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N-Acetylcysteine—a safe antidote for cysteine/glutathione deficiency

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Glutathione (GSH) deficiency is associated with numerous pathological conditions. Administration of N-acetylcysteine (NAC), a cysteine prodrug, replenishes intracellular GSH levels. NAC, best known for its ability to counter acetaminophen toxicity, is a safe, well-tolerated antidote for cysteine/GSH deficiency. NAC has been used successfully to treat GSH deficiency in a wide range of infections, genetic defects and metabolic disorders, including HIV infection and COPD. Over two-thirds of 46 placebo-controlled clinical trials with orally administered NAC have indicated beneficial effects of NAC measured either as trial endpoints or as general measures of improvement in quality of life and well-being of the patients.

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Loss of balance between the antioxidant defence and oxidant production in the cells, which commonly occurs as a secondary feature in many human diseases, is loosely termed as 'oxidative stress'. This balance is important because the intracellular redox environment must be more reducing than being oxidative to maintain optimal cell function. Four major inter-dependent redox couples — GSH/GSSG, NADPH/NADP$^+$, NADH/NAD$^+$ and thioredoxin [Trx(SH)2/TrxS-S] — interact to regulate this redox environment [1]. The loss of antioxidant capacity in an oxidatively stressed cell is, however, mainly due to a decrease in GSH and/or an increase in GSSG, because glutathione (GSH) is the most abundant intracellular free thiol. Thus, oxidative stress in vivo mainly translates to deficiency of GSH and/or its precursor, cysteine.

Antioxidant supplementation has been studied extensively as a method to counter disease-associated oxidative stress. Several antioxidants have been used with varying degrees of success. Although the commonly used antioxidants, which include vitamin C, vitamin K and lipoic acid can directly neutralize free radicals, they cannot, however, replenish the cysteine required for GSH synthesis and replenishment [2]. Thus, not surprisingly, the cysteine prodrug N-acetylcysteine, which supplies the cysteine necessary for GSH synthesis, has proven to be more effective in treating disease-associated oxidative stress. NAC has been used in the clinic to treat a variety of conditions including drug toxicity (acetaminophen toxicity) [3•], human immunodeficiency virus/AIDS [4,5], cystic fibrosis (CF) [6,7], chronic obstructive pulmonary disease (COPD) [8], diabetes [9], etc.

In this review, we summarize the biochemical and pharmacological aspects of NAC that make it a 'wise choice' to treat cysteine/GSH deficiencies. We then focus on the various NAC formulations that are currently available. Comprehensive reviews of placebo-controlled trials with NAC have been published previously [10••–14]. Here, we briefly comment on the various clinical trials with NAC with special reference to acetaminophen toxicity, HIV and CF, in which our laboratory has a special interest.

Biochemistry and function
In vitro and in vivo studies have shown that NAC acts as a cysteine prodrug and a GSH precursor [15]. It can also reduce disulphide bonds in proteins [16,17], scavenge free radicals [18] and bind metals to form complexes [19]. However, its principal use pharmacologically is to replenish the cysteine and GSH that are lost due to acetaminophen toxicity.

Chemically NAC is similar to cysteine. The presence of the acetyl moiety, however, reduces the reactivity of the thiol as compared with that of cysteine. Thus as compared with the cysteine, NAC is less toxic, less susceptible to oxidation (and dimerization) and is more soluble in water, making it a better source of cysteine than the parenteral administration of cysteine itself [20]. Although NAC (and GSH) can directly scavenge free radicals, the rate constants for their reaction with reactive oxygen species (ROS) are several orders of magnitude lower than those of antioxidant enzymes such as

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superoxide dismutase (SOD), catalase and glutathione peroxidase [21]. Thus, the direct free radical scavenging activity of NAC is not likely to be of great importance for its antioxidant activity *in vivo*.

The direct antioxidant activity of NAC has been proposed primarily based on data from *in vitro* studies, where NAC has been shown to reduce oxidant-induced cell damage and cell death by apoptosis [15]. Recent studies from our laboratory, however, indicate that the observed beneficial effects of NAC on cells in culture is due, at least in part, to replenishment of the intracellular GSH that is lost in cells maintained under typical cell culture conditions. This GSH loss, as we have shown, is substantially greater in cells maintained at the atmospheric oxygen levels (i.e. 20% oxygen) typically used in CO_2 incubators than in cells maintained at more physiological oxygen levels (5% oxygen). It can be prevented by adding NAC to the cultures, though NAC does not completely prevent the adverse effects of culturing cells at atmospheric oxygen (Atkuri et al., 2007, PNAS in press).

In vivo metabolism

NAC's primary function *in vivo* is to supply cysteine necessary for GSH synthesis and replenishment. Consistent with this, pharmacokinetics studies have shown that NAC undergoes extensive first pass metabolism in the liver and kidneys resulting in very low concentrations of 'free' NAC in the plasma [22,23] and virtually undetectable levels of NAC in other body fluids such as broncho-alveolar lavage [24].

