Clinical Pharmacology

GSH Rescue by N-Acetylcysteine

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Summary. Reduced glutathione (GSH) is the main intracellular low molecular weight thiol. GSH acts as a nucleophilic scavenger and as an enzyme-catalyzed antioxidant in the event of electrophilic/oxidative tissue injury. Therefore, GSH has a major role as a protector of biological structures and functions. GSH depletion has been recognized as a hazardous condition during paracetamol intoxication. Conversely, GSH rescue, meaning recovery of the protective potential of GSH by early administration of N-acetylcysteine (NAC), has been found to be life-saving. Lack of GSH and electrophilic/oxidative injury have been identified among the causes of the adult respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis (IPF), and the acquired immunodeficiency syndrome (AIDS). Experimental and early clinical data (in ARDS) point to the role of NAC in the treatment of these conditions. Recently, orally given NAC has been shown to enhance the levels of GSH in the liver, in plasma, and notably in the bronchoalveolar lavage fluid. Rescue of GSH through NAC needs to be appreciated as an independent treatment modality for an array of different diseases, all of which have one feature in common: pathogenetically relevant loss of GSH.

Key words: Glutathione depletion – Glutathione rescue – N-acetylcysteine – Adult respiratory distress syndrome – Idiopathic pulmonary fibrosis – Acquired immunodeficiency syndrome

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Abbreviations: AIDS = Acquired immunodeficiency syndrome; ARC = AIDS-related complex; ARDS = Adult respiratory distress syndrome; DTC = Diethyldithiocarbamate; FiO_2 = Fraction inspired oxygen; GSH = Reduced glutathione; GSSG = Glutathione disulfide; HIV = Human immunodeficiency virus; IPF = Idiopathic pulmonary fibrosis; NAC = N-acetylcysteine; NFKB = Nuclear transcription factor kappa B; $PaO2$ = Arterial oxygen pressure; $PaO2/FIO2$ = Respiratory index; TNF = Human tumor necrosis factor

Glutathione Background

Reduced glutathione (GSH) is ubiquitous in nature as the principal intracellular low molecular weight thiol. The two characteristic structural features of GSH are the γ-Glu linkage and the reactive thiol (-SH) group. Intracellular stability and biochemical functions of GSH are closely linked to both elements. GSH exerts metabolic and protective activities primarily intracellularly, but also in the extracellular space [13, 15, 24, 27].

GSH is synthesized intracellularly from the amino acids glycine, glutamate, and the thiol providing amino acid cysteine. Synthesis of GSH in the liver has been recognized as highly efficient, but other organs such as the lungs and the kindeys are also endowed with substantial synthesis capacities. Cell membranes in general are impermeable to the tripeptide glutathione. Hence, GSH is synthesised intracellularly only from the single amino acid constituents or their precursors [15, 24]. Since glycine and glutamate are abundantly available in the intracellular space, an adequate supply and transmembrane transport of cysteine into the cell becomes the rate-limiting step in the biosynthesis of GSH. Conversely, GSH can serve as a storage and transport form of cysteine in the extracellular space [30]. When intracellular cysteine is required, the breakdown of GSH is initiated by γ-glutamyl transpeptidase on the external surface of the cell membrane, followed by transmembrane transport of the single amino acid. Interestingly, enhancement of tissue glutathione concentration in the liver is achieved by feeding synthetic antioxidants. In mechanistic terms, this phenomenon has been attributed to a shift from predominantly hepatorenal towards enterohepatic circulation of glutathione through increased biliary glutathione flux [20]. The administration of exogenous N-acetylcysteine (NAC) also effectively meets intracellular

needs of cysteine for the synthesis of GSH by supplementing precursor pools in a more physiological way [13, 27].

GSH acts as a nucleophilic scavenger of electrophilic xenobiotic compounds and their metabolites, converting electrophilic centers via enzymatic conjugation into thioether bonds. In addition, GSH, as the only substrate of selenium-dependent GSH peroxidase [17] and also as a chemical reducing agent and antioxidant, has an extremely important role. By virtue of these features GSH is considered to be an outstanding protector of biological structures and function.

