SELENIUM METABOLISM AND FUNCTION

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Summary

Selenium related research has entered an exciting phase with the biochemical characterisation and cloning of hitherto unrecognised, functional selenocysteine-containing proteins and the identification of a mechanism whereby selenium is incorporated into such proteins. As well as describing selenium incorporation into proteins, this paper reviews recent findings on 1) the occurrence of three types of glutathione peroxidase with potential antioxidant functions in different cell compartments; 2) the purification and cloning of selenoprotein P, which contains up to 10 selenocysteinyl, 23 histidyl and 17 cysteinyl residues/mole; and 3) the identification of iodothyronine 5'-deiodinase as a selenoenzyme.

I. INTRODUCTION

The nutritional essentiality of selenium was first recognised in 1957 when it was shown to be an active component of factor 3, which prevented liver necrosis in rats which were also vitamin E-deficient (Schwarz and Foltz 1957). Selenium-containing proteins were subsequently shown to exist and in 1973 glutathione peroxidase (GSHPx) was identified as a "functional" selenoprotein (Rotruck et al. 1973). The involvement of selenium in peroxide metabolism was used to explain synergistic effects of selenium and vitamin E supplementation in the prevention of disorders including cardiac and skeletal muscle myopathies and liver necrosis in farm and laboratory animals (see Combs and Combs 1986). GSHPx was postulated to destroy the peroxides in the cell cytoplasm which could provide a source of potentially injurious free radicals and cause peroxidation of polyunsaturated fatty acids in the cell membrane (Hoekstra 1975). Furthermore, the antioxidant properties of sulphur amino acids could be explained by their involvement in the supply of GSH to antioxidant systems. The 'antioxidant hypothesis' has been the basis of much research into the functions and metabolism of selenium. However, it is now apparent that any antioxidant functions of selenium are more complex than originally suggested and may be specifically targeted to different intracellular and extracellular sites (Arthur et al. 1987a). Additionally, non-antioxidant functions for selenium have been demonstrated directly and inferred from the identification of specific selenoproteins (Reiter and Wendel 1984, 1985; Arthur et al. 1987a, 1987b; Hill et al. 1987; Behne et al. 1988; Evenson and Sunde 1988; Burk 1989; Bansal et al. 1991). This review gives a brief account of selenium metabolism and then describes research on selenoproteins that form the basis of the biological functions of selenium in mammalian systems.

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II. SELENIUM METABOLISM

The chemical similarities between selenium and sulphur led to the hypothesis that their metabolism follows the same or similar pathways. Additionally, selenium was found to occur in plant, animals and bacteria as the seleno-analogue of the sulphur amino acids, cysteine and methionine. The metabolism of selenium has been reviews by Sunde (1990) who has emphasised the crucial role of selenide or a chemically equivalent form of selenium in the processes of conversion of inorganic to organic forms of selenium.

The synthesis of seleno-amino acids, selenoproteins, seleno tRNAs and the genes controlling these processes have been characterised for bacterial systems (see Bock et al. 1991a, 1991b; Burk 1991). In studies with mutant forms of *E. coli* at least four gene products, SelA, SelB, SelC and SelD, were identified as essential for synthesis of proteins containing selenocysteine. The SelC gene product is a unique form of tRNA, which acts as a serine carrier and recognises the opal UGA stop codon in mRNA. A similar serine-binding tRNA which recognised UGA has been identified throughout the animal kingdom (Lee et al. 1990). SelA codes for a pyridoxal phosphate-containing selenocysteine synthetase enzyme which converts the serine on the tRNA, specified by SelC to selenocysteine in the presence of a SelD protein product which is chemically equivalent to selenide (Bock et al. 1991a, 1991b). SelD enzyme activity requires ATP and magnesium and its product is thought to be a phosphoselenoate (Ehrenreich et al. 1992).

