein S, Dean OM, Berk M.

**Source**

School of Medicine, Barwon Health, Deakin University, P.O. Box 291, Geelong, 3220, Australia.

**Abstract**

**BACKGROUND:**

N-acetylcysteine (NAC) has been in clinical practice for several decades. It has been used as a mucolytic agent and for the treatment of numerous disorders including paracetamol intoxication, doxorubicin cardiotoxicity, ischemia-reperfusion cardiac injury, acute respiratory distress syndrome, bronchitis, chemotherapy-induced toxicity, HIV/AIDS, heavy metal toxicity and psychiatric disorders.

**SCOPE OF REVIEW:**

The mechanisms underlying the therapeutic and clinical applications of NAC are complex and still unclear. The present review is focused on the chemistry of NAC and its interactions and functions at the organ, tissue and cellular levels in an attempt to bridge the gap between its recognized biological activities and chemistry.

**MAJOR CONCLUSIONS:**

The antioxidative activity of NAC as of other thiols can be attributed to its fast reactions with OH, NO_2, CO_3^- and thiyl radicals as well as to restitution of impaired targets in vital cellular components. NAC reacts relatively slowly with superoxide, hydrogen-peroxide and peroxynitrite, which cast some doubt on the importance of these reactions under physiological conditions. The uniqueness of NAC is most probably due to efficient reduction of disulfide bonds in proteins thus altering their structures and disrupting their ligand bonding, competition with larger reducing molecules in sterically less accessible spaces, and serving as a precursor of cysteine for GSH synthesis.

**GENERAL SIGNIFICANCE:**

The outlined reactions only partially explain the diverse biological effects of NAC, and further studies are required for determining its ability to cross the cell membrane and the blood-brain barrier as well as elucidating its reactions with components of cell signaling pathways.
**Hum Exp Toxicol.** 2013 Apr 24. [Epub ahead of print]

**In vitro effect of N-acetylcysteine on hepatocyte injury caused by dichlorodiphenyltrichloroethane and its metabolites.**

van Tonder JJ, Gulumian M, Cromarty AD, Steenkamp V.

**Source**

1Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.

**Abstract**

The organochlorine pesticide, dichlorodiphenyltrichloroethane (DDT), is still used to combat the spread of malaria in several developing countries despite its accumulation and known hepatotoxic effects that have been demonstrated both in vitro and in vivo. N-Acetylcysteine (NAC) is a recognized hepatoprotective agent that has been reported to reduce hepatotoxicity initiated by many different compounds. The aim of this study was to determine whether NAC could counter in vitro hepatocyte injury induced by DDT or its two major metabolites, dichlorodiphenyldichloroethylene and dichlorodiphenyldichloroethane. HepG2 cell cultures were used to assess the following parameters of toxicity: cellular viability, intracellular levels of reactive oxygen species (ROS), mitochondrial membrane potential and initiation of apoptosis. None of the three test compounds induced ROS generation, yet exposure to any of the three compounds produced mitochondrial hyperpolarization, which was countered by NAC pretreatment. All three test compounds also induced apoptotic cell death, which was inhibited by NAC. Despite NAC counteracting some adverse intracellular changes due to organochlorine exposure, it appeared to aggravate the cytotoxic effects of the organochlorine compounds at low test concentrations. As the same outcome may also occur in vivo, results from the present study raise concern about the use of NAC as treatment for DDT-induced hepatotoxicity.

**Int J Neuropsychopharmacol.** 2013 Apr 16:1-17. [Epub ahead of print]

**N-acetyl-cysteine prevents toxic oxidative effects induced by IFN-α in human neurons.**


**Source**

Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy.