Glutathione Depletion and Rescue

GSH depletion to about 20–30% of physiological levels has the consequence of impairing this defense, allowing cell injury to proceed until cell death occurs. Obviously, successful protection results in a transient "loss" of GSH. Any single GSH moiety, once it is conjugated to electrophils and transported out in this form, and also when oxidized, is not immediately available for subsequent needs. Oxidized glutathione is reduced once again to the functional form via the glutathione reductase pathway. Under these conditions the loss of glutathione remains reversible. Conjugated GSH, however, is exported from the cell and processed to mercapturic acids, which are excreted in the urine. In these reactions, GSH is lost irreversibly and can be replaced only via ex novo synthesis. Irreversible loss of GSH occurs preferentially following oxidative stress. Under conditions of intense oxidative stress the rate of glutathione disulfide (GSSG) formation – through oxidation of GSH – is such as to surpass, and possibly exhaust, the intracellular glutathione reductase capacities; as a consequence an accumulation of intracellular GSSG will result. GSSG in turn, being toxic to the intracellular milieu beyond a critical concentration, is exported from the cell and hence lost to the reductase pathway [15, 27].

Loss of glutathione, be it through conjugation or oxidation, will be counterbalanced through increased interorgan transport of thiol moieties [15, 24] and ex novo synthesis of GSH as long as sufficient amounts of cysteine remain available. Interestingly, chronic stress on specific glutathione pools has been found to induce an adaptive overload of glutathione in the very sites under stress. It is relevant that Cantin and coworkers [10] have reported increased levels of GSH in the alveolar epithelial lining fluid of healthy smokers. Severe and sustained deficiency of glutathione, however, will leave cellular and tissue structures vulnerable to oxidant and electrophilic aggression and their sequence, spelling progressive deterioration and cell death.

It is important to realize that insufficient defense through GSH is an early step in this cascade of events. Once the subsequent development has taken over, recovery of GSH at the intracellular level may still prevent further damage, but will be unable to restore the integrity of the previously affected tissues. The lessons learned from the treatment of paracetamol intoxication are clear: the administration of NAC, if initiated within hours of the paracetamol overdose, will provide a timely glutathione rescue and lead to "restitutio ad integrum". Any delayed intervention is much less likely to obtain a similar result [26, 27].

Intoxication with paracetamol and its treatment through administration of NAC represents a classical example of GSH deficiency, electrophilic/oxidative tissue injury, and its appropriate treatment. It is thus somewhat surprising that the expansion of this knowledge to other states of GSH deficiency and electrophilic or oxidative injures in organs other than the liver became so tedious and cumbersome. But there were reasons. Direct detection of the electrophilic/oxidative attack in vivo, especially in the clinical setting, is still elusive and monitoring of the GSH/GSSG status is complicated, particularly when tissue parameters are more important than serum levels. Paracetamol intoxication is an acute event; by contrast, many of the other forms of glutathione stress, whether to the liver, the lung, or other organs, are more chronic than acute in nature, thereby leaving some space for other compensating defense mechanisms besides GSH and hence blurring the picture. Obviously the endogenous antioxidant defence mechanisms are working in concert, and although GSH is a "first violin," the rest of the orchestra counts as well. Further, even with an identified lack of glutathione, often the question is: "Does it matter? Is it relevant for a particular pathogenesis?" Lastly, it was unclear whether the administration of NAC, either orally or intravenously, would increase the pool of GSH in a target tissue other than the liver. Fortunately the current state of the art shows that the concepts of GSH deficiency and rescue in electrophilic/oxidative tissue injury are steadily becoming more applicable in clinical medicine. Clearly, some of the questions raised have been answered, and if not totally so, then at least to an important degree. Some clinical examples that have attracted interest in this context will be discussed briefly.

Glutathione Rescue
in the Adult Respiratory Distress Syndrome

The adult respiratory distress syndrome (ARDS) is of multifactorial origin, but at a certain stage of its development strong oxidative stress through massive polymorphonuclear activation in the pulmonary vascular bed becomes a predominant condition [6]. Mechanical ventilation with high concentrations of oxygen further enforces the release of reactive oxygen metabolites [21]. In experimental models of ARDS [2], hyperoxia [33], and otherwise-induced oxidant lung injury [25], NAC was highly effective with respect to pulmonary and cardiovascular recovery. There were also clear-cut improvements in survival. Oxidant injury was compensated by NAC, and this finding was felt to indicate a role for a lack of glutathione in the pathogenesis and a place for NAC in the clinical treatment [1].

