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Rhodanese: One of Natures "Sulphur" Biotransformation Machinery

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Abstract: ***Rhodanase (EC2.8.1.1) is a sulphur transferase enzyme. It is widely distributed across all levels of living organism; microbes, fungi, plants and animals. Sulphur is a basic requirement for existence and sustenance of life, as notable in the myriad of chemical substances in which it is incorporated such as; proteins containing cysteine and/or methionine amino acid, proteins containing iron- sulphur center prosthetic groups, glutathione, sulphated carbohydrates, hydrogen sulphide, and thiosulphate. Rhodanese plays an important role in the metabolism of sulphur in cells of organism. It helps to maintain homeostatic balance of sulphur pool in cell. The functional roles of sulphur also include cyanide detoxification, hydrogen sulphide detoxification, neuro-modulation, repair of iron sulphur centres, and maintenance of respiratory rates. Further study of this enzyme is desired for more insight into its role cellular metabolism and possible medical application.***

1. Introduction

In order to understand the ubiquitous nature of rhodanese, it would be essential to briefly provide an insight into the chemistry of sulphur in relation to life. The iron–sulphur world theory states that sulphur was crucial for the origin of life itself (Wächtershäuser, 1988, 1992). The oxidation state of sulphur ranges from -2 (sulphide) to +6 (sulphate) and undergoes a constant cycle of oxidation and reduction reactions. Sulphur is introduced into the biomass by assimilatory sulphate reduction to the state of sulphide (an endergonic reaction) that is restricted to prokaryotes, fungi and plants, which is then incorporated into a stable organic molecule: L-cysteine (Stockdreher, 2014). This amino acid is the central precursor for other sulphur containing biomolecules in the cell, i.e. proteins, cofactors, carbohydrates, sulpholipids, vitamins and antibiotics (Brüser *et al.*, 2000; Dahl *et al*., 2002; Kessler, 2006).

Lang (1933) reported that certain tissues of mammals contained an enzyme which is able to catalyze *in vitro* the reaction between thiosulphate and cyanide leading to the production of thiocyanate and sulphite. The responsible enzyme was designed 'rhodanese', from the German name for thiocyanate ('rhodanid'), with the ending 'ese' indicating that this compound was formed by enzymatic reaction (Cipollone *et al.,* 2007b). According to the official nomenclature rules, the proper name of the enzyme is thiosulphate:cyanidesulphur transferase (TST, EC 2.8.1.1), based on the reaction catalyzed *in vitro*; however, the trivial name of rhodanese is commonly used.

In vitro, rhodanese catalyzes the transfer of sulphur atom from thiosulphate to a nucleophilic acceptor like cyanide and reduced lipoate (Villarejo and Westley, 1963; Villarejo and Westley, 1963a) via a ping pong reaction with the formation of an enzyme- sulphur complex intermediate (Green and Westley 1961; Westely and Nakamoto, 1962).

The thiosulphate sulphur transferase (TST) gene encoding human rhodanese, is located on chromosome 22 (Aita *et al*., 1997) and two single nucleotide polymorphisms (SNP), c.306A>C and c.853C>G leading to amino acid substitutions, E102D and P285A, have been reported (Billaut-Laden *et al.,* 2006). The allelic frequencies for the SNPs in the French Caucasian population are 1 (E102D) and 5 (P285A) percent, respectively (Libiad *et al.,* 2015).

This review tries to highlight the distribution, structure, mechanism, roles in nature and medical relevance.

Distribution of rhodanese in nature

Rhodanese has been studied from numerous of sources, which include bacteria, yeast, plants, and animals. The expression of rhodanese has been detected in many tissues of animals like the liver, proventriculus, oesophagus, gizzard, cecum, brain, large intestine, duodenum, crop, spleen, trachea, pancreas, heart, kidney, lung (Dudeck *et al.,* 1980; Westley 1981; Drawbaugh and Marrs 1987; Aminlari and Gilanpour 1991; Aminlari and Shahbazi 1994; Aminlari *et al*., 1994, 2000, 2002; Al-qarawi *et al*., 2001; Agboola *et al.,* 2006; Baghshani and Aminlari 2009). The enzyme which was originally detected in the mitochondrion has now been found to be located in the cytosol and other organelles (Nagahara and Nishino 1996; Agboola and Okonji, 2004). Although some cyanide may be formed *in vivo*, this is not sufficient to explain the abundance and the ubiquity of rhodanese (Finazzi Agro *et al.,* 1971).

The existence of rhodanese has been controvertial in many plants due to its low activity (Kakes and Hakvoort, 1992; Lieberei and Selmar, 1990). Hatzfeld and Saito (2000) were the first to isolate and characterize in plants two cDNAs encoding rhodanese isoforms in *Arabidopsis thaliana,* AtRDH1 and AtRDH2. Rhodanese purified from tapioca leaves showed properties similar to that of bovine rhodanese (Boey *et al.,* 1976; Hatzfeld and Saito, 2000).

Rhodanese activity has been demonstrated in chloroplasts from several plants and its activity correlate with the labile sulphide concentration in the plant (Tomati, 1972). Rhodanese has been purified from cabbage leaves and shown to be able to reactivate ferredoxin from apoferredoxin (Tomati *et al.,* 1974a; 1974b). Ehigie *et al.* (2013) investigated and detected the expression of rhodanese in crude plant extracts of nine randomly selected plant tubers which includes sweet potato (*Ipomoea batatas*), yellow yam, Irish potato (*Solanum tuberosum*), bitter yam (*Diascorea*

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bulbifera), cocoyam, sweet yam (*Diascorea esculentum*), water yam (*Diascorea alata*) and cassava (*Manihot esculentum*).

