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REVIEW ARTICLE

Toxicology and pharmacology of selenium: emphasis on synthetic organoselenium compounds

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Abstract The advance in the area of synthesis and reactivity of organoselenium, as well as the discovery that selenium was the cause of severe intoxication episodes of livestock in the 1930s and the subsequent determination that selenium was an essential trace element in the diet for mammals, has motivated intense studies of the biological properties of both organic and inorganic selenium compounds. In this review, we shall cover a wide range of toxicological and pharmacological effects, in which organoselenium compounds are involved but the effects of inorganic compounds were not discussed in detail here. The molecular toxicity of inorganic selenium was described in relation to its interaction with endogenous –SH groups to allow a comparison with that of synthetic organoselenium compounds. Furthermore, in view of the recent points of epidemiological evidence that overexposure to selenium can facilitate the appearance of chronic degenerative diseases, we also briefly revised the history of selenium toxicity and physiology and how environmental selenium can reach inside the mammalian cells. The biological narrative of the element selenium, in the last century, has been marked by a contrast between its toxic and its beneficial effects. Thus, the potential therapeutic use of simple organoselenium compounds has not yet been sufficiently explored and, consequently, we cannot discard this class of compounds as promising pharmaceutical agents. In effect, the future of the organochalcogens as pharmacological agents will depend on more detailed toxicological studies in the oncoming years.

Keywords Selenium · Diselenides · Toxicology · Pharmacology · Thiol · Organoselenium · Ebselen · Oxidative stress

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Introduction

The advance in the area of synthesis and reactivity of organoselenium and organotellurium compounds, as well as the discovery that selenium was the cause of severe intoxication episodes of livestock in the 1930s and the subsequent determination that selenium was an essential trace element in the diet for mammals, has motivated intense studies of the biological properties of both organic and inorganic selenium compounds. In fact, the clinical demonstration that ebselen exhibited borderline neuroprotective effects against pathological conditions associated with brain ischemia about a decade ago (Saito et al. 1998; Yamaguchi et al. 1998; Ogawa et al. 1999; Parnham and Sies 2000) and the extensive data obtained with animal models demonstrating that ebselen was effective against the deleterious effects caused by ischemia/reperfusion (Dawson et al. 1995; Takasago et al. 1997; Imai et al. 2001; Lapchak and Zivin 2003; Ozaki et al. 1997; Hamacher et al. 2009; Seo et al. 2009; Tunc et al. 2009; Gul et al. 2010) further reinforces the importance of studying the pharmacology and toxicology of organoselenium compounds. The study of the environmental and dietary toxicity of inorganic and naturally occurring organic selenium compounds, which was somewhat abandoned, has returned to the mainstream of public

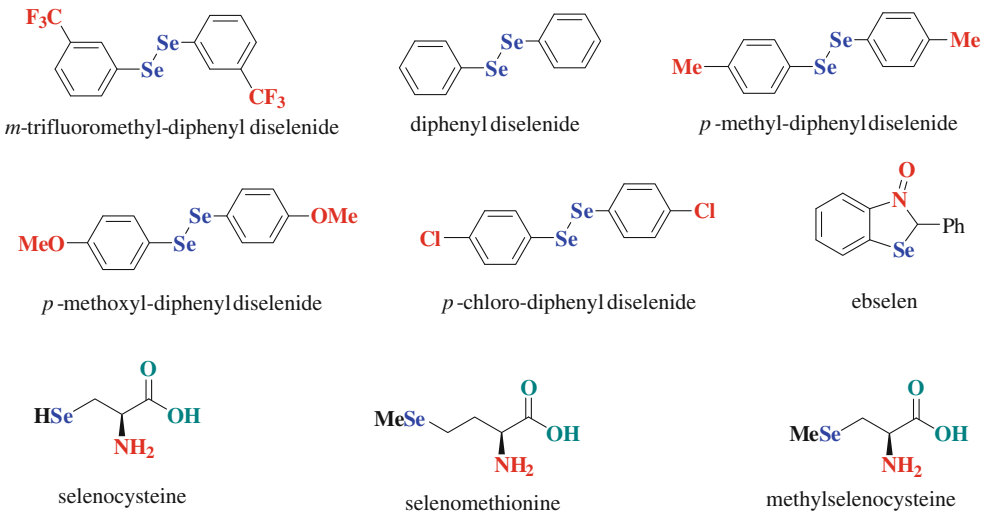

Fig. 1 The chemical structures of representative organoselenium compounds discussed in this review

attention in view of the epidemiological points of evidence, indicating that long-term overexposure to dietary selenium can facilitate the development of chronic degenerative diseases such as amyothrophic lateral sclerosis, diabetes type II, and some types of cancer (Bleys et al. 2007a, b; Stranges et al. 2007; Bonvicini et al. 2008; Vinceti et al. 2009, 2010; Stranges et al. 2010).

In this review, we shall cover a wide range of toxicological and pharmacological effects, in which organoselenium compounds are involved but the effects of inorganic compounds will not be discussed in detail here. However, the molecular toxicity of inorganic selenium will be described in relation to its interaction with endogenous –SH groups to allow a comparison with that of synthetic organoselenium compounds, particularly diselenides (Fig. 1). Furthermore, particularly in view of the recent points of epidemiological evidence that overexposure to selenium can facilitate the appearance of chronic degenerative diseases (for review, see Vinceti et al. 2009, 2010), we will also briefly revise the history of selenium toxicity and physiology and how environmental selenium can reach inside the mammalian cells. Since it is not possible to cite all of the findings that have taken place, we apologize to those whose work has been omitted.

The chemical structures of representative organoselenium compounds that will be discussed in this review are shown in Fig. 1.

A brief history of selenium: an element with two faces

Selenium was discovered by the Swedish chemist Jöns Jacob Berzelius in 1817, and the name of the element was given in honor of the Greek Goddess of the moon, Selene (Arner 2010; Comasseto 2010). About one century ago, selenium was incorporated in the periodic table (Chen and Berry 2003) and now, together with oxygen, sulfur, tellurium, and polonium, it is a member of the group 16 (formerly group 6A), or the group of chalcogens. Consequently, selenium shares with sulfur and tellurium some physical and chemical properties.