One early trial [3] into manifest but early clinical ARDS and NAC revealed distinct depressions of red cell glutathione which were readily restored by a short-term (72 h) intravenous NAC regimen. In parallel there were significant improvements of cardiac output, oxygen delivery, and oxygen consumption. The short-term treatment with NAC had no effect on survival of patients, however, which emphasizes the fact that loss of glutathione is an early event. By the time of established ARDS the loss of GSH has already triggered subsequent events which fail to respond to GSH rescue [7]. Indeed, increased formation of GSSG has been found to be an extremely early indicator of pulmonary oxygen stress [14]. When NAC was administered in a 72- h intravenous regimen to a group of patients with early acute lung injury [31] and judged to be at risk of ARDS, the positive results of early administration became evident. There was an improvement in survival (NAC: 80%, placebo: 66%, NS, not published). In the NAC-treated groups the needs for endotracheal intubation and mechanical ventilation were more rapidly and significantly reduced, with $FIO2$ falling significantly, and $PaO2/FIO2$ being strongly improved ($P = 0.06$).

These clinical findings are in line with the hypothesis that had been formulated based on what is known about glutathione, its protective features, and its role in paracetamol intoxication. Moreover, they show that the principles of GSH loss and rescue through NAC appear to hold also for an electrophilic/oxidative injury localized outside the liver.

Currently research into the interrelationship among GSH, ARDS, and NAC is building up substantially. GSH depletion in the initial stages of ARDS has recently been reported for plasma and even more so for granulocyte levels [23]. Intravenous NAC treatment in these patients resulted in a significant rise of GSH, particularly when compared to placebo patients, in whom a relentless drop of GSH developed. Spontaneous oxygen radical production as determined by luminol-amplified chemiluminescence was contained after NAC, but increased after placebo treatment.

Idiopathic Pulmonary Fibrosis and Glutathione Rescue

Lack of GSH has also been detected in the alveolar epithelial lining fluid of patients with idiopathic pulmonary fibrosis (IPF) [9]. In addition, there is good evidence that high levels of reactive oxidant metabolites are being released by inflammatory cells in the lungs of IPF patients, resulting in important epithelial-cell damage and inflammation [11]. In pathogenetic terms there is a certain similarity between ARDS and IPF, although the latter is of a chronic nature, contrasting with the dramatically acute events in ARDS. Since reactive oxygen metabolites which are released from inflammatory cells cause tissue lesions in IPF patients, it seems reasonable to assume a role for GSH deficiency in this part of the pathogenesis. Subsequently tissue injury itself becomes the appropriate stimulus for enhanced tissue repair including fibrogenesis as a correlate of scarring, and hence the result is tissue fibrosis. Recent in vitro evidence also indicates a role for GSH on this side of the pathogenesis of IPF [12]. Human lung fibroblasts, when incubated with bronchoalveolar lavage fluid from IPF patients, displayed markedly increased proliferation. In the presence of physiologic concentrations of added GSH, however, the fibroblast proliferation was strongly suppressed. Similar effects were obtained by coincubation with cysteine or NAC but not with GSSG. Although the underlying mechanisms are thus far only partially clarified, the authors conclude that GSH in the extracellular milieu can suppress fibroblast proliferation in response to mitogens and that this activity is linked to the presence of a free sulfhydryl group. They also feel that GSH deficiency in IPF may favor fibroblast proliferation. GSH rescue in IPF patients would seem to be a promising addition to the treatment of this disease. So far, however, clinical data to this end are not available.

Human Immunodeficiency Virus and Glutathione Rescue

Glutathione deficiency has also been reported for symptom-free HIV-seropositive individuals [8]. GSH concentrations in plasma and alveolar epithelial lining fluid were found to amount to only 30% and 60%, respectively, of the levels detected in healthy control individuals. These data argue for a generalized deficiency of GSH, which is in contrast to the localized lack in IPF and somewhat similar to the pattern in ARDS. Four of the 14 HIV-seropositive individuals were on treatment with zidovudine, five had serological evidence of previous exposure to hepatitis B virus, and four had mild alterations in one of their lung function indices. It seems at least questionable whether these HIV-positives were still strictly symptom-free. Marked GSH deficiency and total absence of symptoms are hard to reconcile with each other. Is GSH deficiency in HIV-infected individuals epiphenomenal, or is it truly contributing to the course of the disease? Is there a role for GSH rescue in the treatment of the acquired immunodeficiency syndrome (AIDS)?