The absence of SelB product results in the accumulation of selenocysteinyl tRNA. The gene product of SelB is similar in derived sequence to elongation factor Tu and initiation factor 2^{α}. Thus studies on the specificity of binding suggest that it is a selenocysteinyl tRNA-specific translation factor which is similar to elongation factor Tu but has a more specific function (Bock et al. 1991a, 1991b). This may include recognition of UGA as a codon for selenocysteine incorporation and not as a stop codon. Stem loop structures in the 3' untranslated regions of the mRNAs of bacterial formate dehydrogenase and glycine reductase and of mammalian GSHPx and iodothyronine deiodinase are also involved in this recognition function (Bock et al. 1991a, Berry et al. 1991b). These similarities in stem loop structures, the occurrence of mammalian suppressor tRNAs which recognise UGA and the partial characterisation of mammalian selenocysteine synthase suggest that the mechanisms for selenocysteine incorporation in eucaryotes and prokaryotes are very alike (Mizutani et al. 1991, 1992). This is consistent with the demonstration that the carbon skeleton of selenocysteine in rat GSHPx and in bacterial enzymes comes from serine (Sunde and Evenson 1987; Sunde 1990).

Selenomethionine can be incorporated into several proteins in place of methionine, The extent of this incorporation being inversely related to the concentration of methionine in the diet. Although this selenium is normally biochemically/biologically inactive, it may be utilised for a short time by animals that are given selenium-deficient diets (Walchulewski and Sunde 1988).

III. SELENOPROTEINS

The identification of selenoproteins has often relied on in vivo-labelling with ^{75}Se to trace proteins of unknown function through standard chromatographic separation techniques. A drawback of this procedure is the possibility of non-specific association of ^{75}Se with proteins by binding to thiol groups or non-specific replacement of sulphur in sulphur-containing amino acids. However, these problems can be avoided if tissue homogenates and fractions are separated by SDS-PAGE under reducing conditions, followed by location of proteins by autoradiography or direct determination of ^{75}Se in portions of divided gels (Behne et al. 1988; Evenson and Sunde 1988). These techniques result in the identification of at least thirteen

selenoproteins or protein subunits to which selenium is strongly bound. Incorporation of ^{75}Se into proteins in rat liver is prevented by cycloheximide administration, indicating that the process is dependent on protein synthesis (Evenson and Sunde 1988). Thus recognition of specific mechanisms for the incorporation of selenocysteine into protein and the detection of many selenoproteins imply that there are multiple biochemical and biological functions for selenium.

IV. INTRACELLULAR CYTOSOLIC GLUTATHIONE PEROXIDASE

As indicated above the identification of the "classical" cytosolic GSHPx as a selenoprotein provided a plausible explanation for the nutritional interaction between selenium, vitamin E and sulphur-containing amino acids. However, subsequent research has indicated that the role of selenium in biological systems, including those with antioxidant functions, is much more complex than can be explained by "classical" GSHPx activity (Reiter and Wendel 1984, 1985; Arthur et al. 1987a; Burk 1989). For example, the protective effects of selenium against hepatic lipid peroxidation and necrosis caused by diquat administration in selenium-deficient rats, could not be correlated with increases in GSHPx activity (Burk 1989). Furthermore, GSHPx cannot use phospholipid hydroperoxides as substrate and only reacts with the long-chain fatty acid peroxides after they are released by phospholipase A_2 activity (Grossmann and Wendel 1983). Other functions of selenium which cannot be linked to changes in "classical" GSHPx activity include regulation of drug-metabolising enzyme activities, glutathione metabolism, haem degradation, and interaction with some sequelae of vitamin E deficiency (Reiter and Wendel 1984, 1985; Arthur et al. 1987a; Hill et al.; 1987; Burk 1989).