**Abstract**

Currently IFN-α is widely used for effective treatment of viral infections and several malignancies. However, IFN-α can cause neuropsychiatric disturbances and mental impairments, including fatigue, insomnia, depression, irritability and cognitive deficits. Molecular and cellular mechanisms leading to such side-effects are still poorly understood. Neurons seem to be an important target in mediating cellular effects induced by exposure to this cytokine, but so far little is known about IFN-α-induced effects on these cells. We have investigated the ability of IFN-α (2-100 ng/ml) to induce damage and toxicity to the human neuroblastoma SH-SY5Y cell line, commonly used for studying such phenomena, and the mechanisms underlying these effects. After 24 h treatment, IFN-α increased mitochondrial activity, whereas cell density was reduced in a dose- and time-dependent manner. This effect did not depend on reduced cell proliferation, but rather the activation of apoptosis, as revealed by an increased Bax:Bcl-2 mRNA ratio after 72-h IFN-α exposure. At this time-point, IFN-α also reduced the expression of the brain-derived neurotrophic factor gene, and induced an increase in reactive oxygen species (ROS). A co-treatment with N-acetyl-cysteine (NAC; 5 mm), a potent antioxidant and mitochondrial modulator, was able to counteract all of these IFN-α-induced effects. These findings demonstrated that IFN-α induces neurotoxicity and apoptosis that is, in part, very likely due to mitochondrial damages and production of ROS. We suggest that NAC, already tested for the treatment of psychiatric disorders, may be useful to prevent IFN-α-induced central side-effects in a safe and effective way. **Cell Biochem Funct.** 2013 Apr 16. doi: 10.1002/cbf.2967. [Epub ahead of print]
Protective effect of N-acetylcysteine against ischemia/reperfusion injury in rat urinary bladders.

Shin JH, Kim GH, Song KH, Na YG, Sul CK, Lim JS.

Source

Department of Urology, School of Medicine, Chungnam National University Hospital, Daejeon, 301-721, Korea.

Abstract

Ischemia/reperfusion (I/R) injury represents an important cause of bladder contractile dysfunction. One of the major causes leading to this dysfunction is thought to be reactive oxygen species formation. In this study, we investigated the potential benefit of N-acetylcysteine (NAC), a potent antioxidant that neutralizes free radicals, in a rat model of urinary bladder injury. NAC treatment rescues the reduction of contractile response to I/R injury in a dose-dependent manner. In addition, all levels of reactive oxygen species, lipid peroxidation, and NADPH-stimulated superoxide production in the I/R operation + NAC (I/R + NAC) group also decreased compared with a marked increase in the I/R operation + saline (I/R + S) group. Moreover, an in situ fluorohistological approach also showed that NAC reduces the generation of intracellular superoxides enlarged by I/R injury. Together, our findings suggest that NAC has a protective effect against the I/R-induced bladder contractile dysfunction via radical scavenging property. Copyright © 2013 John Wiley & Sons, Ltd.


Comparison of N-acetylcysteine and mesna as uroprotectors with ifosfamide combination chemotherapy in refractory germ cell tumors.

Munshi NC, Loehrer PJ Sr, Williams SD, Langefeld C, Sledge G, Nichols CR, Roth BJ, Neuman A, Walsh WB, Einhorn LH.

Source

Indiana University, Indianapolis.

Abstract

From January 1983 through August 1988, 318 consecutive patients with refractory germ cell neoplasms were treated with ifosfamide-containing combination chemotherapy. The patients received ifosfamide at 1.2 gm/m2/day with cis-platin 20 mg/m2/day for 5 days and etoposide 75 mg/m2/day for 5 days or vinblastine 0.11 mg/kg on days 1 and 2 for each cycle. Of 277 evaluable patients, NAC was used as an uroprotector in the initial 86 patients while the latter 191 consecutive patients received mesna to reduce urothelial toxicity. Dosages of NAC was 2.0 gm po q 6 hr and for mesna 120 mg/m2 IV push prior to ifosfamide and then 1200 mg/m2/day as continuous infusion of 5 consecutive days. All patients received 3.0 liters of normal saline per day. The number of courses of chemotherapy given in the two groups were similar. Twenty-four of the 86 patients (27.9%) receiving NAC developed hematuria (13 patients - grade 1, 4 patients - grade 2, and 7 patients - grade 3 toxicity). While 8 out of 191 (4.2%) mesna patients developed hematuria (6 - grade 1 and 2 - grade 3) (p < 0.0001). The incidence of severity of renal toxicity was similar in the two groups. Ifosfamide dosage was reduced solely for urothelial toxicity in 11 patients receiving NAC compared with none of the patients receiving mesna (p < 0.0001). Chemotherapy response was similar in the two groups. In conclusion, mesna provides better urothelial protection from ifosfamide-induced toxicity than NAC and allows better maintenance of the drug dosage.

