With Diabetes in Mind: A Thiol Signaling Network

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Abstract

The redox regulation system is in charge of maintaining normal cellular activities. Similar to the phosphorylation cascade, controlled variations in redox couples potential act as signal transduction components. The thermodynamic disequilibrium of the primary redox switches allows rapid and sensitive reactions to changes in redox environments, therefore cellular redox biology necessitates both compartmentalization and communication of redox systems. Numerous sulphur species with distinct functional groups (thiols, disulphides, polysulphides, sulphenic, sulphinic, and sulphonic acids, etc.) participate in a sophisticated network of sulphur-based redox processes, resulting in the multiple oxidation states of sulphur. Increased generation of reactive oxygen species and disruptions of thiol redox homeostasis have been linked to human diseases such as diabetes mellitus and its cardiovascular consequences. The review examines the literature on some etiopathogenic elements as well as treatment possibilities. In experimental contexts, the dual toxic-protective feature of sulphydryl-donor compounds raises the general difficulty of developing antioxidants for therapeutic application.

Keywords: Oxidation-reduction • Sulphydryl compounds • N-acetylcysteine • Diabetes mellitus • Arterial hypertension

Introduction

Sulphur (S) is found in the body of the reference man in roughly 140 g. Liquids (SO42 in drinking water) and solid food products are the two main dietary sources of S-containing molecules in human nutrition (organic S in the form of cysteine and methionine). Because cysteine is a metabolic product of methionine catabolism, methionine consumption may be adequate to meet an adult's metabolic needs for exogenous sulphur. However, considering the literature's uncertainty, WHO/FAO/UNU Experts determined that methionine and cysteine intake should be separated (10.4 mg/kg per day and 4.1 mg/kg per day, respectively). Sulphur in the body is divided into three compartments: 1) a nonmetabolic, poorly exchangeable pool found in keratin, collagen, connective tissue, cartilage, tendons, and other tissues; 2) labile molecules and non-protein-bound thiols such as glutathione (GSH); and 3) muscle mass. Methionine is broken down into homocysteine, which can then be remethylated back into methionine by the folate and vitamin B12-dependent methionine synthase. Homocysteine can give serine a sulphur group, resulting in cystathionine [1]. Cystathionine is made up of cysteine and -ketoglutarate. The carbon skeleton of cysteine, cystine, and methionine can be totally oxidised, and the amino nitrogens can be integrated into urea via the Krebs-Henseleit cycle. For S-containing amino acid insufficiency, there is currently no validated biomarker. Despite its several disadvantages, GSH plasma or intracellular concentrations and redox state are currently used as surrogate endpoints in clinical trials [2]. The GSH/GSSG (glutathione disulphide) ratio can be used to estimate a sy--stem's redox status. The redox environment can be assessed by measuring the molar concentrations of GSH and GSSG in homogeneous fluids like plasma, but compartmentation in cells or tissues might be problematic. The total concentration of GSH and GSSG in many cell types is mostly a reflection of the cytosol's redox environment (depending on the portion of cell volume occupied by the nucleus).

Disulphide Redox Systems

Numerous sulphur compounds with unique S-containing functional groups (thiols, disulphides, polysulphides, sulphenic, sulphinic, and sulphonic acids, among others) participate in a complex network of sulphur-based redox processes, whose compartmentation has been widely examined. Furthermore, sulphur compounds' metal-binding properties enable the formation of bioinorganic metal complexes, and iron-sulphur (Fe-S) clusters are important electron carriers and enzyme cofactors in the mitochondrial respiratory chain, iron homeostasis, tricarboxylic acid cycle enzymes, and DNA repair. In cysteine, the sulphur has an oxidation state of -2. As a result, cysteine in proteins can participate in redox reactions such as thiol-disulphide exchange, single- or two-electron transfer, hydrogen-atom transfer, and nucleophilic substitution in addition to structural responsibilities. When protein folding offers a favourable environment for the stability of the cysteine sulphydryl group in the anionic state, these redox processes are favoured. The electrostatic environment of cysteine thiols in proteins can, in fact, have a significant impact on thiol-disulphide exchange reaction rates. Disulphides, which are typically thought of as structurally stabilising components in proteins, have recently been discovered to be members of the redox-sensitive thiol-based regulatory switch family, which is involved in protein function preservation, restoration, and modulation. Thiol/disulphide oxidoreductases like thioredoxins, glutaredoxins, and protein disulphide isomerases have a conserved thioredoxin domain with the classic Cys-X-X-Cys active site motif [3,4]. The big thioredoxin-like superfamily, on the other hand, contains both protein disulphide oxidoreductases with a traditional thioredoxin domain and non-oxidoreductases with a thioredoxin-fold domain. Because changes in the oxidation/reduction state of redox couples affect protein structure, function, interactions, trafficking, and degradation, the redox regulatory system regulates normal cellular activities. Furthermore, cell compartments have varied redox properties, and thiol/disulphide control mechanisms are not in thermodynamic equilibrium within each compartment. Cellular redox biology necessitates redox system compartmentation and communication such that the thermodynamic disequilibrium of the primary redox control nodes or switches (acting as sensor or rheostat) allows for rapid and sensitive responses to redox environment disturbances. In human plasma, cystine and cystine is the most common low-molecular-weight thiol/disulphide pair. The average redox value of Cys/CySS in plasma is around 80 mV. This means that the Cys/CySS couple is out of balance with the plasma GSH/GSSG pool, which has a redox state of around 140 mV. Plasma also includes intact thioredoxin-1 and its truncated version, both of which is released to the extracellular compartment by cells and has cytokine and chemokine-like properties. It's worth mentioning that a lack of essential cysteines impacts numerous mammalian transactivators in this regard. Thioredoxins are engaged in the regulation of transcription factors such as AP-1, NFkB, p53, and Sp1, which can influence expression from the thioredoxin gene promoter (through direct and/or indirect pathways). The redox status of cytoplasm can be changed by physiologic stimulation at the plasma membrane, as evaluated by cytosolic GSH/GSSG and thioredoxin-1. Similar to the phosphorylation cascade, controlled variations in redox couples potential act as signal transduction components. In erythrocytes (which lack intracellular organelles), the steady-state redox potential (Eh) of GSH/GSSG is 193 mV, but in cells with nuclei and mitochondria, it is 200 mV. Cellular thioredoxin-1 has an Eh value of 280 mV. Because oxidative stress is expected to have a role in diabetic complications, notably vascular dysfunction, innovative antioxidant treatment techniques are gaining popularity. Agents that inhibit ROS, such as vitamin E, C, and alpha lipoic acid, showed promise in animal models and early human research, but larger trials have failed to show improved cardiovascular outcomes [5,6]. Other drugs used for various clinical purposes, such as statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and thiazolinediones, appeared to be more effective in improving cardiovascular outcomes, likely due to their success in reducing ROS production at an earlier part of the cascade. We'll concentrate on NAC, which has been proposed as a promising treatment in this field. NAC has predominantly been used in the treatment of chronic obstructive