Although GSHPx is capable of metabolising a wide range of lipid hydroperoxides in the cell, this may represent a small fraction of the total cell antioxidant potential and also constitute a minor function of selenium. Hepatic GSHPx activity is altered by selenium intake throughout the normal nutritional range and thus has been used as a sensitive indicator of selenium status. However, metabolic function is apparently normal in selenium-deficient rats, even when the hepatic GSHPx activity is <0.1% of normal. This questions all but the very narrowly defined and specific antioxidant role for "classical" GSHPx in the liver and has led some researchers to reassess the role of the enzyme. Thus "classical" GSHPx may provide a regulated store of selenium which can be diverted into other selenoproteins when selenium supplies are limiting (Burk 1989; Sunde 1990). Such a function requires that GSHPx levels are extremely sensitive to selenium supply. It is perhaps fortunate, therefore, that GSHPx was the first selenium-containing enzyme to be identified, since it provided a useful indicator of status and the study of its potential functions has revealed effects of selenium deficiency which could only be explained by the existence of other functional selenoproteins.

V. PHOSPHOLIPID HYDROPEROXIDE GLUTATHIONE PEROXIDASE (PGSHPx)

In 1982, Ursini and co-workers purified a protein from pig liver which protected membrane preparations from peroxidation initiated by ascorbate/iron or NADPH. The protein from pig heart and liver is a 20-23 KDa monomer which contains one gram atom of selenium/mol (Ursini et al. 1982, 1985). The PGSHPx can metabolise phospholipid hydroperoxides which are not metabolised by "classical" GSHPx. In addition it can metabolise lipid peroxides in liposomes, oxidise erythrocyte ghosts and peroxidise low density lipoprotein (Thomas et al. 1990; Maiorino et al. 1991). Sequencing and cloning experiments have shown that the PGSHPx is not a monomer of the "classical" GSHPx but is a separate enzyme (Schuckelt et al. 1991). In the mouse PGSHPx is found in the same organs as the "classical" GSHPx but is

much more resistant to the effects of selenium deficiency (Zhang et al. 1989; Weitzel et al. 1990). Although isolated from soluble fractions of tissues, the PGSHPx can be associated with membranes; this has led to the proposal that it is more important than "classical" GSHPx in the antioxidant systems which prevent peroxidative damage to cell membranes. The major biochemical basis of the nutritional interaction between selenium and vitamin E may therefore be the protection by PGSHPx and the vitamin of cell membranes against peroxidation (Maiorino et al. 1989). In the cytosol "classical" GSHPx metabolises peroxides which are a potential source of free radicals to initiate peroxidation in the membrane. Thus in selenium-deficient animals with low cytosolic GSHPx activity, sufficient PGSHPx activity may be retained to prevent damage by all but the most severe oxidative stress.

Related to antioxidant systems, it has been suggested that a non-selenium GSHPx activity of the hepatic glutathione S-transferases (GSTs), which are induced in selenium deficiency, can compensate for loss of GSHPx activity. However, the induced GST protein includes isozymes which do not have GSHPx activity and changes in GST activity can be dissociated from those in GSHPx on repletion of selenium-deficient mice. Thus the increases in GST activity in selenium deficiency are unlikely to compensate for loss of GSHPx activity and may be indicative of a more general effect of the deficiency on metabolism (Reiter and Wendel 1984; Arthur et al. 1987a, 1987b).

VI. PLASMA GLUTATHIONE PEROXIDASE

Cohen and co-workers purified and characterised plasma GSHPx after they demonstrated plasma peroxidase activity was not precipitated by antibodies to the "classical" GSHPx (Takahashi and Cohen 1986; Takahashi et al.1987). Like "classical" GSHPx, plasma GSHPx is a tetrameric protein and is made up of subunits of M_r 23KDa to 25 KDa, each with 1 gram atom of selenium. Additionally, in common with several plasma proteins, it is a glycoprotein and its migration on electrophoresis changes under reducing conditions indicating intramolecular -S-S- bonds. The amino acid sequence of rat plasma GSHPx is different from that of the intracellular "classical" GSHPx. Cloning of the rat and human plasma GSHPx has shown that as with other selenoproteins, TGA codes for selenocysteine at the active site (Takahashi et al. 1990; Yoshimura et al. 1991). Northern blotting and immunoblotting experiments have demonstrated that plasma GSHPx is synthesised almost exclusively in the kidney of the rat with no expression in the liver (Yoshimura et al. 1991). Its function may actually lie in the metabolism of GSH in the kidney, since GSH concentration in the renal vein is only 40-50% of that in the renal artery. This function may be the protection of the membranes involved in blood filtration and urine production and would be in addition to a proposed antioxidant function in the protection of endothelial cells.