Indian J Gastroenterol, 2013 Mar 10. [Epub ahead of print]
The protective effects of n-acetylcysteine against acute hepatotoxicity.
Sahin S, Alatas O.

Source
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Abstract

OBJECTIVES:

N-acetylcysteine (NAC) increases tissue levels of glutathione and has been widely investigated as a protective and antioxidative agent. This study evaluated the protective effect of NAC on under carbon tetrachloride (CCl\textsubscript{4})-induced acute liver injury in the rat.

METHODS:

Three-month-old Sprague-Dawley rats were intraperitoneally administered 4 mL/kg CCl\textsubscript{4} (1:1 dissolved in olive oil, group 1) or 4 mL/kg CCl\textsubscript{4} + NAC 150 mg/kg, 3 and 6 h after CCL\textsubscript{4} (group 2) or 4 mL/kg olive oil (group 3, control). Twenty-four hours after administering CCl\textsubscript{4}, all of the rats were sacrificed. Biochemical assessment of serum transaminases and malonaldehyde (MDA) and tissue MDA, myeloperoxidase (MPO), and nitric oxide was done. Histopathological assessments were performed.

RESULTS:

Serum transaminases and tissue and serum MDA and tissue MPO were all increased in group 1 compared to control and were significantly decreased in the group treated with NAC. Histopathological comparison of the groups showed a decrease in congestion, polymorphonuclear leukocytes, mononuclear leukocytes, vacuolar degeneration of hepatocyte, and hepatocellular necrosis in the group treated with NAC.

CONCLUSION:

Our results suggest that NAC prevents experimental acute hepatic failure by preventing oxidative stress.


Dietary antioxidants (selenium and N-acetylcysteine) modulate paraoxonase 1 (PON1) in PCB 126-exposed rats.
Shen H, Li M, Wang B, Lai IK, Robertson LW, Ludewig G.

Source
Interdisciplinary Graduate Program in Human Toxicology, The University of Iowa, Iowa City, IA, USA.

Abstract

Environmental pollutants polychlorinated biphenyls (PCBs), especially dioxin-like PCBs, cause oxidative stress and associated toxic effects, including cancer and possibly atherosclerosis. We previously reported that PCB 126, the most potent dioxin-like PCB congener, not only decreases antioxidants such as hepatic selenium (Se), Se-dependent glutathione peroxidase, and glutathione (GSH) but also increases levels of the antiatherosclerosis enzyme paraoxonase 1 (PON1) in liver and serum. To probe the interconnection of these three antioxidant systems, Se, GSH, and PON1, we examined the influence of varying levels of dietary Se and N-acetylcysteine (NAC), a scavenger of reactive oxygen species (ROS) and precursor for GSH synthesis, on PON1 in the absence and presence of PCB 126 exposure. Male Sprague-Dawley rats, fed diets with differing Se levels (0.02, 0.2, or 2 ppm) or NAC (1 %), were treated with a single intraperitoneal
injection of corn oil or various doses of PCB 126 and euthanized 2 weeks later. PCB 126 significantly increased liver PON1 mRNA, protein level and activity, and serum PON1 activity in all dietary groups but did not consistently increase thiobarbituric acid levels (thiobarbituric acid reactive substances, TBARS), an indicator of lipid oxidation and oxidative stress, in liver or serum. Inadequate (high or low) dietary Se decreased baseline and PCB 126-induced aryl hydrocarbon receptor (AhR) expression but further increased PCB 126-induced cytochrome P450 1A1 (CYP1A1) expression, the enzyme believed to be the cause for PCB 126-induced oxidative stress. In addition, a significant inverse relationship was observed not only between dietary Se levels and PON1 mRNA and PON1 activity but also with TBARS levels in the liver, suggesting significant antioxidant protection from dietary Se. NAC lowered serum baseline TBARS levels in controls and increased serum PON1 activity but lowered liver PON1 activities in animals treated with 1 µmol/kg PCB 126, suggesting antioxidant activity by NAC primarily in serum. These results also show an unexpected predominantly inverse relationship between Se or NAC and PON1 during control and PCB 126 exposure conditions. These interactions should be further explored in the development of dietary protection regimens.