Selenium as a component of selenoproteins

Nowadays, selenium is recognized as an essential dietary element for mammalian and for different classes of living organisms, including archaea, algae, bacteria, and for many eukaryotes (Shamberger 1981; Foster and Sumar 1997; Araie and Shiraiwa 2009; Stock and Rother 2009; Lobanov et al. 2009; Valdiglesias et al. 2010). In effect, mammals has about 25 selenoproteins, and higher number of selenoproteins are found in sea-water organisms like fish and algae (Lobanov et al. 2007, 2009; Araie and Shiraiwa 2009). In contrast, there is no concrete evidence for a key physiological role of Se in high plants and fungi, which makes the phylogenesis of selenoproteins complex and intriguing.

In mammalians and in different classes of organisms listed above, selenium behaves as a kind of "supersulfur", exclusively in the chemical form of a selenol/selenolate (R-SeH/R-Se-; Fig. 2). Indeed, selenolate is a softer and stronger nucleophile than its thiolate analogue, which confers to a given selenol group a stronger reducing power than that of an analogue thiol group (Nogueira and Rocha 2010).

Nevertheless, we must emphasize that the role played by selenium in different classes of prokaryote and eukaryote cannot be viewed as a simple substitution of the sulfur analogue. In the case of mammals, one of the most important

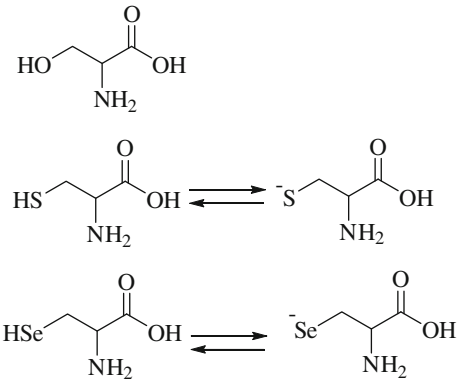

Fig. 2 Structures of serine, cysteine (thiol-thiolate form) and selenocysteine (selenol-selenolate form). The pKa for cysteine is about 8 and pKa for selenocysteine is about 5

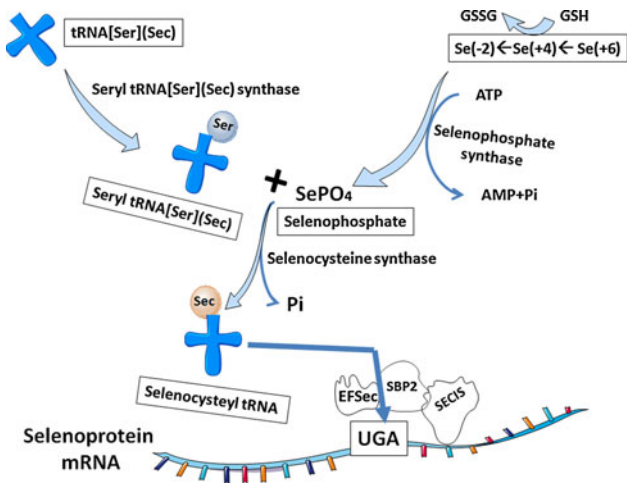

Fig. 3 Schematic representation of the complex and energetically expensive co-translational incorporation of selenocysteine in selenoproteins. The incorporation of Se(IV) or Se(VI) into selenocysteine requires NADPH and reduced glutathione (GSH) as reducing agents. After Se(IV) or Se(VI) metabolism to Se-(II), Se incorporation in the organic moiety of serine is assisted by the concerted action of two enzymes: first, selenophosphate synthase catalyzes the introduction of a phosphate in the Se-(II) to form selenophosphate. Selenophosphate is then incorporated in a specific serine-charged t-RNA[Ser]Sec, transforming serine in selenocysteine. This selenocysteine-charged t-RNA can now deliver the selenocysteyl residue into a selenoprotein. The incorporation of selenocysteine in the UGA codon needs the assistance of an elongation factor (EFSec), selenocysteine insertion sequence (SECIS) and SECIS binding protein 2 (SBP2), these elements are required to recode the UGA termination codon to UGA selenocysteine codon

soft nucleophiles found in cells and in the extracellular fluids is the sulfhydryl group (thiol/thiolate; Fig. 2), which can be found in the low-molecular-weight compounds (e.g., cysteine and glutathione) or in high-molecular-weight proteins. The concentration of low-molecular-weight thiols can be as high as 5–10 mmol/L, depending on the tissue considered (Cooper and Kristal 1997; Dringen 2000; Maciel et al. 2000). The selenohydryl group (selenol/selenolate; Fig. 2) is a softer and a more powerful nucleophile center than the sulfhydryl group in living cells; however, selenol groups are much less abundant than thiols and they are found only in a small number of selenoproteins (Lobanov et al. 2007, 2009; Araie and Shiraiwa 2009). These considerations clearly indicate the importance of selenium in biology and demonstrated that even a molar excess of sulfhydryl/thiol/thiolate groups over selenohydryl/selenol/selenolate groups cannot carry out the partially elucidated role of selenium in cell physiology. In effect, the evolutionary pressure that has introduced selenium in biology is still not completely understood, and certainly, selenium is performing a critical chemistry that sulfur cannot do in the biological system.

Major milestones along the course of identification that selenium is an element with biological functions were the biochemical confirmation that the mammalian glutathione peroxidase is a selenoprotein (Flohe et al. 1973; Rotruck et al. 1973; Oh et al. 1974) and the demonstration that this element is present in selenoproteins in the form of selenocysteine in prokaryotes (Cone et al. 1976) and eukaryotes (Forstrom et al. 1978). In short, in the form of selenocysteinyl residues, selenium is found in different selenoproteins, where it behaves as a softer and more potent nucleophile than its sulfur or oxygen analogues (cysteine and serine, respectively, Fig. 2; Bock et al. 1991; Burk and Hill 1993; Stadtman 1996; Arner 2010; Nogueira and Rocha 2010). Thereafter, it was determined that the majority of selenoproteins contain one selenocysteinyl residue in their structures (for recent, elegant and concise reviews about selenoproteins, see Lu and Holmgren 2009 and Lobanov et al. 2009). There are some exceptions such as the fish and mammalian selenoprotein P, which contains around ten selenocysteinyl residues in its functional structure (Lobanov et al. 2007, 2009; Araie and Shiraiwa 2009). Furthermore, the number of selenoproteins in invertebrates and vertebrates varies from one in some nematodes to about 30 in fish (Lobanov et al. 2009). As briefly commented at the beginning of this review, another intriguing question about the role of selenium in life is why plants and fungi do not require selenoproteins?