VII. PLASMA SELENOPROTEIN P

Following in vivo ^{75}Se labelling in rat a 55KDa selenoprotein was identified in plasma or serum (Burk and Gregory 1982). This protein "selenoprotein P" is distinct from plasma GSHPx and may account for 60-70% of plasma selenium. As it is inherently unstable the protein proved difficult to isolate but, this was eventually achieved using affinity purification with a monoclonal antibody (Yang et al. 1987). Electrophoretic separation before and after incubation with glycanases showed a decrease in subunit molecular weight from 57 KDa to 43 KDa, consistent with selenoprotein P being a glycoprotein (Read et al.1990). It contains 7.5 selenocysteinyl, 17 cysteinyl and 23 mol of histidyl residues/mole (Read et al. 1990).

This unusual composition was confirmed by cloning of the enzyme; the cDNA contained 10 inframe TGA termination codons specifying selenocysteine incorporation (Hill et al. 1991).

Despite this biochemical and molecular biological information and the result of studies on the expression of selenoprotein P in animals of different selenium status, its function has not been established (Yang et al. 1989; Burk et al. 1991). A transport role has been hypothesised on the basis of the rapid accumulation of ^{75}Se in plasma selenoprotein P in rats before incorporation of the isotope into other selenoproteins. However, it seems energetically wasteful to convert selenium into selenocysteine in selenoprotein P if it then has to be reconverted to an inorganic form prior to reconversion to selenocysteine in other selenoproteins. It is perhaps most likely that selenoprotein P has an antioxidant/redox function, particularly as it has metal binding potential. It is significant that selenoprotein P levels increase before GSHPx when selenium-deficient rats are treated with small doses of selenium to confer protection against diquat toxicity (Hill et al. 1991).

VIII. TYPE I IODOTHYRONINE 5'-DEIODINASE

The only other selenoprotein with a well characterised function is type I 5'-iodothyronine deiodinase (IDI). IDI was tentatively identified as a selenoprotein after the discovery that selenium deficiency increases plasma thyroxine (T_4) and decreases plasma triiodothyronine (T_3) concentrations in rats (Beckett et al. 1987, 1989, 1990; Arthur et al. 1987a, 1988, 1990a, 1991a). This was confirmed by in vivo labelling of the protein with ^{75}Se and by its partially purification from rat liver and subsequent labelling with a ^{125}I containing bromoacetyl rT_3 affinity label (Arthur et al. 1990b). The identity of IDI as a selenoprotein was further substantiated when the rat liver enzyme was cloned and the mRNA was shown to contain a single inframe UGA codon specifying selenocysteine at the active site (Berry et al. 1991).