Exp Physiol. 2013 Apr 26. [Epub ahead of print]

Mitochondrial dysfunction and therapeutic approaches in respiratory and limb muscles of cancer cachectic mice.


Source

1 IMIM-Hospital del Mar, UPF, PRBB, CIBERES;

Abstract

Abnormalities in mitochondrial content, morphology, and function were reported in several muscle wasting conditions. We specifically explored whether experimental cancer-induced cachexia may alter mitochondrial respiratory chain (MRC) complexes and oxygen uptake in respiratory and peripheral muscles, and whether signaling pathways, proteasome, and oxidative stress may influence that process. We evaluated complex I, II, and IV enzyme activities (specific activity assays) and MRC oxygen consumption (polarographic measurements) in diaphragm and gastrocnemius of cachectic mice bearing the LP07 lung tumor with and without treatment with N-acetylcysteine, bortezomib, and nuclear factor (NF)-κB (sulfasalazine) and mitogen-activated protein kinases (MAPK, U0126) inhibitors, n=10/group, all groups. Whole body and muscle weights and limb muscle force were also assessed in all rodents at baseline and after one month. Compared to controls, cancer cachectic mice showed a significant reduction in body weight gain, smaller sizes of diaphragm and gastrocnemius, lower muscle strength, and decreased activity of complexes I, II, and IV, and oxygen consumption in both muscles. Blockade of NF-κB and MAPK actions restored muscle mass loss and force, and MRC dysfunction in both muscles, while partly reducing tumor burden. Antioxidants improved mitochondrial oxygen uptake without eliciting significant effects on muscle mass loss and force or tumor size, whereas the proteasome inhibitor reduced tumor burden without significantly influencing muscle mass and strength or mitochondrial function. In conclusion, NF-κB and MAPK signaling pathways modulate muscle mass and performance and MRC function of respiratory and limb muscles in this model of experimental cancer cachexia, thus offering targets for therapeutic intervention.

Ren Fail. 2013 Apr 8. [Epub ahead of print]

The Effects of N-Acetylcysteine and Ozone Therapy on Oxidative Stress and Inflammation in Acetaminophen-Induced Nephrotoxicity Model.

Ucar F, Yavuz Taslipinar M, Alp BF, Aydin I, Aydin FN, Agilli M, Toygar M, Ozkan E, Macit E, Oztosun M, Cayci T, Ozcan A.

Source
Abstract

Introduction: Acetaminophen (APAP) is an analgesic and antipyretic agent. In overdoses, it is associated with nephrotoxicity. We examined the potential protective effects of N-acetylcysteine (NAC) and NAC + ozone therapy (OT) combination against APAP-induced nephrotoxicity. Materials and methods: Thirty-two male Sprague-Dawley rats were divided into four groups: sham, control (APAP), NAC, and NAC + OT. In the APAP, NAC, and NAC + OT groups, kidney injury was induced by oral administration of 1 g/kg APAP. The NAC group received NAC (100 mg/kg/day). NAC + OT group received NAC (100 mg/kg/day) and ozone/oxygen mixture (0.7 mg/kg/day) intraperitoneally for 5 days immediately after APAP administration. All animals were killed at 5 days after APAP administration. Renal tissues and blood samples were obtained for biochemical and histopathological analyses. Neopterin, tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-10 levels were measured in sera. Malondialdehyde (MDA) levels and glutathione peroxidase (GPx) activities were determined in renal homogenates. Results: NAC and NAC + OT significantly decreased MDA and TNF-α levels and increased IL-10 levels and GPx activities. Serum neopterin and IL-6 levels were not different among all groups. APAP administration caused tubular necrosis in the kidney. The degrees of renal necrosis of the APAP group were higher than the other groups. Renal injury in rats treated with combination of NAC and OT were found to be significantly less than the other groups. Conclusions: Our results showed that NAC and OT prevented renal injury in rats and reduced inflammation. These findings suggest that combination of NAC and OT might improve renal damages because of both oxidative stress and inflammation.