Thus, the physiological or the natural biological chemistry of selenium in prokaryotic and eukaryotic cells is mediated basically by its incorporation into selenoproteins. The incorporation of a selenium atom in vertebrate selenoproteins is complex and expensive and requires several enzymatic steps and unique macromolecular components, including the participation of a specific t-RNA that is initially charged with serine (t-RNA[Ser]Sec), the selenocysteine insertion sequence (SECIS) element, and protein factors (an elongation factor EFSec and the SECIS binding protein 2, SBP2; for a schematic representation of selenocysteine incorporation into proteins, see Fig. 3; Bock et al. 1991; Burk and Hill 1993; Allmang and Krol 2006; Allmang et al. 2009; Carlson et al. 2009).

Indeed, the extremely high chemical reactivity of selenocysteine in the presence of oxygen precludes its existence as free aminoacid in aerobic cell environment. Thus, to circumvent this chemical problem, the machinery of synthesis of selenoproteins has evolved to an expansion of the existing genetic code and the UGA codon, which is normally a termination code for eukaryotic and prokaryotic proteins, codifies for a selenocysteine, when it is present within the RNA sequences of selenoproteins. In fact, selenocysteine incorporation via an in-frame UGA codon is accomplished by a recoding the machinery that guides ribosomes not to stop at UGA codon on the mRNA from selenoproteins (Allmang et al. 2009).

Selenocysteine is enzymatically synthesized by the incorporation of a selenium atom from a selenophosphate in place of oxygen in O-phosphoseryl-tRNA([Ser]Sec) and then generating selenocysteyl-tRNA([Ser]Sec) (Allmang and Krol 2006; Allmang et al. 2009; Carlson et al. 2009). The reason why selenocysteine "needs" to be formed from a hydroxyl group of serine and not from a thiol of cysteine is an intriguing question of biochemistry of selenoprotein synthesis. This can have both chemical and biological reasons, i.e., perhaps it is "easier" to enzymatically substitute the oxygen atom by a selenium atom than to substitute the sulfur atom by a selenium atom. Biologically, perhaps the machinery used to synthesize selenoproteins has required a serine to avoid the misincorporation of cysteine in place of selenocysteine, i.e., the entire machinery of selenocysteine incorporation into a nascent peptide of a selenoprotein could commit more mistakes in deciphering between a cysteine and a selenocysteine when compared with a serine residue. Here, we will not give details about the beautiful studies with both prokaryotes and eukaryotes that unrevealed the incorporation of selenium into selenoproteins and that have brought to the biology new dimensions about central aspects of cell biochemistry and physiology of selenol group (for either comprehensive or important reviews about the history of selenium incorporation into proteins, see Bock et al. 1991; Burk and Hill 1993; Stadtman 1996).

Selenium as a toxic element

In contrast to its essentiality, the history of selenium was first marked by its toxicity in mammals, which is certainly related to the fact that the range between deficiency, essentiality, and toxicity is narrow for selenium (Frost and Olson 1972; Shamberger 1981; Rayman 2008; Vinceti et al. 2001, 2009; Valdiglesias et al. 2010). Selenium was first recognized as poison for livestock and mammals, and then, the element became notorious for its toxicity. The experimental demonstration that selenium was toxic to vertebrates created a strong negative view of the element, which was termed "selenophobia" (Frost and Olson 1972). "Selenophobia" persisted even after experimental demonstration of nutritional essentiality of selenium in prokaryotes (Pinsent 1954) and rodents (Schwarz and Foltz 1957). The identification of its role in antioxidant enzymes (Flohe et al. 1973; Rotruck et al. 1973; Arner and Holmgren 2000; Chen and Berry 2003) and its possible protective effect against some types of cancer (Vinceti et al. 2000, 2009; Rayman 2008; Brozmanová et al. 2010; Micke et al. 2009) have halted most of the "selenophobia" in recent decades. In fact, the over-the-counter intake of nutritional supplements with "the antioxidant" selenium has been stimulated by different sources, and the use of dietary supplements is common worldwide (Rayman 2008; Soni et al. 2010), which some sporadic disastrous consequences (Schuh and Jappe 2007). However, the recent growing epidemiological points of evidence indicating that chronic nutritional or environmental overexposure to selenium can increase the risk of some types of cancer, diabetes type II, and amyotrophic lateral sclerosis (Vinceti et al. 1996, 1998, 2001, 2009, 2010; Stranges et al. 2010) strongly indicates that "selenophobia" must not be abandoned. Most importantly, these epidemiological data clearly indicate that the dietary levels of selenium intake and, principally, the use of dietary supplements with selenium should be carefully controlled. Consequently, the prolonged intake of any type of selenium-containing formulation (either inorganic or organic) for nutritional or therapeutic purposes should be done under medical supervision. Otherwise, we are under the risk of seeing selenium in the list of chemicals causing silent wide-reaching nutritional pandemics.

A brief history of the identification of selenium as a toxic element

Selenium toxicity was experimentally demonstrated at the begin of the twentieth century (Franke 1934a, b; Franke and Painter 1935; Painter 1941; Moxon and Rhian 1943), and this was retrospectively associated with the cases of intoxication of horses at the Fort Randall in USA in 1856 and with poisoning of farming animals in the same region some years later. Indeed, the first conclusive retrospective association of selenium intake with intoxication of horses could be done thanks to observation made by Madison, a physician from the USA army, who described a fatal disease among the horses that had grazed in a certain area near to the fort [Madison TC (1860) cited by Moxon and Rhian (1943) and by Painter (1941)]. Madison observed that cavalry horses brought from non-seleniferous to seleniferous areas started to lack vitality, become emaciated, and lost weight and the long hair from the mane and tail within 1 month after they were moved to the seleniferous areas

near to the Fort Randall. This disease appearing in livestock after ingestion of plants containing about 25 ppm of Se for several days or weeks was termed "alkali disease" (Moxon and Rhian 1943). This was the first well-documented description of mammalian intoxication by naturally occurring selenium in plants.