Reactive oxygen species have been implicated in the development of AIDS [18]. So far it is not quite clear whether oxidative stress is a cause or a consequence of GSH deficiency in HIV infection, but both conditions appear to be linked to each other interdependently in a vicious circle. In 1989 Dröge's group [16] reported that intracellular concentrations of GSH in blood monocytes and lymphocytes were slightly decreased in asymptomatic HIV-positive individuals when compared to normal controls, and stepwise stronger depletions were found in ARC (AIDS-related complex) or AIDS. In this last group, since at the time it was the only one treated, zidovudine treatment caused a certain recovery of the glutathione levels. On the other side, in vitro data show that thiol compounds such as NAC increased the ability of mononuclear cells from patients with ARC or AIDS to form T-cell colonies [34] and inhibited HIV expression after stimulation with human tumor necrois factor (TNF) [29]. Intracellular thiols were found to regulate the activation of nuclear transcription factor kappa B (NFKB) and thereby the transcription of the HIV virus [32].

Stimulation with TNF decreased intracellular thiols and enhanced NFKB activation, whereas added NAC restored thiol levels and blocked the activation of NFKB. When intracellular levels of GSH were strongly depleted, the expression of HIV through TNF was greatly enhanced [22, 29].

From their data the authors concluded that the intracellular levels of GSH and/or reactive oxygen species regulate the extent of HIV expression. These in vitro data are further corroborated by positive clinical data from AIDS patients and symptom-free HIV-positive individuals who were treated with diethyldithiocarbamate (DTC). DTC has a free thiol group in its molecule, and although it is not a precursor of GSH, a general sulfhydryl-sparing effect is conceivable [4, 28]. Unfortunately, and in spite of rapidly accumulating evidence in the experimental setting, clinical data with respect to GSH rescue in HIV infection are not available, although the case for this treatment modality appears strong, particularly in the early stages of the disease. Organ sites frequently exposed to electrophilic/oxidative injury are the liver and the lungs; consequently the potential clinical benefits of GSH rescue in HIV infection should first become evident in these sites.

GSH Rescue and N-acetylcysteine

GSH rescue for paracetamol intoxication and some other toxin-induced pathologies (e.g., carbon tetrachloride) is the state-of-the-art treatment modality. In these conditions the employment of NAC to achieve GSH recovery has been found superior. In case of early acute lung injury with a potential risk of ARDS, NAC has also been found effective, be it in a therapeutic sense or in terms of GSH repletion. For IPF and HIV infection, the concept of GSH rescue is less developed; in particular, clinical data are missing. In addition, these latter conditions are chronic in nature, as opposed to paracetamol intoxication or early lung injury. Intravenous administration of NAC, although effective in acute situations, in a chronic regimen has considerable practial limitations, and the question arises whether oral administration would be equally trustworthy. Oral administration of NAC has been recognized as efficient as intravenous treatment for paracetamol intoxication, and GSH levels in liver and plasma are readily restored [19].

In addition, NAC given by the oral route has been found to increase the concentrations of GSH in plasma and the bronchoalveolar lavage fluid [5]. These increases were found to be transient, which on one side calls for a regular administration of NAC. On the other side, the rapid clearance of extracellular GSH and its intracellular feedback-controlled synthesis help to avoid unphysiological accumulations of the tripeptide. At this point it seems important that pathologies due to an excess of GSH have not been reported so far, but could

become a potential threat in case of exaggerated GSH corrections. NAC via cysteine is submitted to the physiological feedback control mechanism of GSH synthesis, and thus any such "overcorrection" appears rather unlikely.

Conclusions

GSH deficiency is being recognized as an important pathogenetic actor in a number of diseases, and consequently GSH rescue is becoming a treatment modality of steadily increasing relevance. The current state of the art indicates the administration of NAC intravenously or orally, in acute or chronic regimens, as the most appropriate way to achieve GSH rescue, in particular if intracellular losses of GSH need to be compensated. All experience to date also stresses the necessity to initiate treatment as early as possible. In addition, NAC has been used clinically frequently and for many years in the treatment of airway diseases such as chronic bronchitis, and has been reported to be a well-tolerated and very safe agent (for review see [19]). The experience with NAC in chronic bronchitis also emphasizes the advantage of starting treatment early.