Interactive effects of N-acetylcysteine and antidepressants.

Costa-Campos L, Herrmann AP, Pilz LK, Michels M, Noetzold G, Elisabetsky E.

Source

Laboratório de Etnofarmacologia, Departamento de Farmacologia, Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Rua Sarmento Leite, 500, 90050-170 Porto Alegre, RS, Brazil; Programa de Pós-graduação em Neurociências, Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Rua Sarmento Leite, 500, 90050-170 Porto Alegre, RS, Brazil.

Abstract

N-acetylcysteine (NAC), a glutathione precursor and glutamate modulator, has been shown to possess various clinically relevant psychopharmacological properties. Considering the role of glutamate and oxidative stress in depressive states, the poor effectiveness of antidepressant drugs (ADs) and the benefits of drug combination for treating depression, the aim of this study was to explore the possible benefit of NAC as an add on drug to treat major depression. For that matter we investigated the combination of subeffective and effective doses of NAC with subeffective and effective doses of several ADs in the mice tail suspension test. The key finding of this study is that a subeffective dose of NAC reduced the minimum effective doses of imipramine and escitalopram, but not those of desipramine and bupropion. Moreover, the same subeffective dose of NAC increased the minimum effective dose of fluoxetine in the same model. In view of the advantages associated with using the lowest effective dose of antidepressant, the results of this study suggest the potential of a clinically useful interaction of NAC with imipramine and escitalopram. Further studies are necessary to better characterize the molecular basis of such interactions, as well as to typify the particular drug combinations that would optimize NAC as an alternative for treating depression.
N-acetylcysteine possesses antidepressant-like activity through reduction of oxidative stress: behavioral and biochemical analyses in rats.

Smaga I, Pomierny B, Krzyżanowska W, Pomierny-Chamiolo L, Miszkel J, Niedzielska E, Ogórka A, Filip M.

Source

Department of Toxicology, Faculty of Pharmacy, Jagiellonian University, Medical College, Krakow, Poland.

Abstract

The growing body of evidence implicates the significance of oxidative stress in the pathophysiology of depression. The aim of this paper was to examine N-acetylcysteine (NAC) - a putative precursor of the most important tissue antioxidant glutathione - in an animal model of depression and in ex vivo assays to detect oxidative stress parameters. Imipramine (IMI), a classical and clinically-approved antidepressant drug was also under investigation. Male Wistar rats which underwent either bulbectomy (BULB; removal of the olfactory bulbs) or sham surgery (SHAM; olfactory bulbs were left undestroyed) were treated acutely or repeatedly with NAC (50-100mg/kg, ip) or IMI (10mg/kg, ip). Following 10-daily injections with NAC or IMI or their solvents, or 9-daily injections with a corresponding solvent plus acute NAC or acute IMI forced swimming test on day 10, and locomotor activity were performed; immediately after behavioral tests animals were decapitated. Biochemical tests (the total antioxidant capacity - TAC and the superoxide dismutase activity - SOD) were performed on homogenates in several brain structures. In behavioral studies, chronic (but not acute) administration of NAC resulted in a dose-dependent reduction in the immobility time seen only in BULB rats while chronic IMI produced a significant decrease in this parameter in both SHAM and BULB animals. On the other hand, chronic administration of NAC and IMI resulted in a significant increase in cellular antioxidant mechanisms (SOD activity) that reversed the effects of BULB in the frontal cortex, hippocampus and striatum. Our study further supports the antidepressant-like activity of NAC and links its effect as well as IMI actions with the enhancement of brain SOD activity.