The investigations conducted by Franke and collaborators at South Dakota Agricultural and Experiments Station with plant feed samples obtained from the seleniferous soils near to the Fort Randall were critical for the identification of selenium as the etiological agent of "alkali disease". Franke and collaborators demonstrated that ingestion of these "toxic grains and forages containing high selenium levels" was extremely toxic to rats (Franke 1934a, b; Franke and Painter 1935; Painter 1941; Moxon and Rhian 1943). They also demonstrated that "most of the poison" was associated with plant protein fraction and they could remove all the selenium from the "toxic protein" hydrolysate and found that the selenium-free hydrolysate was not toxic to rats (Franke and Potter 1935). Indeed, the majority of selenium in plants is found in selenoaminoacids, such as methylselenocysteine (MetSeCys) and selenomethionine (Dumont et al. 2006). However, at that time, there were several confounding factors in the "toxic plants" that could account for their toxicity in rats. Consequently, Franke and Painter (1935) added selenite to a basal diet and unequivocally indicated that selenium was the sole causative factor of toxicity in rats and, by inference, the etiological agent causing the "alkali disease" in livestock.

As described above, the first well-documented case of selenium intoxication in mammals was a consequence of ingestion of pasture with high selenium level. Of particular biochemical and toxicological significance, the main chemical forms of selenium bioaccumulated in plants are organic, namely selenomethionine and methylselenocysteine (Dumont et al. 2006; Fig. 1). The high selenium content in these plants was a consequence of the high levels of selenium in the soil where they have grown (Painter 1941; Zhu et al. 2009). This illustrative report highlight the critical role of selenium content in soil in its biogeochemistry and, particularly, in the potential environmental toxicity of selenium. However, we would like to emphasize that two major types of environmental selenium toxicity can be defined from literature data: (1) a natural environmental selenium toxicity (which is mainly determined by the natural occurrence of selenium in a particular soil or in aquatic sediments) and (2) an anthropogenic environmental selenium toxicity (which is determined by the indiscriminate release of selenium in the environment by humans, commonly for agricultural proposes or as a supplement in farming (Cahpman 1999; Lemly 1999; Fordyce 2007; Schrauzer and Surai 2009). In recent times, a third class of selenium toxicity has been observed in humans after consumption of dietary selenium supplement containing non-appropriated selenium levels (Schuh and Jappe 2007). Furthermore, severe selenium toxicity (often followed by fatality) has been occasionally described after suicidal, criminal, occupational, or accidental poisoning with selenium compounds (Schellmann et al. 1986; Quadrani et al. 2000; Lech 2002; Hunsaker et al. 2005, Spiller and Pfiefer 2007; Sutter et al. 2008; Kamble et al. 2009).

Toxicity of organic selenium

Interaction of selenium with thiols

Here, we will not give details about the pathophysiological consequences of selenium intoxication, but readers can find this in excellent classical reviews or in original reports about the acute or chronic toxicity of selenium to livestock and humans that were cited early in this review, because our intention is to give more details about the biochemistry of interaction of organoselenium compounds, particularly diselenides with thiols of biological significance. The molecular mechanism(s) involved in selenium toxicity is not well defined; however, the interaction of inorganic and organic selenium with thiols seems to play a central role in their molecular toxicity. In effect, Painter (1941) suggested that the toxicity of selenite could be related to the oxidation of endogenous thiols. Accordingly, selenite (Se(IV)) can catalytically oxidize sulfhydryl groups (Tsen and Tappel 1958), producing disulfide and an unstable intermediary containing –S–Se–S– bonds (Ganther 1968). Consequently, from a toxicological point of view, the catalytic oxidation of endogenous low- and high-molecular-weight thiols by cationic or organic forms of selenium can play a role in the long-term toxicity observed in humans and animals exposed to daily doses of selenium slightly above those considered safe from a nutritional point of view. More recently, it has been proposed that selenium-mediated thiol oxidation can produce reactive oxygen species (ROS) that could mediate the toxicity of inorganic and organic forms of selenium (Seko et al. 1989; Kitahara et al. 1993; Spallholz 1994; Davis and Spallholz 1996; Stewart et al. 1998; Spallholz et al. 2004; Chen et al. 2007; Plano et al. 2010). Accordingly, in vitro studies have indicated that oxidative stress can be a factor involved in selenium-induced toxicity and apoptosis in different types of cells in culture (Kitahara et al. 1993; Shen et al. 2001b; Kim et al. 2007; Xiang et al. 2009).

However, experimental demonstration of catalytic oxidation of thiols on the long-term toxicity of environmentally or nutritionally relevant doses of both inorganic and organic selenium compounds can be difficult because the oxidation of thiols may be restricted to a transitory interaction of selenium compounds with few high-molecular-weight targets involved in the regulation of cell metabolism

or cell signaling. In effect, selenium can modify the activation of different signaling pathways after in vivo or in vitro exposure to both organic and inorganic selenium forms (Ghose et al. 2001; Shen et al. 2001a; Sarker et al. 2003; Muller et al. 2005; Posser et al. 2011). Therefore, the systematic study of oxidation of sulfhydryl groups from metabolically important thio-containing proteins by inorganic and organic selenium compounds will facilitate the identification of potential in vivo targets that trigger selenium toxicity. Since molecules containing vicinal thiols are more efficiently oxidized by selenium forms than monothiol molecules (Barbosa et al. 1998; Maciel et al. 2000; Farina et al. 2003a), it will be important to study the interaction of inorganic and organic selenium with proteins containing thiols in close proximity in their tertiary structure. Alternatively, the computational identification of metabolically relevant proteins containing vicinal thiol groups could point out which proteins or metabolic pathways are more likely to be the targets of inorganic and organic selenium toxicity.