Structure of rhodanese

Rhodanese from the mitochondrial of bovine (*Bos taurus*) was the first and best characterized and conventionally referred to as Rhobov (Sorbo, 1953; Westley *et al.,* 1983; Nandi, *et al.,* 2000). Rhobov primary structure composition is 293 amino acids residues long. The protein consists of two equally sized globular domains, the inactive N-terminal and the catalytic C-terminal rhodanese domain, showing identical α/β topology and each domain is about 120 amino acids residues long with a low sequence homology. A connecting loop separates the two domain of the enzyme (Ploegman *et al.,* 1978a). The two domains have a highly homologous tertiary structure, but show little sequence similarity (Hatzfeld and Saito, 2000). The active site comprises of six amino acid residues that hosts at its first position the Cys residue involved in the catalytic process which is situated at the C- terminal domain (Cipollone *et al.,* 2007b). This conserved cysteine binds the sulfane moiety of thiosulfate at the active site (Ploegman *et al.,* 1978a). The counterpart of the Cys residue in the N-terminal domain is an Asp residue with no catalytic property (Ploegman *et al.,* 1978b) (Figure 2.3). The uniqueness of rhodanese is resident in two patterns of amino acid residues sequences called 'rhodanese signatures', that can be recognized at the N-terminal end ([F/Y]-X3-H-[L/I/V]-P-G-A-X2-[L/I/V/F]) and at the C-terminal region of the protein ([A/V]-X2-[F/Y]-[D/E/A/P]-G- [G/S/A]-[W/F]-X-E-[F/Y/W]). The 'rhodanese signatures' have a remarkable degree of conservation amongst rhodaneses and therefore they are used for the recognition of these proteins encoded by different genomes (Cipollone *et al.,* 2007b).

Mechanism of action of rhodanese

Rhodanese catalytic activity process occurs through a double displacement (ping-pong) mechanism involving the stable formation of a persulphide-containing enzyme intermediate (ES) (Horowitz and Criscimagna, 1983a; Pagani *et al.,* 2000; Cipollone *et al.,* 2004) as illustrated inFigures1, 2 and 3. It follows a non-sequential ping-pong mechanism in the generation of thiocyanate from thiosulphate and cyanide (Jack *et al.,* 2015). The reaction proceed in two half reactions (Figures 1, 2 and 3). In the first half reaction, the sulphane sulphur is transferred from the substrate to the active site cysteine to form a persulphide enzyme intermediate, while in the second half reaction, a thiophilic acceptor attacks the enzyme-bound persulphide intermediate forming product and regenerating the free form of the enzyme (Schlesinger and Westley, 1974; Westley *et al.,* 1983). The transferring sulphur is bound to an invariant catalytic Cys residue and is transferred formally as S^0 by nucleophilic reaction with cyanide, to yield thiocyanate thereby regenerating the active Cys residue for a new round of catalysis. The chemical species intervening in sulphur delivery is sulphane sulphur, a sulphur atom covalently bound to the sulfur atom of Cys, which has an apparent oxidation state of 0 or -1 (Horowitz and Criscimagna, 1983b; Pagani *et al.,* 2000; Cipollone *et al.,* 2004).

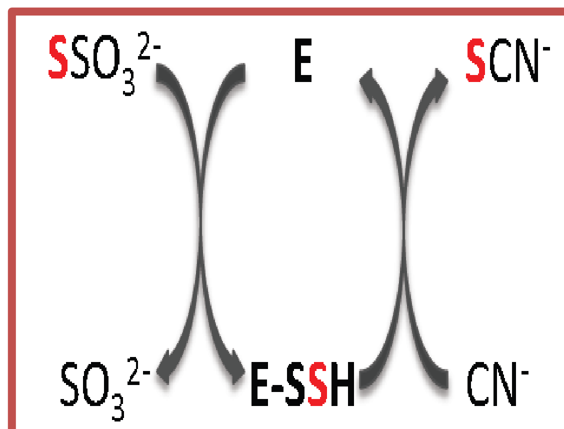

Figure 1: Representative reactions catalyzed by rhodanese. Thiosulphate is the sulphane sulphur donor and an enzyme-bound persulphide intermediate (E-SSH) is formed whereas cyanide is the sulphur acceptor (Libiad *et al.,* 2014).

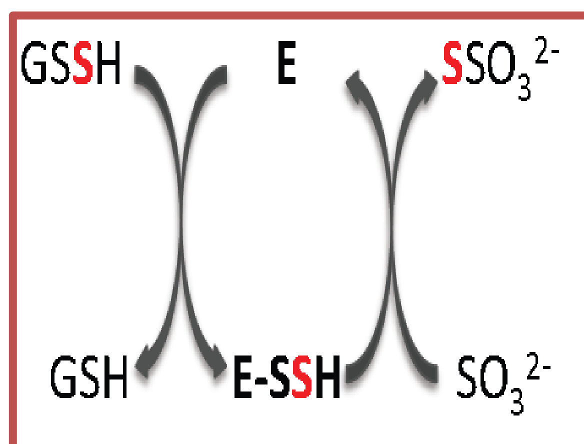

Figure 2: Representative reactions catalyzed by rhodanese. GSSH is the sulphur donor and an enzyme-bound persulphide intermediate (E-SSH) is formed whereas sulphite is the sulphur acceptors (Libiad *et al.,* 2014).

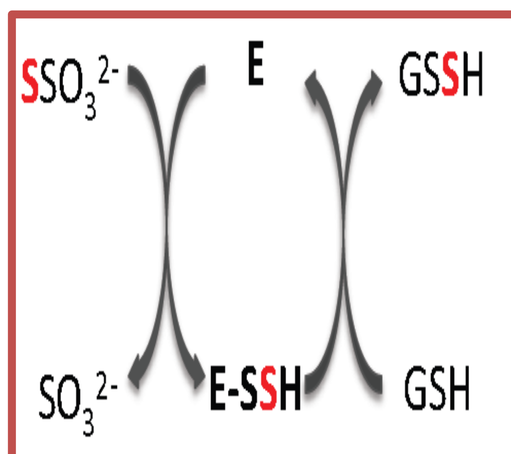

Figure 3: Representative reactions catalyzed by rhodanese. Thiosulphate is the sulphane sulphur donor and an enzyme-bound persulphide intermediate (E-SSH) is formed whereas glutathione (GSH) is the sulphur acceptor (Libiad *et al.,* 2014)

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2. Functional role of rhodanese