N-acetylcysteine exerts therapeutic action in a rat model of allergic rhinitis.

Guibas GV, Spandou E, Meditskou S, Vyzantiadis TA, Priftis KN, Anogianakis G.

Source

Laboratory of Experimental Physiology, School of Medicine, Aristotle University, Thessaloniki, Greece.

Abstract

BACKGROUND:

The pathophysiologic mechanism of allergy is dependent on the action of many redox-sensitive proinflammatory mediators. However, even though redox disturbances are believed to be a hallmark of inflammation, little is known of the effect of redox imbalance to the pathophysiology of allergic rhinitis. We thus opted to investigate the relation of oxidative stress and allergic rhinitis, through the utilization of a potent antioxidant substance (N-acetylcysteine [NAC]) in a rat model of allergic rhinitis and the evaluation of its action on specific markers of inflammation.

METHODS:

NAC (50 mg/kg and 250 mg/kg) was intraperitoneally administered to ovalbumin (OVA)-sensitized rats prior to intranasal challenge with OVA. Mucosal congregation of inflammatory cells (eosinophils and mast cells), mucosal expression of redox-sensitive enzymes (inducible nitric oxide synthase [iNOS] and cyclooxygenase
2 (COX-2), and the blood levels of a key proinflammatory mediator (tumor necrosis factor-α [TNF-α]) were evaluated.

RESULTS:

Intranasal OVA challenges lead to mucosal inflammation, induction of the mucosal expression of iNOS and COX-2 and elevation of TNF-α blood levels. NAC significantly inhibited accumulation of inflammatory cells and downregulated iNOS expression and TNF-α serum levels. The role of COX-2 appeared to be 2-fold and its expression was divergently modulated by NAC.

CONCLUSION:

Our findings suggest that redox balance is involved in the pathophysiology of allergic rhinitis in rats and that NAC can potentially suppress the allergen-induced nasal inflammatory cascade. The investigation of the role of oxidative stress in atopy could help in the evaluation of the therapeutic potential of antioxidant substances in allergic diseases.

Toxicol Ind Health. 2013 Jan 8. [Epub ahead of print]

Protective effects of alpha lipoic acid versus N-acetylcysteine on ifosfamide-induced nephrotoxicity.
El-Sisi AE, El-Syaad ME, El-Desoky KI, Moussa EA.

Source
Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Tanta, Tanta, Egypt.

Abstract

Ifosfamide (IFO) is a highly effective chemotherapeutic agent for treating a variety of pediatric solid tumors. However, its use is limited due to its serious side effect on kidneys. The side-chain oxidation of IFO in renal tubular cells produces a reactive toxic metabolite that is believed to be responsible for its nephrotoxic effect. Therefore, this study was carried out to investigate the possible underlying mechanisms that may be involved in IFO-induced nephrotoxicity, including free radical generation and the possible role of alpha lipoic acid (ALA) versus N-acetylcysteine (NAC) in protection against this toxicity. Male albino rats were injected intraperitoneally with saline, IFO (50 mg/kg daily for 5 days), IFO + ALA (100 mg/kg daily for 8 days) and IFO + NAC (200 mg/kg daily for 8 days). Kidney malondialdehyde, nitric oxide and glutathione contents and serum biochemical parameters and histopathological analysis were determined. Both ALA and NAC markedly reduced the severity of renal dysfunction induced by IFO. NAC was more nephroprotective than ALA. This study suggests that oxidative stress is possibly involved in the IFO-induced nephrotoxicity in rats. The study also suggests the potential therapeutic role for ALA and NAC against IFO-induced nephrotoxicity.


N-acetylcysteine attenuates subcutaneous administration of bleomycin-induced skin fibrosis and oxidative stress in a mouse model of scleroderma.
Zhou CF, Yu JF, Zhang JX, Jiang T, Xu SH, Yu QY, Zhu QX.