In vitro molecular toxicity of organoselenium compounds

The basic molecular mechanism(s) involved in the toxicity of organoselenium compounds are still not completely understood. One of the reasons for this is the fact that simple organoselenium compounds, such as diphenyl diselenide, have multiple targets. The absence of a single molecular target generates a complex puzzle that will require a long period to be deciphered. However, the chemistry of interaction of inorganic selenium with thiols has helped to shed some light on this problem. In effect, to some extent, the interaction of organoselenium compounds with thiols has some similarities to that observed with inorganic selenium. One interesting aspect that can be indicated is the interaction of the sulfur atom of thiols with the inorganic or organic selenium atom from different compounds. The formal establishment of a –S–Se bond between thiols and selenium, particularly in some organo-monoselenides, can be difficult; nevertheless, such type of interaction can easily occur between inorganic selenium and organo-diselenide compounds. Here, we will only briefly discuss the interaction of thiols with monoselenides, and we will give emphasis on the interaction of low- and high-molecular-weight thiols with diphenyl diselenide.

The toxicity of organo-monoselenides can be associated with their metabolic transformation to their respective selonoxides (Chen and Ziegler 1994; Akerboom et al. 1995; Rooseboom et al. 2001; Krause et al. 2006). The selenoxide moiety can react with thiols, regenerating the original monoselenide and disulfides. In line with this, we have demonstrated that methyl phenylselenide and phenyl selenoacetylene, which do not oxidize thiols, can oxidize the

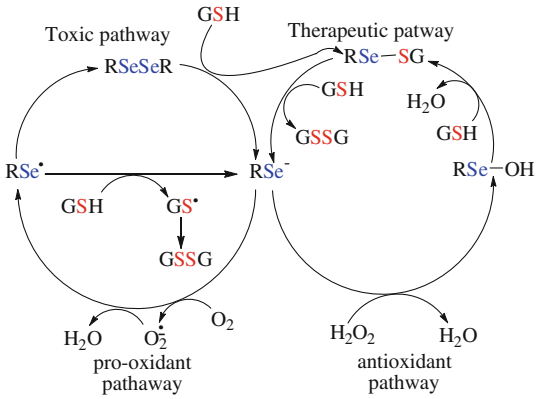

Fig. 4 Oxidation of thiols by diselenides. This figure depicts two pathways of interaction between thiol groups and diselenides. The toxic pathway is that leads to the formation of potentially toxic intermediates (superoxide anion and hydrogen peroxide). The therapeutic pathway is that leads to the formation of the selenol intermediate, which can, in analogy to the native GPx enzyme, decompose peroxides. Modified from Nogueira et al. (2004)

sulfhydryl-containing enzyme delta-aminolevulinic acid dehydratase (δ-ALA-D) after its chemical transformation to their respective selenoxides (Farina et al. 2001; Bolzan et al. 2002). Furthermore, the administration of methyl phenylselenide to rodents caused the inhibition of hepatic δ-ALA-D (Folmer et al. 2004), which can be a consequence of methyl phenylselenide selenoxidation via monooxygenase (Chen and Ziegler 1994; Rooseboom et al. 2001; Krause et al. 2006). In summary, the in vivo toxicity of organo-monoselenides can result from their selenoxidation via monooxygenases, which will form selenoxides that can oxidize cellular molecular targets containing thiol groups. Thus, at least in part, the toxicity of organoselenium compounds of the type R-Se-R can be mediated by interaction of their metabolically formed selenoxides with endogenous thiols.

The interaction of thiols with diselenide compounds can be easily demonstrated (Caldwell and Tappel 1965; Dickson and Tappel 1969; Chaudière et al. 1992; Barbosa et al. 1998; Maciel et al. 2000) and is certainly an important factor in the toxicity of simple diaryl and dialkyl diselenide. Chaudière et al. (1992) have elegantly demonstrated that thiol oxidase activity could help explain part of the toxic effects of diselenides. They have studied the catalytic effect of several diselenides and ebselen, as oxidants of low-molecular-weight thiols (Chaudière et al. 1992; Fig. 4). Subsequently, we have demonstrated that diphenyl diselenide and some derivatives could oxidize dithiothreitol (DTT, a low-molecular-weight thiol) and the enzyme δ-ALA-D. Based on these results, we have proposed that the toxicity of diphenyl diselenide could be associated with δ-ALA-D inhibition, which could compromise the synthesis of heme-containing proteins (Fig. 5).

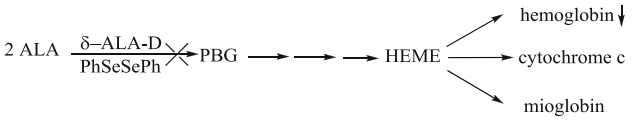

Fig. 5 Schematic representation of pathophysiological consequences of exposure to high dose of diphenyl diselenide (PhSeSePh) in mice. We have demonstrated that exposure to diphenyl diselenide causes inhibition of δ-ALA-D and this can result in a decrease in blood hemoglobin (Maciel et al. 2000; Jacques-Silva et al. 2001)

In this study, we have demonstrated that the inhibitory effect of diphenyl diselenide could be attenuated by the removal of oxygen from the medium (Barbosa et al. 1998). Interestingly, we have also observed that the plant δ-ALA-D was not inhibited by diphenyl diselenide, which was explained by the absence of vicinal thiols in the active center of plant enzyme. Thus, the mammalian δ-ALA-D inhibition by diphenyl diselenide was attributed to the presence of vicinal thiols in the enzyme active center (Barbosa et al. 1998; Farina et al. 2002). The catalytic oxidation of δ-ALA-D by diphenyl diselenide is schematically depicted in Fig. 6). Furthermore, the inhibition of δ-ALA-D could increase the concentration of its substrate, the 5-aminolevulinic acid, which is a pro-oxidant molecule (Pereira et al. 1992; Oteiza and Bechara 1993; Bechara 1996; Penatti et al. 1996; Costa et al. 1997). Consequently, δ-ALA-D inhibition either could disrupt the aerobic metabolism or could increase the production of oxidative stress.

In view of the fact that diphenyl diselenide could potentially interact with any thiol-containing protein, we determined the possible in vitro inhibition of other thiol-containing enzymes by diphenyl diselenide. We have observed that diphenyl diselenide was an inhibitor of erythrocyte and cerebral Na^+, K^+-ATPase (Borges et al. 2005b; Kade et al. 2008; Santos et al. 2009a) and δ-ALA-D from different sources (fruit fly and fish; Golombieski et al. 2008a, b; Soares et al. 2005). Furthermore, diphenyl diselenide was also an in vitro inhibitor of different isoforms of lactate dehydrogenase (LDH) (Kade et al. 2009c; Lugokenski et al. 2011).