Cyanide detoxification

Historically, the biological importance of rhodanese was ascribed to cyanide detoxification via transfer of the sulphane sulphur from thiosulphate to cyanide to generate thiocyanate and sulphite (Figure 1). It has been understood for over eight decades that most of the sub-lethal amount of cyanide absorbed by either inhalation or ingestion is metabolized and detoxified by cyanide reaction with reactive sulphur. In eukaryotes, rhodaneses and mercaptoethanol sulphur transferases (MSTs) are postulated to be involved in detoxification of cyanide. The high concentration of tandem-domain TSTs in tissues and organs exposed to cyanide supports the hypothesis of cyanide detoxification (Sylvester and Sander, 1990). The level of rhodanese expression in different tissues of animals and plants has been found to correlate with the level of cyanide exposure (Wood, 1975; Lewis *et al*., 1992). Although the pattern of distribution of tandem-domain TSTs in various tissues is species specific, rhodanese activity are usually high in liver cells that are in close proximity to the hepatic blood supply, in epithelial cells covering the bronchioles (entry route for gaseous cyanide) and in proximal tubule cells of the kidney (facilitating cyanide detoxification and elimination as thiocyanate in urine) (Aminlari and Gilanpour, 1991). Rhodanese is expressed at its peak in the epithelium of rumen, omasum, and reticulum in cattle (Aminlari and Gilanpour, 1991). In these stomach compartments, cyanide is liberated after ingestion of plant cyanogenic glucosides; rhodanese activity is significantly higher in the stomach than in the liver, supporting the role of cyanide detoxification (Aminlari and Gilanpour, 1991).

However, since rhodanese activity is majorly restricted to the mitochondrial matrix where thiosulphate permeates with low efficiency (Westley *et al.,* 1983), it has been suggested that rhodanese recruits other unknown sulphur source(s) for detoxification of cyanide (Nagahara, *et al.,* 2003). Alternatively, based on compartmental distribution of sulphur transferases (STs), it has been suggested that rhodaneses detoxify cyanide together with mercaptoethanol sulphur transferases (MSTs) (Nagahara *et al*., 2003). MSTs are localised both in cytoplasm and in mitochondria (Nagahara *et al*., 2003). When cyanide diffuses into the cytoplasm, MSTs in the cytosol may catalyze a primary sulphuration reaction of cyanide, while the cyanide that eventually escapes this detoxification step may be catalysed by mitochondrial rhodanese, thereby preventing the lethal inhibition of cellular respiration (Nagahara *et al*., 2003). The therapy for acute cyanide poisoning is the intravenous administration of sodium nitrite and sodium thiosulfate combination therapy. Sodium nitrite oxidizes oxyhemoglobin to methemoglobin whose affinity for cyanide is higher compared to cytochrome c oxidase; on the other hand sodium thiosulfate is the substrate of rhodanese (Cipollone *et al.,* 2007b). Moreover, the rapid decomposition of mercaptopyruvate intravenously administered makes it not potent for cyanide detoxification (Nagahara *et al*., 2003). Thus, rhodanese and MSTs specific roles in physiological detoxification of cyanide remain controversial (Cipollone *et al.,* 2007b).

Interestingly, detoxification of cyanide which was first attributed to Rhobov in eukaryotes (Sorbo 1953; Westley *et al.,* 1983) has also been confirmed in prokaryotes (Cipollone *et al.,* 2007a, Cipollone *et al.,* 2006). Cyanide detoxification was greatly increased in *Bacillus stearothermophilus* mutants with about 5-6 folds rhodanese activity than the wild type (Atkinson, 1975). Moreover, RhdA from the *P. aeruginosa* has been reported to participate in detoxification of cyanide (Cipollone *et al.,* 2004, Cipollone *et al.,* 2007a, Cipollone *et al.,* 2006). Although RhdA is characterised with low affinity for both thiosulfate and cyanide *in vitro*, it has been demontrated to provide protection against cyanide toxicity when overexpressed in *E. coli* as heterologous host (Cipollone *et al.,* 2006). The viability of *P. aeruginosa* growth under cyanogenic conditions is promoted by RhdA (Cipollone *et al.,* 2007a). Hence, *in vitro* biochemical studies which suggest a minor role of RhdA in cyanide detoxification may underestimate the actual role of the enzyme *in vivo* (Cipollone *et al.,* 2007b).

Plants are exposed to cyanide from numerous exogenous and endogenous sources (Most and Papenbrock, 2015). The major source of cyanide in the environment comes from human activities, for example, soil polluted by various industrial wastes containing up to 11,000 mg cyanide kg^{-1} DW soil (Henny *et al.,* 1994). The natural exogenous sources include bacteria, fungi, algae, and plants that are cyanogenic in significant amounts (Most and Papenbrock, 2015). The endogenous source of cyanide in plants arise from the conversion of 1-amino-cyclopropane-1-carboxylic acid to ethylene which liberate cyanide in equimolar amounts as ethylene and is increased during ripening and senescence of the fruit (Yip and Yang, 1988). Cyanide is a potent inhibitor of cytochrome c oxidase in the respiratory chain. Plants can readily uptake cyanides available in their root zone (Doucleff and Terry, 2002). Cyanide stimulation of NADPH oxidase and inhibition of antioxidant enzymes for example catalase induces the production of reactive oxygen species (ROS) and also triggers the production of hydrogen peroxide (H_2O_2) in embryonic axes of sunflower (*Helianthus annuus* L.) (Oracz *et al*., 2009). In higher plants, two metabolic pathways are involved in the assimilation and detoxification of excess cyanide (Most and Papenbrock, 2015). Firstly, the sulphur transferase (Str) pathway as observed in bacteria and mammalians. In mammals, Strs play an important role in the catalysis of cyanide to less toxic thiocyanate that is mainly excreted in the urine (Ressler and Tatake, 2001). In *Pseudomonas aeruginosa*, mitochondrial rhodanese has been demonstrated to be involved in the protection of aerobic respiration from cyanide poisoning through the transfer of sulphane sulphur from thiosulphate to cyanide to produce less toxic thiocyanate (Cipollone *et al.,* 2008). However, in plants, the contribution of Str to cyanide detoxification may be incidental or negligible (Meyer *et al*., 2003). More recently, it was observed that the β-cyano-L-alanine (β-CAS) pathway is the main mechanism for maintaining cyanide homeostasis in higher plants (Machingura and Ebbs, 2014). Previously, it was suggested that β-cyano-L-alanine synthase (CAS) plays a more crucial role in cyanide detoxification than Str activity in *A. thaliana* (Meyer *et al*., 2003). In β-cyano-L-alanine synthase (CAS) pathway, the cyanide is first substituted for the sulfhydryl group of cysteine to form β-CAS with the

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liberation of hydrogen sulphide (Hatzfeld *et al*., 2000). Subsequently, the β-CAS produced is hydrolyzed by the gene product of NIT4, which is a dual enzyme complex with nitrilase and nitrile hydratase activity, generating asparagine, aspartate and ammonia, respectively (Piotrowsk *et al,* 2001; Machingura and Ebbs, 2014).