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Buchbesprechung

R. Werk: **Medizinische Bakteriologie und Infektiologie. Basiswissen und Diagnostik.** Springer, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona 1990. 64 Abb. 244 Tab. XV, 370 S. Brosch. DM 78,— (ISBN 3-540-52122-4)

Der Autor stellt sich auf 370 Seiten der Aufgabe, das umfangreiche Wissen der medizinischen Mikrobiologie und der klinischen Infektiologie zusammenzuführen und auf knappem Raum darzustellen. Diesem im Vorwort formulierten hohen Anspruch wird das Buch aber nicht gerecht. Schon der Buchtitel ist unpräzise (es werden nicht nur Bakterien, sondern auch andere Mikroorganismen besprochen) und weckt dann unerfüllte Hoffnungen, da infektiologisches Wissen nur sehr bruchstückhaft und in pauschalen Formulierungen vermittelt wird.

Im Kapitel 1 werden allgemeine Grundlagen für ein medizinisch-mikrobiologisches Laboratorium in umfassender Form und kompetent vermittelt. In Kapitel 2 erfährt der Leser in übersichtlicher Form alles Wissenswerte über die technischen Arbeitsläufe in einem mikrobiologischen Laboratorium. Es sind die Techniken der Sterilisation dargestellt ebenso wie bakteriologische Kulturmedien, ihre Zusammensetzung, Herstellung, Supplementierung bis hin zu Fehlerquellen und Qualitätskontrollen. Als besonders informativ wird das Unterkapitel „Mikrobiologische Arbeitstechniken" empfunden, wobei insbesondere die Darstellung der verschiedenen Techniken des Beimpfens von Nährmedien hervorzuheben ist.

Das Kapitel 3 ist das umfangreichste dieses Kompendiums und handelt hetero-ätiologische Infektionssyndrome, wie zum Beispiel Tonsillitis, Sinusitis, Pneumonien, Infektionen des Gastrointestinaltraktes, Infektionen der Gallenwege und des Urogenitaltraktes, Osteomyelitis, Sepsis, Endokarditis, Meningitis und andere ab. In jedem Unterkapitel wird zunächst das Krankheitsbild unter Berücksichtigung pathogenetischer Aspekte besprochen, dann das in Betracht kommende Erregerspektrum dargestellt und schließlich die mikrobiologische Diagnostik unter schematischer Darstellung der Verarbeitungen der Untersuchungsmaterialien erläutert. Jedem Kapitel schließt sich ein Literaturverzeichnis an.

Die inhaltliche Aufteilung dieses Kapitels und die didaktische Darstellung sind gut. Für den mikrobiologisch interessierten Internisten sind einige Darstellungen, insbesondere zur Materialverarbeitung, zu ausführlich, andererseits sind kursorische Angaben zu anderen diagnostischen Methoden als der Kultur ohne großen Informationsgehalt. Der infektiologisch interessierte Kliniker vermißt ein klares nosologisches Konzept und wird mit zahlreichen, unpräzisen und oberflächlichen Begriffen konfrontiert (was ist z.B. eine aufsteigende Urosepsis, warum muß bei einer nosokomialen Pneumonie in Erkrankungen mit und ohne Bakteriämie unterschieden werden?).

Das Kapitel 4 handelt von der In-vitro-Testung von Chemotherapeutika und beginnt mit ansprechenden Erläuterungen zur Technik der Empfindlichkeitstestung. Danach erfolgen ausführliche Tabellen über die Bewertung der Grenzwertkonzentrationen zahlreicher antibakteriell wirksamer Substanzen. Mit einem ausgezeichneten Abschnitt über die aktuelle Resistenzsituation klinisch wichtiger Bakterien und einem ausführlichen Literaturverzeichnis schließt dieses Kapitel. Das Buch endet mit einer Aufstellung von weiterführender Literatur, Fachzeitschriften und Handbüchern sowie einem Verzeichnis von Herstellern diagnostischer Materialien.

Dem von dem Autor im Vorwort seines Buches beklagten Defizit an infektiologischem Grundwissen und den sich daraus ergebenden individual-medizinischen Folgen ist zuzustimmen. Dieses Buch will dem interessierten Arzt mikrobiologische und infektiologische Grundkenntnisse vermitteln. Zwar bleibt das Buch in seinen klinischen Anteilen unbefriedigend, doch ist es in seinem mikrobiologischen Teil ausführlich und enthält einige tabellarische Übersichten, die in vergleichbaren Kompendien vermißt werden. Es ist als Einstiegslektüre für Medizinstudenten und junge Ärzte geeignet, die sich einem Gebiet nähern wollen, das im Medizinstudium noch immer zu kurz kommt. Daran gemessen, weist das Buch ein akzeptables Preis-Leistungs-Verhältnis auf.   B. Ruf (Berlin)