Of particular toxicological significance, ebselen and diphenyl diselenide can induce mitochondrial dysfunction in vitro (Yang et al. 2000a, b; Morin et al. 2003; Puntel et al. 2010). We have observed that ebselen and diphenyl diselenide induce mitochondrial dysfunction, which was associated with mitochondrial thiol group oxidation. The inability of cyclosporine A to reverse mitochondrial effects induced by ebselen and diphenyl diselenide suggested that the redox-regulated mitochondrial permeability transition (MPT) pore was mechanistically regulated in a manner that is distinct from the classical MPT pore (Puntel et al. 2010). In contrast to our results, Morin et al. (2003) have demonstrated that mitochondrial dysfunction induced by ebselen was strictly dependent on the presence of Ca^{2+} and independent of pyrimidine nucleotide oxidation. The reasons for the discrepancy are not clear at the moment. In spite of this, the deregulation of mitochondrial functioning seems to be related to the oxidation of thiol groups located in the inner mitochondrial membrane, which reinforces the role of thiol group oxidation as a central molecular mechanism involved in the toxicity of organoselenium compounds. Indeed, ebselen and diphenyl diselenide induced mitochondrial protein aggregate formation via intermolecular –S–S– cross-link that was prevented by DTT. Furthermore, the selenium-induced mitochondrial dysfunction mediated by thiol oxidation may help explain the induction of apoptosis by ebselen, diphenyl diselenide, and other organochalcogens (Yang et al. 2000a, b; Plano et al. 2010; Posser et al. 2011) and the anticancer activity of diphenyl diselenide in female rats exposed to *N*-nitroso-*N*-methylurea (Barbosa et al. 2008a).

In vivo toxicity of organoselenium compounds

Supporting our in vitro data, in vivo exposure to high doses of diphenyl diselenide was shown to cause the depletion of

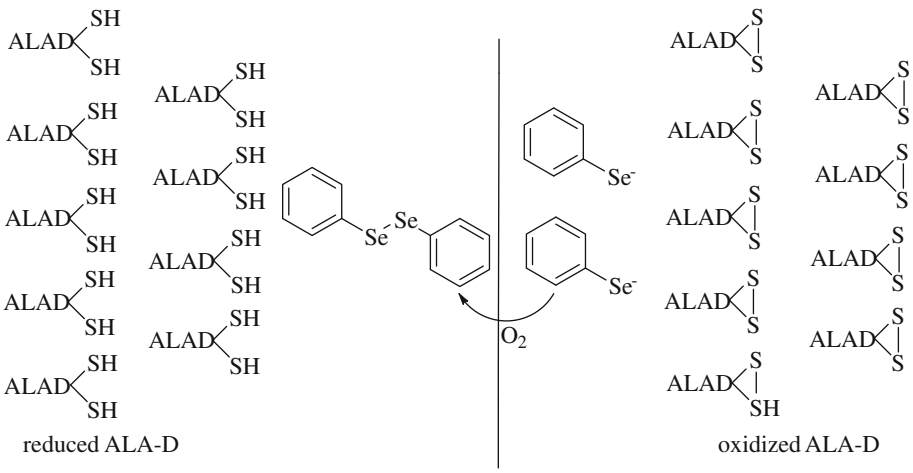

Fig. 6 Catalytic oxidation of δ-ALA-D by diphenyl diselenide. Oxidation of δ-ALA-D by diphenyl diselenide generates the unstable intermediate selenol (selenophenol) that is oxidized back to diphenyl diselenide by molecular oxygen

Table 1 Lethal dose (LD_{50}) for a single intraperitoneal administration of diphenyl diselenide and ebselen in rodents and in rabbits

Compounds	Animal species	LD_{50} (μmol kg^{-1})
Ebselen	Rats	400
	Mice	340
Diphenyl diselenide	Rats	1,200
	Mice	210
	Rabbits	311

non-protein –SH (NPSH) groups in different tissues of rodents (Adams et al. 1989; Maciel et al. 2000) and to inhibit hepatic and cerebral δ-ALA-D (Maciel et al. 2000; Jacques-Silva et al. 2001; Barbosa et al. 1998; Kade and Rocha 2010). Of particular toxicological significance, the inhibition of δ-ALA-D by high doses of diphenyl diselenide caused a reduction in the blood hemoglobin content, supporting our early assumption that the synthesis of heme-contaning proteins could be hampered by diphenyl diselenide (Fig. 5). Furthermore, diphenyl diselenide (at doses that did not inhibit δ-ALA-D) could enhance the effects of fluphenazine on the hepatic δ-ALA-D of mice (Dalla Corte et al. 2009).

The acute and chronic toxicity of organoselenium compounds has not been extensively reported in the literature. In spite of this, here, we will discuss only the findings obtained with ebselen and diphenyl diselenide and some analogues. Data about other organoselenium compounds can be found in the study by Nogueira et al. (2004) and references herein. Nozawa group has studied the toxicity of ebselen (36.5 and 365 μmol kg^{-1}) in mice after intragastric administration and reported no toxicity, when body weight and death were used as endpoints of toxicity (Nozawa et al. 1996). Otherwise, we have observed that ebselen was more toxic than diphenyl diselenide after acute intraperitoneal administration in rats (Table 1) (Meotti et al. 2003).

In contrast to diphenyl diselenide, which was more toxic for mice than for rats, ebselen showed similar acute lethal potency in rats and mice when administrated by intraperitoneal route (Meotti et al. 2003). We have also observed that diphenyl diselenide caused no mortality after acute administration by the subcutaneous (Meotti et al. 2003, Nogueira et al. 2003) or oral (Wilhelm et al. 2009a) route. In mice, the LD_{50} for diphenyl diselenide was higher than 1 mmol kg^{-1} after gastric gavage (Savegnago et al. 2007c). However, a significant reduction in the body weight gain was observed after exposure to 0.025–1 mmol kg^{-1} of diphenyl diselenide, when compared with the control group. Therefore, diphenyl diselenide was less toxic to mice when administered by the oral or subcutaneous route than by the intraperitoneal route.