Sulphur and selenium metabolism

Rhodanese-like proteins may have a role in sulphur and selenium metabolism. The expression of the P21 rhodanese-like protein from *A. ferrooxidans* (a chemolithotrophic bacterium) seems to be induced during growth on various oxidizable sulphur compounds to yield thiosulphate that is used as electron donor (Ramırez *et al.,* 2002). The disruption of the gene encoding the rhodanese-like enzyme CysA from *Saccharopolyspora erythraea* results in cysteine auxotrophy (Donadio, *et al*., 1990). However in the aforementioned cases above, there is no significant effect on the cellular TST activity. It is noteworthy to know that the pathway for cysteine biosynthesis in *S. erythraea* differs from that established, for example, in *E. coli*, just as the former includes thiosulphate as an intermediate (Cipollone *et al.,* 2007b). Hence, P21 and CysA may perform the specific function to synthesizing thiosulphate (Ramırez *et al.,* 2002). Ogasawara and co-workers (2001) reported that free enzyme form of bovine rhodanese can bind selenium at ratio 1:1 *in vitro*, resulting in the generation of the stable perselenide form (E-Se) of rhodanese. The reaction of SeO_3^{2-} and glutathione at physiologically meaningful amounts produced perselenide form (E-Se) of rhodanese (Cipollone *et al.,* 2007b). Therefore, perselenide form of rhodanese has been proposed to be necessary to produce the reactive form of selenium for the biosynthesis of selenophosphate ($SePO_3^{3-}$) which is the active selenium-donor compound required by prokaryotes and eukaryotes for the synthesis of SeCys-tRNA, the precursor of selenocysteine in selenoenzymes (Cipollone *et al.,* 2007b).

Synthesis or repair of iron-sulphur proteins / cellular enzymatic antioxidant system

Rhodanese possibly contribute to the native architecture of reconstituted iron-sulphur protein(s) by mobilizing sulfur for the generation or repair of iron-sulphur clusters (Cipollone *et al.,* 2007b). Tomati *et al.* (1974b) suggested the reactivation of ferredoxin from apoferredoxin by rhodanese. The iron-sulphur clusters electron carriers of ferrodoxins, succinate dehydrogensase, and mitochondrial NADH dehydrogenase can be repaired via incubation rhodanese, a sulphur donor, a sulphur acceptor (dihydrolipoate), and an iron source (Bonomi *et al.,* 1977; Pagani and Galante, 1983; Pagani *et al.,* 1984). The participation of rhodanese in the formation of iron-sulfur clusters has been challenged due to the strong evidence that Nif/Isc-related proteins are involved in the mobilization of sulphur from cysteine for the synthesis of iron-sulphur clusters (Urbina *et al.,* 2001). However, Cereda *et al.* (2009) in their preliminary phenotypic characterization of the gene of rhodanese from *Azotobacter vinelandii* (rhdA) mutant suggested that rhodanese from *Azotobacter vinelandii* (RhdA) may protect over Fe–S enzymes, which are labile targets for oxidative damage. Conversely, rhodanese is a constituent of the cellular enzymatic antioxidant system. The possible role of RhdA as a redox switch which helps *A.vinelandii* in maintaining the cellular redox homeostasis was studied through the use of an *in vitro* model system that showed reversible chemical modifications in the highly reactive RhdA Cys^{230} thiol (Cereda *et al.,* 2009).

Aerobic energy metabolism

Probably, the main physiological role of rhodanese is to supply of sulphur for the production of iron sulphur centre proteins of the respiratory chain in mammalian tissues, while cyanide detoxification may be a secondary benefit (Oke, 1973; White *et al.,* 1981). An expression study in *E. coli* demonstrated that rhodanese is subject to catabolite repression and was summarised to play a role in aerobic energy metabolism (Alexander and Volini, 1987). Rhodanese forms stable complexes via disulfide bonds with membrane-bound enzymes, and catalyzes the production of iron-sulfur centers in mitochondria (Ogata and Volini, 1990). Rhodanese activity is inactivated by phosphorylation and may convert it into a sulfurase that remove the sulfur from iron-sulfur centers (Ogata *et al.,* 1989). Rhodanese regulate the respiration rate, by controlling of the status of the iron-sulfur centers of enzymes of the electon transport chain (Ogata and Volini, 1990; Ogata *et al.,* 1989). The rhodanese activity is regulated by a protein kinase/phosphatase and would be the terminal step of hormonal or neurotransmitter signaling pathways acting on oxygen utilization or oxidative phosphorylation pathways (Hatzfeld and Saito, 2000).

H_2S detoxification

It has been reported that rhodanese in the large intestine is the main enzyme involved in Hydrogen sulphide (H_2S) detoxification which is generated normally in the intestine (Picton *et al.,* 2002). H_2S is a potent poison normally present in the colonic lumen which may play a role in ulcerative colitis (UC) (Picton *et al.,* 2002).

Neuromodulator

Moreover, rhodanese has been detected in mouse brain (Wrobel, *et al.,* 2006), and discovered to be localized in areas that synthesize cyanide, suggesting a neuromodulatory role (Borowitz, *et al.,* 1997). Therefore, a regulatory role of rhodanese in tuning (via conversion of cyanide to thiocyanate) the neuromodulator properties of cyanide has been postulated (Cipollone and Visca, 2007a).

