

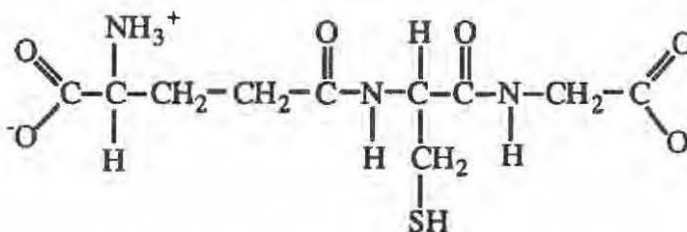
Selenoenzyme Glutathione Peroxidase

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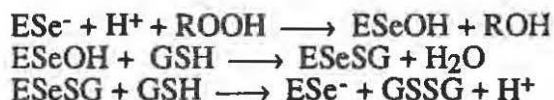
Selenium, discovered by J. Berzelius in 1817, was recognized to have properties intermediate between the metals and the nonmetals [1]. Because of its unique properties, selenium has many diverse uses, including xerography, photography, and plating [2]. Until 1957, however, the element's biological action was known only as being acutely toxic. In 1957, G. C. Mills described the enzyme Glutathione peroxidase as preventing oxidation of hemoglobin by hydrogen peroxide. Mills proposed the reaction of the enzyme with two moles of glutathione (GSH: γ -glutamylcysteinylglycine) [3,4]:



Mill's discovery was greeted with heavy skepticism, primarily since at that time catalase was considered unbeatable for H_2O_2 removal. The work of K. Schwarz and L. Flohe eventually led to the acceptance of glutathione peroxidase and its classification as a selenoenzyme [5,6].

Glutathione (γ -glutamyl-L-cysteinylglycine) peroxidase is the main selenium containing enzyme isolated from mammals. The tetrameric enzyme, with a molecular mass between 75,000 and 100,000, consists of two dimers forming an almost planar tetramer with 222 symmetry. There is one covalently bound selenium atom, present in the form of a selenocysteine, in each subunit. The four subunits are identical, each consisting of 198 amino acid residues [7,8]. X-ray analysis reveals that 63% of the molecule appears to be rigidly fixed by means of well-organized elements of secondary structure: 24% α -helix, 12% β -structure, and 27% β -turns. The selenium atom is exposed to the surface of a flat hydrophobic impression that is surrounded by four positive charges derived from arginine residues [9,10].

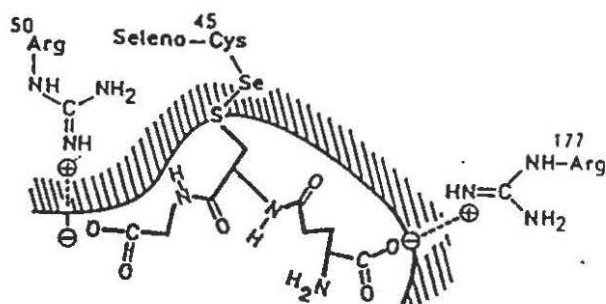
Several variations of the catalytic cycle of glutathione peroxidase have been proposed, all with the selenocysteine as the active site [5,11,12]. The most widely accepted mechanism, the selenocysteine starts as a selenoate anion which is then oxidized to selenenic acid (SeOH) and finally reduced by two glutathione molecules [3].



L. Flohe and other groups have attempted to justify each step in the catalytic cycle by comparing the reactions and stoichiometry of the selenocysteine to analogous thiols, using X-ray photoelectron spectroscopy to determine the oxidation states of the selenium, and studying the various inhibitory effects [13]. Glutathione peroxidase is nonspecific for organic peroxides but very specific for the glutathione molecule [6,14].

The enzymatic activity of the peroxidase can be decreased by the addition of several inhibitors, including the superoxide radical anion and the cyanide anion. Superoxide seems to cause the formation of radical on the selenocysteine which is then subsequently oxidized by oxygen and reduced by various reductants to an inactive species. The inactive species, however, can be reactivated by the presence of glutathione [15]. Inhibition of the glutathione-enzyme complex (ESe-SG) by the cyanide anion seems to occur with an attack on the sulfur of glutathione, forming thiocyanate. The selenoate anion is formed which undergoes autoxidation, generating the inactive form [4,16,17].

The complex formed between glutathione and glutathione peroxidase has been proposed to exist because of electrostatic interaction between the negatively charged carboxyl groups on glutathione and the positively charged arginine residues on the enzyme [18].



The mechanism for the second GSH approach onto the ESe-SG complex is still unknown. Meister and coworkers have suggested that two additional arginine residues around the active site can also participate in electrostatic binding with the second GSH molecule [3].

Selenium is present in plants and animals, including humans. The daily dietary intake in man is about 0.006-0.2 mg [19]. The effect of dietary Se on glutathione peroxidase activity has been shown to be directly related [20].

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