After repeated subcutaneous administration to rats, diphenyl diselenide induced no toxicological effects, when the doses were lower than 100 μmol kg^{-1} (Meotti et al. 2008). However, at doses equal to or higher than this, diphenyl diselenide caused body weight loss and hepatic biochemical alteration, including δ-ALA-D inhibition (Meotti et al. 2008).

Ebselen administration to suckling rats (36.5 μmol kg^{-1}) for 21 days increased hepatic thiobarbituric acid reactive species (TBARS) and decreased NPSH (non-protein thiol groups) (Farina et al. 2004). Consequently, in a similar way to that observed with diphenyl diselenide, the toxicity of ebselen can be related to endogenous thiol depletion and can be associated with the oxidation of thiol-containing enzymes.

Moreover, diphenyl diselenide supplemented in the diet at 30 ppm, a high dose than that of required nutritionally, for 8 months caused no sign of hepatotoxicity or renotoxicity in rabbits. Despite the relative absence of gross toxicity, some biochemical alterations related to pro-oxidant activity, such as the reduction in ascorbic acid levels, was demonstrated (de Bem et al. 2006, 2007). In contrast, it was recently reported that acute intraperitoneal administration of a single low and moderate dose (5 and 50 μmol kg^{-1}, respectively) of diphenyl diselenide was associated with hepatic toxicity, whereas a single high dose of 500 μmol kg^{-1} killed 85% of the rabbits within 5 days (Straliotto et al. 2010). To study the influence of chemical structure in the diaryl diselenide toxicity, oral acute toxicity of disubstituted diaryl diselenides was evaluated in mice. The LD_{50} values for disubstituted diaryl diselenides were similar to that found for diphenyl diselenide (LD_{50} > 1 mmol kg^{-1} for $(p\text{-Cl–}C_6H_4Se)_2$, $p\text{-}(CH_3O\text{–}C_6H_4Se)_2$ and $(PhSe)_2$ and >0.62 mmol kg^{-1} for $(m\text{-}CF_3\text{–}C_6H_4Se)_2$). Therefore, we have demonstrated that the introduction of functional groups into the aryl group of diaryl diselenide did not introduce additional toxicity (Savegnago et al. 2009).

Methylselenocysteine is a monomethylated selenoamino acid that can be found in plants (Dumont et al. 2006), and it is also being considered for pharmacological approaches. To characterize methylselenocysteine toxicity, rats were exposed daily by gavage at doses of 0.5–2.0 mg kg^{-1} day^{-1} and beagle dogs received daily gavage doses of 0.15–0.6 mg kg^{-1} day^{-1} for 28 days. In rats, methylselenocysteine induced dose-related hepatomegaly, mild anemia, and thrombocytopenia. Hepatocellular degeneration, arrested spermatogenesis, and atrophy of corpora lutea were also observed. Female rats were more sensitive to methylselenocysteine toxicity than were male rats. In dogs, methylselenocysteine induced mild anemia. Although no alterations in hepatic morphology were observed in female dogs, midzonal hepatic necrosis was seen in male dogs exposed to all dose levels of methylselenocysteine (Johnson et al. 2008). In the form of selenomethionine, selenium functions as an essential micronutrient at levels of 0.1–0.2 ppm (mg kg^{-1})

in the diets of experimental animals, but it becomes toxic at levels exceeding 5 ppm (Jacobs and Frost 1981). Since plants and particularly selenium-accumulating plants can transform inorganic selenium obtained from soil into organoselenium compounds, including methylselenocysteine and selenomethionine (Dumont et al. 2006; Zhu et al. 2009), the earliest reports on selenium toxicity made by Franke and collaborators (Franke 1934a, b; Franke and Painter 1935; Painter 1941; Moxon and Rhian 1943) can be associated with an excessive ingestion of these two selenoaminoacids.

Neurotoxicity of diphenyl diselenide Although diphenyl diselenide represents a compound with relatively low toxicity, we have consistently observed that it can cause neurotoxic effects in rodents, depending on the dose, vehicle, the route of administration, and age of the animals. Accordingly, studies carried out by our research group demonstrated that exposure for 2 weeks to high doses (250 μmol kg^{-1}, subcutaneous) of diphenyl diselenide increased 3 times the total selenium content in the brains of mice (Maciel et al. 2003). Additionally, strong evidence has been accumulated indicating that diphenyl diselenide presents convulsant activity. In fact, intraperitoneal, but not subcutaneous or oral (Savegnago et al. 2007c), administration of diphenyl diselenide provoked seizures in mice (Brito et al. 2006), suggesting that the neurotoxicity of diphenyl diselenide depends on the route of administration and possibly depends on its metabolism to a neurotoxic intermediate that can be accumulated to toxic levels only in mice after intraperitoneal administration. In contrast to that observed after intraperitoneal administration of diphenyl diselenide to mice, subcutaneous injection of diselenide protected mice from the convulsant and lethal effect of 4-aminopyridine (Brito et al. 2009). Consequently, the organoselenium neurotoxic effect is related to species and the route of administration, since diphenyl diselenide administration, either intraperitoneal or subcutaneous (Nogueira et al. 2003), produced no seizure episodes in rats. In the same way, rabbits exposed to lethal doses of diphenyl diselenide did not present overt sign of neurotoxicity (Straliotto et al. 2010).

Further, in the case of alteration in the chemical structure of diphenyl diselenide, the introduction of functional groups into the aryl group of diaryl diselenide (*p*-methyldiphenyl diselenides, *p*-chlorodiphenyl diselenides, *o*-aminodiphenyl diselenides, and *m*-trifluoromethyldiphenyl diselenides) abolished the convulsive effect in mice. In the case of alkyl diselenides, the latency for onset of seizures increased as the aliphatic chain increased from 1 to 3 carbon atoms. Furthermore, dibutyl diselenide, dipentyl diselenide, and dihexyl diselenides did not induce seizures in mice (Nogueira et al. 2003).