Orally delivered NAC is readily taken up in the stomach (low pH in the stomach makes the neutral species of NAC the predominant form and hence easily penetrable) and gut [25] and is sent to the liver via the portal route where it is almost entirely converted to cysteine [23]. The liver incorporates most of the cysteine into GSH, which is then largely secreted into circulation [26].

NAC has most widely been used for countering acetaminophen (or paracetamol) toxicity and associated liver injury. Acetaminophen mediated liver toxicity is due to the generation of its metabolite *N*-acetyl-*p*-benzoquinoneimine by the hepatic cytochrome P450 enzymes. Detoxification of this metabolite requires high concentrations of GSH. Thus excessive GSH depletion during acetaminophen overdose can cause permanent liver damage. NAC administration supplies the cysteine required for the *de novo* synthesis of hepatic GSH.

NAC administration and toxicity

NAC has been administered orally, intravenously and topically (e.g. as aerosol). Topical delivery of NAC has not been shown to increase systemic NAC, cysteine or GSH levels. Further, aerosol delivery can result in NAC oxidation, which may have negative consequences [27]. Intravenous administration of NAC transiently increases plasma NAC to very high levels (during administration) and is known to cause adverse effects. Although clinical situations sometimes dictate the need for intravenous administration of NAC [3•], most needs for NAC therapy can be met by oral NAC administration. In the interests of brevity, we therefore largely restrict this review to consider settings in which NAC has been administered orally.

Oral administration of NAC at doses up to 8000 mg/day is not known to cause clinically significant adverse reactions [5]. A small fraction of individuals to whom oral NAC was administered reported experiencing nausea, vomiting and heartburn. In a placebo-controlled trial testing NAC at an average dose of 6900 mg/day, for example, 14/60 subjects reported gastric distress. On analysis, however, 7 of the 14 subjects reporting such adverse events were in the placebo arm [5], suggesting that the distress that was encountered was related to the ingestion of the excipient (which was later recognized as containing lactose). Consistent with this interpretation, no adverse effects were reported in a recent phase II clinical trial for CF in which NAC (or placebo) was administered orally as lactose-free flavoured effervescent tablets (BioAdvantex Pharma Inc., Mississauga, Ontario) (Tirouvanziam et al., unpublished). Similarly, a review of over 46 placebo-controlled trials where NAC was administered orally to a total of 4000 subjects did not reveal significant adverse effects from NAC treatment.

In contrast, severe and in some instances life-threatening anaphylactoid reactions, which include urticuria, hypotension and vomiting, have been reported after intravenous administration of NAC [3•]. These reactions subside rapidly when NAC administration is discontinued or the rate of intravenous administration of NAC is decreased. NAC is not known to interact with other drugs although extensive studies in these aspects have not been performed.

Overall, the data available from NAC trials suggest that when cysteine is delivered orally in a non-toxic form (e.g. as NAC rather than as cysteine itself), toxicity associated with high cysteine intake is negligible. Thus, since cysteine is known to spare methione, addition of NAC (a source of cysteine) to parenteral nutrition formations may be useful [28••].

NAC formulations

The best known NAC formulation in the US is Mucomyst™ (or the generic version thereof). Although it is commonly administered orally for the treatment of acetaminophen overdose, it has a strong, disagreeable flavour and therefore is usually mixed with a fruit juice or a soft drink before consumption. In contrast, NAC is

produced and packaged in Europe in pill and capsule formulations, as well as in a variety of effervescent formulations ('fizzy tabs') that can be dissolved in water, juice or carbonated drinks to create a pleasant tasting, readily tolerated beverage containing soluble NAC that can be rapidly absorbed. A Canadian company (BioAdvantex Pharma, Inc., Mississauga, Ontario) also offers pleasant-tasting effervescent NAC tablets that are manufactured according to European Good Manufacturing Practice (GMP) standards [7••].

The manufacture of NAC requires minimization of NAC oxidation to its dimeric form ('di-NAC'), which is pharmacologically active at very low concentrations with immunologic effects opposite to those of NAC [27]. In an experimental model with rodents, di-NAC was found to be 100–1000 times more effective in enhancing contact sensitivity to oxazolone than NAC. In general, di-NAC constitutes less than 0.1% of NAC produced according to European GMP standards [29].

Several US nutriceutical dealers manufacture and sell NAC alone or in combination with other daily supplements such as vitamins and antioxidants. However, since the FDA does not regulate the production and packaging of nutriceutical products in the US, neither the content nor the purity of the NAC formulations currently produced and marketed in the US can be reliably judged. It is important to note that manufacturing methods for these NAC preparations may not include measures to prevent oxidation of NAC to its dimeric form either during manufacture or while the product is stored.

We have recently suggested [30] that NAC be co-administered, and perhaps co-formulated, with acetaminophen to decrease its potential toxicity. Animal studies suggest that administration of roughly equimolar amounts of NAC and acetaminophen may be sufficient to accomplish this goal [31]. Co-administration of acetaminophen with NAC could minimize acetaminophen toxicity in setting where GSH deficiency is present or is transiently induced by alcohol or other drug ingestion. In addition, co-administration with NAC may safely allow administration of higher doses of acetaminophen when clinically warranted.