Mitochondrial sulphide oxidation pathway

Recently, the role of rhodanese in the mitochondrial sulphide oxidation pathway has been recognized, where it catalyzes the transfer of sulphane sulphur from glutathione persulfide (GSSH) to sulphite to form thiosulphate (Figure 2.6) (Hildebrandt and Grieshaber, 2008; Libiad *et al.,* 2014). It has also been proposed that the role of rhodanese or another thiol sulfurtransferase in the mitochondrial sulphide oxidation pathway is to utilize thiosulphate, forming GSSH instead (Figure 2.7) (Jackson *et al.,* 2012; Melideo, *et al.,* 2014). Kinetic data combined with simulations at physiological substrate concentrations have established that the first enzyme in the mitochondrial sulphide oxidation pathway, sulphide quinone oxidoreductase, preponderantly catalyzes the biosynthesis of GSSH, which is a substrate for rhodanese (Libiad *et al.,* 2014).

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3. Medical significance of rhodanese

1) Shahbazkia *et al*. (2009) related the high activity of rhodanese in testis and ovary of *Felis cattus* to its role in steroidogenesis through formation of iron-sulphur proteins (Shahbazkia *et al*., 2009). During steroidogenesis process iron-sulphur proteins are involved in the oxidative cleavage of the cholesterol side-chain occurring in ovary and testis by cholesterol side-chain cleavage (SCC) enzyme complex (Baron, 1975). The components of cholesterol side-chain cleavage (SCC) enzyme complex are the iron-sulphur proteins adrenodoxin, cytochrome P- 450, and NADPH:ISP reductase (Trzeciak, *et al.,* 1986).
2) Serum rhodanese activity may be a possible candidate for liver function test. In sheep and dog rhodanese activity was elevated after induction of hepatic necrosis (Aminlari *et al.,* 1994a). Shahbazkia *et al*. (2009) suggested that serum rhodanese determination can be used as a hepatic function test in animals. It may also be applicable to humans.
3) Rhodanese protects against continuous oxidative stress, including that induced by radiation (Nakajima, 2015). Persistent oxidative and inflammatory reactions induce changes in hepatic metabolism and may lead to cancer and other pathophysiological conditions (Szabo and Bala, 2013; Yoshimoto *et al*., 2013). Internal or External stresses induce continuous oxidative stresses around mitochondria that may lead to induction of rhodanese activity and the induced rhodanese, collaborating with MST, promotes sulphane sulphur, GSH, or thioredoxin regulations, resulting in activation of anti-oxidative stress systems thereby inhibiting the continuous oxidative stresses (Nakajima, 2015).
4) Rhodanese has also been reported to be a cancer biomarker candidate (Birkenkamp-Demtroder *et al*., 2002; 2005). Interestingly, the activity of rhodanese has been reported to decrease in hepatic tumors, for example in Ehrlich ascites tumor-bearing mice compared to control mice (Iciek *et al.,* 2007). Probably, if its activity is restored, it may repress tumor growth. Rhodanese inducers include many nutrients and it is feasible that its induction could be readily applied clinically (Nakajima, 2015).
5) Rhodanese induction may protect normal tissues from acute high-dose irradiation in the case of radiocancer therapy like antioxidants, which have been investigated for their protective action (Demiryilmaz *et al*., 2012; Kaya *et al.,* 2014)
6) It has been demonstrated that the decrease in rhodanese expression depicts an increase of oxidative stresses and predicts mortality in hemodialysis patients; therefore, its expression might be a prognostic indicator (Krueger *et al*., 2010).

4. Conclusion

The relevance of rhodanese in the homeostatic balance of sulphur pool in cells of living organisms cannot be accidental, looking at the myriad of roles this enzyme is playing to the cells so as to sustain life. However, more study on this enzyme is needed to unravel in detail how rhodanese clearly perform its function inside the cellular milieu.

References

[1] Agboola F.K., and Okonji R.E. (2004). Presence of Rhodanese in the Cytosolic Fraction of the Fruit Bat (*Eidolon helvum*) Liver. *Journal of Biochemistry and Molecular Biology*. 37(3): 275-281.
[2] Agboola FK, Fagbohunka BS, Adenuga GA (2006) Activities of thiosulfate and 3-mercaptopyruvate sulfurtransferases in poultry birds and fruit bat. *Journal of Bololgical Sciences*. 6:833–839.
[3] Aita, N., Ishii, K., Akamatsu, Y., Ogasawara, Y., and Tanabe, S. (1997) Cloning and expression of human liver rhodanese cDNA. Biochem. Biophys. Res. Commun. 231: 56-60
[4] Alexander, K., and Volini, M. (1987) Properties of an Escherichia coli rhodanese. *J. Biol. Chem*. 262: 6595-6604
[5] Al-qarawi A, Mousa HM, Ali BH (2001) Tissue and intracellular distribution of rhodanese and mercaptopyruvate sulphotrans- ferases in ruminants and birds. *Vet Res* 32:63–70. doi:10.1051/ vetres:2001110.
[6] Aminlari M, Gholami S, Vaseghi T, Azadi A, Karimi H (2000) Distribution of rhodanese in different parts of the urogenital systems of sheep at pre- and post-natal stages. *Comp Biochem Physiol* Part B 127:369–374.
[7] Aminlari M, Gilanpour H (1991) Comparative studies on the distribution of rhodanese in different tissues of domestic animals. *Comp Biochem Physiol* Part B 99:673–677. doi:10.1016/0305- 0491(91)90353-F
[8] Aminlari M, Li A, Kunanithy V, Scaman CH (2002) Rhodanese distribution in porcine (Sus scrofa) tissues. *Comp Biochem Physiol* Part B 132:309–313. doi:10.1016/S1096-4959(02)00005-2
[9] Aminlari M, Shahbazi M (1994) Rhodanese (thiosulfate: cyanide sulfurtransferase) distribution in the digestive tract of chicken. *Poult Sci* 73:1465–1469
[10] Aminlari M., Vaseghi T., Sajedianfard J., Samsami M. (1994a). Changes in arginase aminotransferases and rhodanese in sera of domestic animals with experimentally induced liver necrosis. *J Comp Pathol*. 110:1-9.
[11] Aminlari, M., and Gilanpour, H. (1991) Comparative studies on the distribution of rhodanese in different tissues of domestic animals. *Comp. Biochem. Physiol*. B 99: 673-677
[12] Baghshani H., and Aminlari M., (2009). Comparison of rhodanese distribution in different tissues of Japanese quail, partridge, and pigeon. *Comp Clin Pathol* . 18:217–220.
[13] Baron J. (1975). Immunochemical and functional similarities and differences among iron-sulfur proteins involved in mammalian steroidogenesis. *Adv Exp Med Biol*. 58: 55-71.
[14] Billaut-Laden, I., Allorge, D., Crunelle-Thibaut, A., Rat, E., Cauffiez, C., Chevalier, D., Houdret, N., Lo-Guidice, J. M., and Broly, F. (2006) Evidence for a functional genetic polymorphism of the human thiosulfate sulfurtransferase (Rhodanese), a cyanide and H2S detoxification enzyme. *Toxicology* 225, 1-11