Source
Institute of Dermatology, The First Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China; Department of Occupational Health and Environmental Health, School of Public Health, Anhui Medical University, Hefei, Anhui, China.
Abstract

BACKGROUND:

Several lines of evidence suggest that the generation of reactive oxygen species (ROS) is of major importance in the pathogenesis of scleroderma, and thus antioxidant therapy may be useful for patients with an impaired oxidative defence mechanism.

AIM:

To examine the effect of N-acetylcysteine (NAC) on skin fibrosis and oxidative stress in a bleomycin (BLM)- induced mouse model of scleroderma.

METHODS:

We used this mouse model to evaluate the effect of NAC on skin fibrosis and oxidative stress. Skin fibrosis was evaluated by histopathological examination and hydroxyproline content. To measure lipid peroxidation, we used a thiobarbituric acid-reactive species, malondialdehyde (MDA). Oxidative protein damage (carbonyl content) and the activities of catalase (CAT) and superoxide dismutase (SOD) were determined to evaluate oxidative stress in the skin tissue.

RESULTS:

Treatment with NAC attenuated the skin fibrosis induced by BLM, significantly reducing the MDA and protein carbonyl content in these mice. SOD activity in BLM-only mice and BLM plus NAC-treated mice was increased compared with control mice. However, there was no significant difference in skin SOD activity of mice treated with both BLM and NAC compared with those treated with BLM only. In addition, CAT activity was not altered in the BLM plus NAC mice.

CONCLUSIONS:

NAC treatment attenuates skin fibrosis in a BLM-induced mouse model of scleroderma, and this is associated with diminished oxidative stress. The results suggest that NAC may be a potential therapeutic agent for patients with scleroderma.


Antimetastatic potential of N-acetylcysteine on human prostate cancer cells.

Supabphol A, Supabphol R.

Source

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athikom@swu.ac.th

Abstract

OBJECTIVE:

N-acetylcysteine (NAC), is one of the cheapest, safest and widely used over-the-counter-drugs in Thailand. Here the authors examine the antimetastatic potential of NAC on the metastasis of human prostate cancer cells.
MATERIAL AND METHOD:

Cytotoxicity of NAC to human prostate cancer cells, DU145 and PC3, were determined by proliferation assay using the 3-(4, 5-dimethylthiazol, 2-yl)-2, 5-diphenyltetrazolium bromide (MTT) reagent. Cell migration and invasion were assessed by using a chemotaxis chamber containing membrane pre-coated with collagen IV and Matrigel, respectively. Cell attachment onto the surface of the membrane coated with collagen IV was tested for its adhesion potentiality.

RESULTS:

NAC could inhibit the growth of DU145 and PC3 cells. Suppression of migration and invasion of both human prostate cancer cells were observed. Cell attachment to the collagen IV-coated surface was obviously reduced. All inhibitions occurred in a dose-dependent fashion in both cell lines.

CONCLUSION:

NAC could have a high potential in attenuating the migration of the human prostate cancer cells from their primary site and their adhesion and invasion to the remote locations. Hence, NAC might suppress the growth of the primary and the secondary tumors. Our findings suggest that NAC had a high possibility to become an antimetastatic agent for testing in clinical trials. Then, NAC might be used clinically as an optional adjuvant therapeutic drug in addition to the conventional standard treatment of human prostate cancer, obtaining a better outcome with the least toxic and affordable substance.

Int J Colorectal Dis. 2012 Dec 28. [Epub ahead of print]

Role of N-acetylcysteine and GSH redox system on total and active MMP-2 in intestinal myofibroblasts of Crohn's disease patients.

Romagnoli C, Marcucci T, Picariello L, Tonelli F, Vincenzini MT, Iantomasi T.

Source
Dipartimento di Scienze Biochimiche, Università degli Studi di Firenze, viale Morgagni 50, 50134, Florence, Italy.

Abstract

PURPOSE:

Intestinal subepithelial myofibroblasts (ISEMFs) are the predominant source of matrix metalloproteinase-2 (MMP-2) in gut, and a decrease in glutathione/oxidized glutathione (GSH/GSSG) ratio, intracellular redox state index, occurs in the ISEMFs of patients with Crohn’s disease (CD). The aim of this study is to demonstrate a relationship between MMP-2 secretion and activation and changes of GSH/GSSG ratio in ISEMFs stimulated or not with tumor necrosis factor alpha (TNFα).