pulmonary disease as a mucolytic and chemopreventive drug, with therapeutic effects attributed to its capacity to transport cysteine to the portal circulation and thereby restore GSH levels. Second, the impacts on endothelial function have been researched, with mixed results. In patients with coronary artery disease, supplementing with NAC (600 mg/day) reduced homocysteine levels and enhanced endothelium-dependent dilation. In stable cardiac transplant recipients, however, oral NAC supplementation (500 mg/day) had no effect on plasma homocysteine levels or flow-mediated dilation of the brachial artery. In patients with type 2 diabetes and hypertension, oral supplementation with NAC (1200 mg/day) and arginine (1200 mg/day) for six months reduced mean systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, oxidised LDLs, high-sensitive C-reactive protein, intercellular and vascular-cell adhesion molecules, nytrotyrosine, fibrinogen, plasminogen activator inhibitor-1, and intim The combined administration raised HDL cholesterol and nitrites/ nitrates levels in the blood. As a result, the intervention appeared to improve NO bioavailability by lowering oxidative stress and increasing NO synthesis. The effects of varying doses of NAC (0-5 mmol/L) on the action potentials of rat sciatic nerve fibres were studied in vitro and found to be dose-dependent acute inhibition. Because ROS plays a role in cell activity at very low concentrations, total depletion of ROS was expected to disrupt nerve fibre function. Surprisingly, at 1 mmol/L, NAC provided 100% neuroprotection against cadmium-induced neurotoxicity. NAC treatment reduced both post-prandial oxidative state and endothelial activation in patients with type 2 diabetes mellitus. In experimental contexts, NAC's dual toxic-protective feature raises the general difficulty of developing antioxidants for therapeutic application. Indeed, the fundamental principles of free radical chemistry reveal that (1) chain-breaking antioxidants can have pro-oxidant capabilities and accelerate oxidative damage under certain conditions, and (2) extracellular and intracellular redox control interact in a complex way. Although NAC looks to be promising in some therapeutic contexts, long-term randomised clinical trials are still needed to assess the efficacy and safety of chronic NAC administration in humans, taking into consideration some unanticipated adverse effects seen in vitro and in animals. Despite the fact that cardiovascular disease is the leading cause of morbidity and mortality in diabetics, lowering cardiovascular risk factors can successfully prevent or reduce cardiovascular disease [7-10].

Post-translational modifications of proteins are used in signal sensing and transmission. Modulation of thiol-based redox switches in enzymes, receptors, transport proteins, and transcription factors is a well-known signal transduction pathway, and its dysregulation as a result of oxidative stress is linked to cardiovascular disease in diabetes mellitus. Unfortunately, the chemical mechanisms that underpin thiol-based redox regulation are still unknown.

Conclusion

Insulin has metabolic and haemodynamic effects, with the latter being mediated principally by increased NO availability. Insulin resistance is linked to decreased endothelial-mediated vasodilation, which is caused by insulin's failure to drive NO synthesis as well as increased NO consumption. Endothelial dysfunction, in turn, is both a cause and a result of the metabolic abnormalities that characterise insulin resistance. The expression of vascular and intercellular adhesion molecules, the regulation of procoagulant and anticoagulant characteristics of the artery wall, and the maintenance of oxidant/antioxidant balance are all affected by changes in vascular homeostasis. By upregulating adhesion molecules, inflammatory cytokines, and chemokines, oxidant stress increases the inflammatory response. In high-risk people, therapies that improve carbohydrate and lipid metabolism, insulin resistance, vascular function, blood pressure, and procoagulant and inflammatory responses all at the same time can reduce cardiovascular morbidity and death. Every long-term medical therapy, however, requires a careful assessment of the benefits and drawbacks.

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