Licensed Under Creative Commons Attribution CC BY

[15] Birkenkamp-Demtroder K, Christensen LL, Olesen SH *et al* (2002). Gene expres- sion in colorectal cancer. *Cancer Res*. 62(15): 4352–63
[16] Birkenkamp-Demtroder K, Olesen SH, Sorensen FB *et a*l. (2005). Differential gene expression in colon cancer of the caecum versus the sigmoid and recto- sigmoid. *Gut*. 54(3): 374–84
[17] Boey, C., Yeoh, H. and Chew M. (1976). Purification of tapioca leaf rhodanese. *Phytochemistry*, 15: 1343–1344
[18] Bonomi, F., Pagani, S., Cerletti, P. and Cannella, C. (1977) Rhodanese-mediated sulfur transfer to succinate-dehydrogenase. *Eur. J. Biochem*. 72: 17–24.
[19] Borowitz, J. L., Gunasekar, P. G., and Isom, G. E. (1997) Hydrogen cyanide generation by mu-opiate receptor activation: possible neuromodulatory role of endogenous cyanide. *Brain Res*. 768:294–300.
[20] Brüser, T., Lens, P. and Trüper, H. G. (2000) The biological sulfur cycle. In Environmental Technologies to Treat Sulfur Pollution. Lens, P., and Pol, L.H. (eds). IWA Publishing, London, pp 47-86.
[21] Cereda A., Carpen A., Picariello G.,Tedeschi G., and Pagani S., (2009). The lack of rhodanese RhdA affects the sensitivity of *Azotobacter vinelandii* to oxidative events. *Biochemical Journal*. 418:135–143.
[22] Cipollone, R., and Visca, P. (2007) Is there evidence that cyanide can act as a neuromodulator? *IUBMB Life*, in press.
[23] Cipollone, R., Bigotti, M. G., Frangipani, E., Ascenzi, P., and Visca, P. (2004) Characterization of a rhodanese from the cyanogenic bacterium Pseudomonas aeruginosa. *Biochemistry and Biophysics ResearchCommunication*. 325, 85–90.
[24] Cipollone, R., Frangipani, E., Tiburzi, F., Imperi, F., Ascenzi, P., and Visca, P. (2007a) Involvement of *Pseudomonas aeruginosa* rhodanese in protection from cyanide toxicity. *Appl. Environ. Microbiol.* 73, 390–398.
[25] Cipollone,R.,Ascenzi,P.,Frangipani,E.,andVisca,P.(2006)Cyanide detoxification by recombinant bacterial rhodanese. *Chemosphere* 63, 942–949.
[26] Dahl, C., Prange, A. and Steudel, R. (2002) Natural polymeric sulfur compounds. In Miscellaneous Bioploymers and Biodegradation of Synthetic Polymers. Steinbüchel, A. (ed). Wiley-VCH, Weinheim, pp 35-62.
[27] Demiryilmaz I, Sener E, Cetin N *et al* (2012): Biochemically and histopathologicaly comparative review of thiamine's and thiamine pyrophosphate's oxida- tive stress effects generated with methotrexate in rat liver. *Med Sci Monit*.18(12): BR475–81
[28] Donadio, S., Shafiee, A., and Hutchinson, C. R. (1990) Disruption of a rhodanese-like gene results in cysteine auxotrophy in Saccharopo- lyspora erythraea. *Journal of Bacteriology*. 172: 350–360.
[29] Doucleff, M.; and Terry, N., (2002). Pumping out the arsenic. *Nat. Biotechnol*. 20: 1094–1096.
[30] Drawbaugh RB, Marrs TC (1987) Interspecies differences in rhodanese (thiosulfate: cyanide sulfurtransferase, EC.2.8.1.1) activity in liver, kidney, and plasma. *Comp Biochem Physiol Part B* 86:307–310.
[31] Dudeck M, Frrendo J, Koj A (1980) Subcellular compartmentation of rhodanese and β-mercaptopyruvate sulfurtransferase in the liver of some vertebrate species. *Comp Biochem Physiol Part B* 65:383–386.
[32] Ehigie O. L., Okonji R. E., Balogun R. O. and Bamitale K. D. S.(2013). Distribution of Enzymes (Rhodanese, 3-Mercaptopyruvate Sulphurtransferase, Arginase And Thiaminase) in Some Commonly Consumed Plant Tubers in Nigeria. *Special Issue - 2nd International Conference on Engineering and Technology Research.* 4(9):8-14.
[33] Finazzi Agro A., Cannella C., Graziani M.T., And Cavallini D., (1971). A Possible Role for Rhodanese: The Formation of ' Labile ' Sulfur from Thiosulfate. *Febs Letters*. 16(3):172-174.
[34] Green J.R., and Westley J., (1961). *J. Biol. Chem*. 236: 3047.
[35] Hatzfeld Y., and Saito K., (2000). Evidence for the existence of rhodanese (thiosulfate:cyanide sulfurtransferase) in plants: preliminary characterization of two rhodanese cDNAs from *Arabidopsis thaliana*. *Federation of European Biochemical Societies (FEBS) Letters.* 470: 147-150.
[36] Hatzfeld, Y.; Maruyama, A.; Schmidt, A.; Noji, M.; Ishizawa, K.; Saito, K. (2000).β-cyanoalanine synthase is a mitochondrial cysteine synthase-like protein in spinach and Arabidopsis. *Plant Physiol*. 123:1163–1172.
[37] Henny, C.J.; Hallock, R.J.; Hill, E.F., (1994). Cyanide and migratory birds at gold-mines in Nevada, USA. *Ecotoxicology*. 3: 45–58.
[38] Hildebrandt, T. M., and Grieshaber, M. K. (2008) Three enzymatic activities catalyze the oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria. *FEBS .J* 275: 3352-3361
[39] Horowitz PM., and Criscimagna NL.,(1983a). A Study of the Apolar Inter- action of the Enzyme Rhodanese with Octyl Substituted Agarose Gel. *Biochem. Biophys. Res. Commun* 111(2): 595-601
[40] Horowitz, P., and Criscimagna, N. L. (1983b) The use of intrinsic protein fluorescence to quantitate enzyme-bound persulfide and to measure equilibria between intermediates in rhodanese catalysis. *Journal of Biological Chemistry*. 258, 7894–7896.
[41] Iciek M, Marcinek J, Mleczko U, Włodek L (2007). Selective effects of diallyl disul- fide, a sulfane sulfur precursor, in the liver and Ehrlich ascites tumor cells. *Eur J Pharmacol*. 569(1–2): 1–7
[42] Jack, A. S, Anosike, E. O., Brown, H., Ben-Chioma, A. (2015). Some Biochemical Properties of Liver Rhodanese (E. C. 2. 8. 1.1) Isolated from a Typical Marine Fish (*Lutjanus goreensis*) . *International Journal of Science and Research (IJSR).* 4 (10): 1524-1530.
[43] Jackson, M. R., Melideo, S. L., and Jorns, M. S. (2012) Human sulfide:quinone oxidoreductase catalyzes the first step in hydrogen sulfide metabolism and produces a sulfane sulfur metabolite. *Biochemistry* 51: 6804-6815
[44] Kakes, P. and Hakvoort, H. (1992) *Phytochemistry* 31:1501-1505.