Brain, pituitary and brown adipose tissue contain a type II 5'-iodothyronine deiodinase (IDII), which also converts T_4 to T_3. IDII is not a selenoenzyme although its activity is decreased in selenium deficiency; this reflects a feedback response to elevated plasma T_4 caused by selenium deficiency (Beckett et al. 1989; Arthur et al. 1991b; Berry et al. 1991c; Safran et al. 1991; Chanoine et al. 1992). T_4 is a prohormone and T_3 exerts the biological activity of thyroid hormones. Thus selenium, through IDI, plays a crucial role in thyroid hormone metabolism and some of the effects of selenium deficiency may therefore be a consequence of decreased T_3 production (Arthur et al. 1990c; Arthur 1991; Beckett et al. 1992). For example, growth failure in selenium-deficient animals may be caused by impaired T_3-mediated synthesis of growth hormone in the pituitary (Arthur et al. 1990c). Another important consequence of the essential role of selenium in thyroid hormone metabolism is the modification of some of the effects of iodine deficiency by a concurrent selenium deficiency (Arthur et al. 1990d; Vanderpas et al. 1990). However, selenium supplementation of selenium- and iodine-deficient humans may not be beneficial, unless iodine or thyroid hormones are also given to provide substrate for the normalised IDI and IDII activities (Contempre et al. 1991a, 1991b). Selenium deficiency may therefore have a major influence on the outcome of iodine deficiency in human and animals, apart from its direct metabolic effects on thyroid hormone metabolism.

IX. CONCLUSIONS

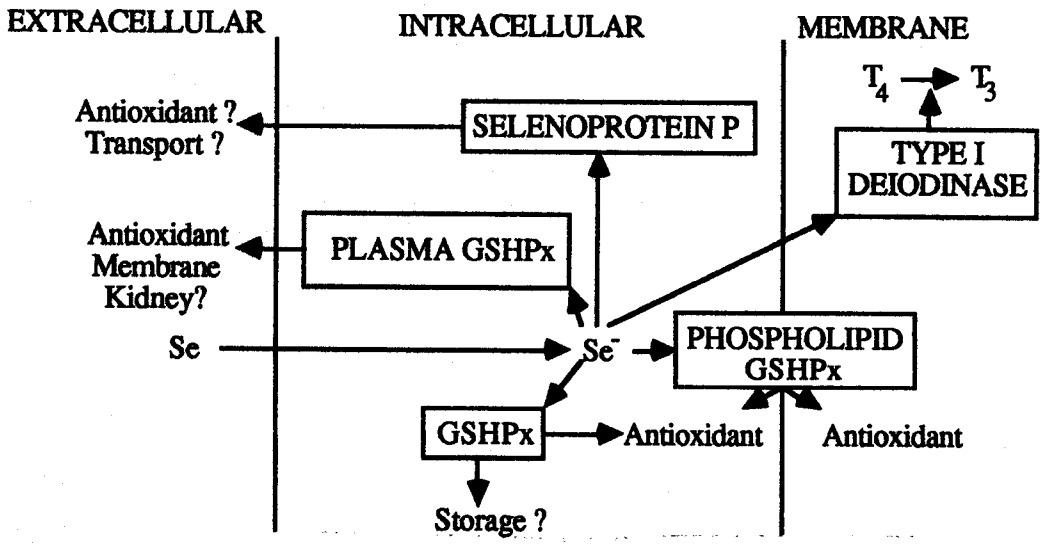

Fig.1. Interrelationships and functions of selenoproteins in intracellular compartments, extracellular compartments and membranes. Se^- represents an intermediate similar to selenide involved in the synthesis of selenocysteine. Plasma GSHPx (in kidney) and selenoprotein P (in liver) are synthesised intracellularly but function in the extracellular compartment.

The functions of selenium in animals are mediated by at least five selenoproteins. The three forms of GSHPx (cytosolic, plasma and phospholipid hydroperoxide) and selenoprotein P are probably essential component of antioxidant systems in different intracellular and extracellular compartments. The function of selenium in thyroid hormone metabolism through IDI is distinct from the antioxidant roles of selenium, although all these activities rely on the redox properties of the selenocysteine residue(s) at the active sites of the selenoenzymes. The currently recognised functions of selenium are summarised in Fig.1., which emphasises the compartmentalisation of the various selenoproteins. However, more research is required on the tissue-specific expression of these and possibly other hitherto unrecognised selenoenzymes. Only then will we be able to understand fully the metabolic functions of this important trace element.

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