METHODS:

ISEMFs were isolated from ill and healthy colon mucosa of patients with active CD. Buthionine sulfoximine, GSH synthesis inhibitor, and N-acetylcysteine (NAC), precursor of GSH synthesis, were used to modulate GSH/GSSG ratio. GSH and GSSG were measured by HPLC and MMP-2 by ELISA Kit.

RESULTS:

In cells, stimulated or not with TNFα, a significant increase in MMP-2 secretion and activation, related to increased oxidative stress, due to low GSH/GSSG ratio, was detected. NAC treatment, increasing this ratio, reduced MMP-2 secretion and exhibited a direct effect on the secreted MMP-2 activity. In NAC-treated and TNFα-stimulated ISEMFs of CD patients’ MMP-2 activity were restored to physiological value. The
involvement of c-Jun N-terminal kinase pathway on redox regulation of MMP-2 secretion has been demonstrated.

**CONCLUSION:**

For the first time, in CD patient ISEMFs, a redox regulation of MMP-2 secretion and activation related to GSH/GSSG ratio and inflammatory state have been demonstrated. This study suggests that compounds able to maintain GSH/GSSG ratio to physiological values can be useful to restore normal MMP-2 levels reducing in CD patient intestine the dysfunction of epithelial barrier.


**Effect of oral N-acetyl cysteine on eradication of Helicobacter pylori in patients with dyspepsia.**

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**Source**

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**Abstract**

Aim: Using mucolytic agents that decrease viscosity of the gastric mucous and therefore, increase the permeability of antibiotics through gastric membrane has been offered as an additive treatment to achieve a higher rate of eradication of Helicobacter pylori (H. Pylori) infection. The aim of this study was to determine the efficacy of oral N-acetyl cysteine (NAC) on eradication of H. pylori infections in patients suffering from dyspepsia: Methods: In this randomized double-blinded clinical trial, 60 H. pylori positive patients who were suffering from dyspepsia were included. They were divided into two groups. Both groups received three-drug regimen including pantoprazole 40 mg BD, ciprofloxacin 500 mg BD and bismuth subcitrate 120 mg two tablets BD. Experimental group (30 cases) received 600 mg of NAC besides three-drug regimen. Control group received placebo. The results of therapy were tested by 14C-UBT and were compared with each other two months after the first visit. Results: H. pylori infection was eradicated in 21 (70%) and 17 (60.7%) patients in experimental and control groups, respectively (P=0.526). Regarding clinical and endoscopic variables, no significant difference was observed between the two groups except for erosive gastritis (0.041) and erosive esophagitis (0.031). Conclusion: Our findings offer that NAC has an additive effect on H. pylori triple therapy with pantoprazole, ciprofloxacin and bismuth subcitrate. Although NAC does not have any known activity against H. pylori, it can reduce the thickness of the mucus layer and increase the permeability of antibiotics at the site of infection. To evaluate this effect, more studies with larger sample size should be performed.


**Inhibition of hyaluronidase by N-acetyl cysteine and glutathione: role of thiol group in hyaluronan protection.**

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**Source**

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**Abstract**
Hyaluronidase inhibitors have immense applications in pathophysiological conditions associated with hyaluronan-hyaluronidase system. The present study demonstrates the inhibitory efficacy of clinically accepted antioxidant N-acetyl cysteine (NAC) against hyaluronidase of serum, testis, and snake and bee venoms. The experimental and molecular dynamic simulation data suggest the non-competitive inhibition and involvement of thiol groups of both NAC and glutathione in exertion of inhibition. The bioavailability, less-toxic and antioxidant nature of NAC and glutathione could become valuable in the management of pathologies triggered by extracellular matrix degradation and to increase the endurance of hyaluronan based biomaterials/supplements, which are highly exciting aspects.