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[45] Kaya V, Yazkan R, Yıldırım M *et al* (2014): The relation of radiation-induced pul- monary fibrosis with stress and the eficiency of antioxidant treatment: An experimental study. Med Sci Monit. 20: 290–96

[46] Kessler, D. (2006) Enzymatic activation of sulfur for incorporation into biomolecules in prokaryotes. FEMS Microbiol Re. 30: 825–840.

[47] Krueger K, Koch K, Juehling A *et al* (2010). Low expression of thiosulfate sulfur- transferase (rhodanese) predicts mortality in hemodialysis patients. *Clin Biochem.* 43(1–2): 95–101

[48] Lang, K. (1933a) Die Rhodanide-bildung in Tiekorper, *Biochem. Ztschr*. 259, 243-256.

[49] Lewis JL, Rhoades CE, Bice DE, *et al*. (1992). Interspecies com- parison of cellular localization of the cyanide metabolizing enzyme within olfactory mucosa. *Anat Rec*. 233:620-7.

[50] Libiad M., Sriraman A., and Banerjee R., (2015). Polymorphic Variants of Human Rhodanese Exhibit Differences In Thermal Stability And Sulfurtransfer Kinetics. Enzymology: *Journal of Biological Chemistry.* 1-23.

[51] Libiad, M., Yadav, P. K., Vitvitsky, V., Martinov, M., and Banerjee, R. (2014) Organization of the human mitochondrial H_2S oxidation pathway.*J. Biol. Chem*. 289: 30901-30910

[52] Lieberei R, Selmar D (1990). Determination of Rhodanese in Plants. Phytochem. (Oxf). 29(5):1421-1424

[53] Machingura, M.; Ebbs, S.D. (2014). Functional redundancies in cyanide tolerance provided by β-cyanoalanine pathway genes in *Arabidopsis thaliana*. *Int. J. Plant Sci*. 175, 346–358.

[54] Melideo, S. L., Jackson, M. R., and Jorns, M. S. (2014) Biosynthesis of a central intermediate in hydrogen sulfide metabolism by a novel human sulfurtransferase and its yeast ortholog. *Biochemistry* 53: 4739-4753

[55] Meyer, T.; Burow, M.; Bauer, M.; Papenbrock, J. (2003). Arabidopsis sulfurtransferases: Investigation of their function during senescence and in cyanide detoxification. *Planta* . 217: 1–10.

[56] Most P., and Papenbrock J., (2015). Possible Roles of Plant Sulfurtransferases in Detoxification of Cyanide, Reactive Oxygen Species, Selected Heavy Metals and Arsenate. *Molecules*. 20: 1410-1423.

[57] Nagahara N, Nishino T (1996). Role of Amino acid residues in the active site of rat liver mercaptopyruvatesulphurtransferases. *J. Biol. Chem*. 271(44): 27395-27401.

[58] Nagahara, N., Li, Q., and Sawada, N. (2003) Do antidotes for acute cyanide poisoning act on mercaptopyruvate sulfurtransferase to facilitate detoxification? Curr. Drug Targets Immune Endocr. Metabol. Disord. 3, 198–204.

[59] Nakajima T., (2015). Roles of sulfur metabolism and rhodanese: Responses to radiation exposure. *Medical Sciences Monitor*. 21: 1721-1725.

[60] Nandi, D. L., Horowitz, P. M., and Westley, J. (2000) Rhodanese as a thioredoxin oxidase. Int. J. *Biochem. Cell Biol*. 30, 973–977.

[61] Ogasawara, Y., Lacourciere, G., and Stadtman, T. C. (2001) Formation of a selenium-substituted rhodanese by reaction with selenite and glutathione: possible role of a protein perselenide in a selenium delivery system. *Proc. Natl. Acad. Sci. USA* 98: 9494–9498.

[62] Ogata, K., and Volini, M. (1990) Mitochondrial rhodanese: membrane-bound and complexed activity. *J. Biol. Chem*. 265: 8087-8093.

[63] Ogata, K., Dai, X., and Volini, M. (1989) Bovine mitochondrial rhodanese is a phosphoprotein. *J. Biol. Chem*. 264:2718-2725

[64] Oke, O. L. (1973) The mode of cyanogen detoxification in cassava (Manihot spp*); in Chronic cassava toxicity*, Proceedings of interdisciplinary workshop, pp. 73-87, International Development Centre Monograph (IDRC-010e), London, UK.

[65] Oracz, K.; El-Maarouf-Bouteau, H.; Kranner, I.; Bogatek, R.; Corbineau, F.; Bailly, C., (2009). The mechanisms involved in seed dormancy alleviation by hydrogen cyanide unravel the role of reactive oxygen species as key factors of cellular signaling during germination. *Plant Physiol.* 150: 494–505.