Disease indications for NAC
Glutathione deficiency occurs frequently in many diseases because of a variety of factors that include viral protein-mediated GSH depletion (e.g. HIV Tat), uncontrolled inflammatory reactions and increased generation of free radicals [32,33]. GSH deficiency may increase either the rate of disease progression or the severity of the disease symptoms. Alternatively, GSH deficiency may not contribute to the specific symptoms of the disease and is recognizable mainly by secondary symptoms such as oxidative damage,

reduced immune function and overall decrease in health. Thus, benefits of NAC therapy may not always be reflected in terms of attenuation of clinical symptoms, particularly the 'hard endpoints' that are used to test drug efficacy. This problem compromises interpretation of data from clinical trials in that the endpoints relevant to correction of GSH deficiency may not always have been measured. That said, 32/44 placebo-controlled trials conducted across a wide range of disease settings have, however, reported beneficial effects of oral NAC treatment, including HIV [4,5,34], CF [6], colon cancer [35], protein energy malnutrition [36], diabetes [37], Alzheimer disease [38], bronchitis [39] and in cardiac dysfunction [40].

A comprehensive review of the findings in these trials is beyond the scope of this brief review. For in-depth analysis, we refer the reader to several recent reviews and meta-analyses [10••–14]. Here, we briefly focus on examples from two areas of particular interest to our laboratory.

HIV/AIDS
GSH levels in CD4 T cells and erythrocytes decrease progressively as HIV disease progresses [41,42,43•]. This decrease, which is most marked at the later stages of the disease, is strongly associated with decreased survival [42]. Several placebo-controlled trials with GSH-deficient HIV-infected subjects have demonstrated that orally administered NAC replenishes erythrocyte and lymphocyte GSH and improves T cell function [4,5,34,44]. None of the trials report placebo-controlled data on the effect of NAC on survival.

Pulmonary diseases
Placebo-controlled trials in patients with chronic lung disease (CLD/COPD) have collectively shown that orally administered NAC ($\geq$600 mg/day) significantly improves response to steroids, increases general well-being and decreases exacerbation rates, emergency room visits, days of illness, costs of hospitalization and work time loss. Although some trials have failed to show beneficial effects of oral NAC, meta-analyses confirm the beneficial effects of NAC in the CLD/COPD patients [8,11,14,45].

In cystic fibrosis (CF), we have recently demonstrated beneficial effects of oral NAC in CF in a 4-week, dose-escalating phase 1 trial. Benefits detected include reduction of the neutrophil burden in CF airways and reduction in elastase and interleukin-8 levels in lung fluid [7••]. Preliminary analysis of data from a placebo-controlled phase II trial that we recently completed is similarly encouraging, suggesting that orally administered NAC (2700 mg/day for 12 weeks) is well tolerated and may prove quite a valuable and inexpensive adjunct therapy to decrease chronic lung inflammation and improve lung function in CF patients.

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Conclusions/future directions

Oral administration of NAC, a safe, well-tolerated drug with no clinically significant adverse effects, has been shown to be beneficial in settings where GSH deficiency occurs, for example, HIV infection, CF and diabetes. Although many trials have been conducted, more are needed to further ascertain the effect of NAC in diseases associated with GSH deficiency.

In individual patients, the extent of GSH deficiency that develops may vary depending on the disease severity, patient diet and other drug use (including alcohol). This caveat is quite important and may be at the heart of controversies where NAC has been shown to work in some trials but not in others (e.g. contrast nephropathy). Resolution of this issue would, however, require trials to routinely include whole blood (rather than plasma) GSH/GSSG measurements, which can be done now by mass spectrometry that are neither easy nor amenable to widespread clinical use. Improvement in the accessibility of these assays would considerably facilitate all studies in which GSH levels are at issue and would as well improve the ability of physicians to judge whether NAC supplementation is advisable for individual patients with diseases in which NAC has been shown to be beneficial.

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Conflict of interest

Two of the authors, Leonard A. Herzenberg and Leonore A. Herzenberg, have a loose working relationship with BioAdvantex Pharma Inc. (Mississauga, Ontario, Canada), a small privately held nutriceutical company that sells OTC oral N-acetylcysteine (NAC) produced to meet European GMP standards. The BioAdvantex market share is <1% of the overall North American market and non-existent elsewhere. BioAdvantex has sponsored two meetings that the Herzenbergs attended, has reimbursed travel for Leonore A. Herzenberg to an NIH-sponsored meeting and has given the Herzenberg laboratory three unrestricted gifts ($20 000) over the past 8 years. In addition, the company has supplied its NAC product to the Herzenberg laboratory.

The Herzenbergs have several issues or pending patents relating to NAC usage and have a small number of shares (no current market value) in Thiolex Development Corporation (Delaware, USA), a privately held affiliate of BioAdvantex. The shares were obtained by Stanford University as part of a licensing arrangement and distributed to the authors pursuant to the University policy.

None of the authors has any other competing interests, financial or otherwise.

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