[66] Pagani, S., and Galante, Y. M. (1983). Interaction of rhodanese with mitochondrial NADH dehydrogenase. *Biochim. Biophys. Acta* 742: 278–284.

[67] Pagani, S., Bonomi, F., and Cerletti, P. (1984) Enzymic synthesis of the iron-sulfur cluster of spinach ferredoxin. *Eur. J. Biochem*. 142: 361–366.

[68] Pagani, S., Forlani, F., Carpen, A., Bordo, D., and Colnaghi, R. (2000) Mutagenic analysis of Thr-232 in rhodanese from *Azotobacter vinelandii* highlighted the differences of this prokaryotic enzyme from the known sulfurtransferases. *FEBS Letter*. 472, 307–311.

[69] Picton R, Eggo MC, Merrill GA, Langman MJS, Singh S.(2002). Mucosal protection against sulphide: importance of the enzyme rhodanese. *Gut* . 50: 201-5.

[70] Picton, R., Eggo, M. C., Merrill, G. A., Langman, M. J., and Singh, S. (2002). Mucosal protection against sulphide: importance of the enzyme rhodanese. *Gut* 50: 201-205

[71] Piotrowsk i, M.; Schonfelder, S.; Weiler, E.W. (2001). The *Arabidopsis thaliana* isogene NIT4 and its orthologs in tobacco encode β-cyano-L-alanine hydratase/nitrilase. *J. Biol. Chem*. 276: 2616–2621.

[72] Ploegman JH., Drent G., Kalk KH., and Hoi WG., (1978). Struc- ture of bovine liver rhodanese. I. Structure determination at 2.5 A resolution and a comparison of the conformation and sequence of its two domains. *J. Mol. Biol* . 123: 557-594.

[73] Ploegman,J.H.,Drent,G.,Kalk,K.H.,Hol,W.G.J.,Hienrikson,R.L., Keim, P., Wenig, L., and Russell, J. (1978) The covalent and tertiary structure of bovine liver rhodanese. *Nature* 273,124–129.

[74] Ramırez, P., Toledo, H., Guiliani, N., and Jerez, C. A. (2002) An exported rhodanese-like protein is induced during growth of Acidithiobacillus ferrooxidans in metal sulfides and different sulfur compounds. *Appl. Environ. Microbiol.* 68: 1837–1845.

[75] Ressler, C.; Tatake, J.G. (2001). Vicianin, prunasin, and β-cyanoalanine in common vetch seed as sources of urinary thiocyanate in the rat. *J. Agric. Food Chem*. 49:5075–5080.

[76] Schlesinger, P., and Westley, J. (1974). An expanded mechanism for rhodanese catalysis. *J. Biol. Chem.* 249: 780-788

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[77] Shahbazkia H.R., Aminlari M., Tavana M.,(2009). Distribution of the enzyme rhodanese in tissues of the cat (*Felis catus*). *Journal of Feline Medicine and Surgery*. 11:305-308
[78] Sorbo, B. H. (1953) Rhodanese. *Acta Chem. Scand*. 7, 1137–1145.
[79] Stockdreher Y. (2014). Analysis of cytoplasmic sulfur trafficking during sulfur globule oxidation in *Allochromatium vinosum*. PhD Dissertation,University of Bonn.
[80] Sylvester, M., and Sander, C. (1990) Immunohistochemical localization of rhodanese. *Histochemistry Journal*. 22: 197–200.
[81] Szabo G, Bala S (2013). MicroRNAs in liver disease. *Nat Rev Gastroenterol Hepatol*. 10(9): 542–52
[82] Tomati U (1972). Rhodanese Activity in chloroplast. *Physiol. Plant*. 4 (2): 193-196.
[83] Tomati, U., Matarese, R. and Federici, G. (1974b) Ferredoxin activation by rhodanese.*Phytochem.* 13, 1703-1706.
[84] Trzeciak W.H., Waterman M.R., Simpson E.R., (1986). Synthesis of the cholesterol side-chain cleavage enzymes in cultured rat ovarian granulosa cells: induction by follicle-stimulating hormone and dibutyryl adenosine 3',5'-monophosphate. *Endocrinology* 119: 323-30.
[85] Urbina, H. D., Silberg, J. J., Hoff, K. G., and Vickery, L. E. (2001) Transfer of sulfur from IscS to IscU during Fe/S cluster assembly. *J. Biol. Chem*. 276: 44521–44526.
[86] Villarejo M., and Westley J., (1963) *J. Biol. Chem*. 238: PC 1185.
[87] Villarejo M., and Westley J., (1963a). *J. Biol. Chem.* 238: 4016.
[88] Wächtershäuser (1992) Groundworks for an evolutionary biochemistry: The iron-sulphur world. Prog Biophys Mol Biol 58(2): 85-201.
[89] Wächtershäuser, G. (1988) Before enzymes and templates: theory of surface metabolism. Microbiol Rev 52(4): 452–484.
[90] Westely J., and Nakamoto T., (1962).*J. Biol. Chem*. 237:547.
[91] Westley J., Adler H., Westley L., and Nishida C.,(1983). The sulphur- transferases. *Fundam. Appl. Toxicol*. 3: 377-382.
[92] White, A., Handle, P., Smith, E. L., Hill, R. L. and Lehman, I. R. (1981) *Principles of Biochemistry,* 6th ed., pp. 391-734, McGraw Hill, Kogakusha, Tokyo, Japan.
[93] Wood J.L., (1975). Biochemistry of thiocyanic acid. In*: Newmann AA, ed. Chemistry and Biochemistry of Thiocyanic Acid and its Derivatives*. New York: Academic Press: 156-221.
[94] Wrobel, M., Czubak, J., Srebro, Z., and Jurkowska, H. (2006) Rhodanese in mouse brain: regional differences and their metabolic implications. *Toxicol. Mech. Methods* 16:169–172.
[95] Yip, W.-K.; Yang, S.F., (1988). Cyanide metabolism in relation to ethylene production in plant tissues. *Plant Physiol*. 88:473–476.
[96] Yoshimoto S, Loo TM, Atarashi K *et al* (2013). Obesity-induced gut microbial me- tabolite promotes liver cancer through senescence secretome. *Nature*. 499(7456): 97–101

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