In addition to the influence of the species considered, the neurotoxicity of diphenyl diselenide is also modified by the age of the rats. In fact, diphenyl diselenide administrated by the oral route, which causes no sign of neurotoxicity in adult rats, caused seizure in rat pups (Prigol et al. 2007). In an extension of this study, we showed a significant negative correlation between the latency for the first seizure episode and the levels of diphenyl diselenide in the brains of rat pups (Prigol et al. 2010).

Data on toxicokinetic of oral administration of diphenyl diselenideat the dose of 500 mg kg^{-1} to adult rat and mouse revealed that peak plasma diphenyl diselenide levels were 13.13 and 10.11 μg ml^{-1} (C_{max}), respectively, and occurred at 0.5 h (T_{max}) post-dosing (Prigol et al. 2009d).

Pharmacology of organoselenium compounds

The pioneering study of Schwarz and Foltz in the early 1950s provided the initial observations of that selenium, the essential part of the kidney extract from which selenium was first identified, the active organic Factor 3, prevents liver necrosis in rats fed a selenium-deficient torula yeast-based diet (Schwarz and Foltz 1957). The association between selenium and liver pathology led rapidly to the recognition that selenium is a nutritionally important trace element and the picture of selenium story started to change (Oldfield 1987; Navarro-Alarcon and Cabrera-Vique 2008), particularly after the demonstration of its molecular function in mammalian cells. The identification of selenocysteine in the active center of hepatic rat glutathione peroxidase brought to scene a new nucleophile, i.e., the selenolate. This group participates as a powerful reducing agent in antioxidant enzymes such as glutathione peroxidase and thioredoxin reductase (Flohe et al. 1973; Rotruck et al. 1973; Oh et al. 1974; Lu and Holmgren 2009; Nogueira and Rocha 2010).

Since glutathione peroxidase catalyzes the reduction of a wide variety of hydroperoxides but has some shortcomings, such as instability, poor availability, and high molecular weight, which limit its therapeutic application, considerable efforts have been made to find organoselenium compounds capable of imitating the enzymatic properties of glutathione peroxidase and free of drawbacks. In this context, several research groups have developed a number of small molecules, including substituted diselenides, N-Se heterocycles, and other type of organoselenium compounds with glutathione peroxidase-like activity (Bhabak and Mugesh 2010). Additionally, semisynthetic enzymes, obtained by enzyme engineering, have been also suggested as glutathione peroxidase-like catalytic molecules (Ren et al. 2002; Luo et al. 2003).

Antioxidant activity

Oxidative stress is the harmful condition characterized by a shift toward the pro-oxidant in the pro-oxidant/antioxidant balance in living cells. Several factors including exposure to xenobiotic, radiation, trauma, infection, air pollution, excess intake of lipids and sugar, and strenuous physical activity could favor a pro-oxidative status of the cells and, consequently, can facilitate the development of a variety of diseases. In fact, oxidative stress has been implicated in many diseases such as Alzheimer, Parkinson, myocardial infarction, atherosclerosis, and diabetes.

Organoselenium compounds, able of propagating the redox cycle of selenium, with the property of imitating the redox physiological chemistry of selenol/selenolate groups, might supplement natural cellular defenses against the oxidizing agents. Therefore, synthetic organoselenium compounds could represent a novel therapeutic target for diseases where oxidative stress plays a role (Arteel and Sies 2001). However, one of constrains in the development of organoselenium compounds is their instability, when they are in the selenol intermediate form, their poor water solubility, and the futile thiol oxidase cycle that consumes thiol without decomposing peroxide. Indeed, here two aspects must be considered: (1) an efficient and rapid interaction of a –Se–Se– bond with reduced thiols is essential for the formation of selenol intermediate molecules (RSeH); but (2) an extremely reactive selenol that could easily react with oxygen is inadequate, because a diselenide of this type could initiate a futile cycle that could consume a large quantity of endogenous thiols without decomposing peroxides. For an organoselenium compound to act as an antioxidant, it must show nucleophilicity necessary for glutathione peroxidase-like activity, free radical scavenger activity, and low toxicity. In this way, pharmacological research with organoselenium compounds has provided fascinating challenges in dose–response relationships because of its contrasting behavior that is dose dependent (Nogueira and Rocha 2010).

Glutathione peroxidase-like activity

The first organoselenium compound reported in the literature as glutathione peroxidase mimetic molecule was ebselen. Ebselen in the presence of glutathione catalyzes the reduction in a wide variety of hydroperoxides and can assist cellular defense system against so-called oxidative stress (Parnham and Kindt 1984; Wendel et al. 1984; Müller et al. 1984). The mechanism of the catalytic reduction in hydroperoxides by ebselen was proposed by Maiorino and co-workers and appeared kinetically identical to that of the enzyme reaction, a ter uni ping-pong mechanism (Maiorino et al. 1988). As demonstrated in Fig. 7, ebselen reacts with

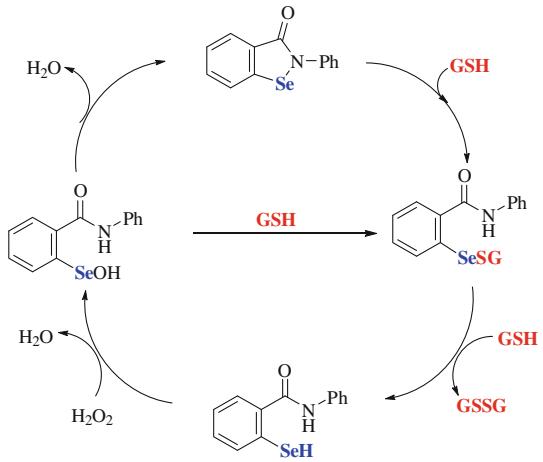

Fig. 7 The mechanism of the catalytic reduction of hydroperoxides by ebselen. Modified from Nogueira et al. (2004)

the thiols to afford a selenenyl sulfide. The selenenyl sulfide reacts with a second equivalent of GSH to yield a single product that is characterized as selenol. Finally, the selenol reacts with H_2O_2 or organic hydroperoxide to form H_2O or the respective alcohol (ROH) and ebselen selenenic acid, which spontaneously produces another molecule of H_2O and regenerates ebselen. However, it is difficult to accept that the selenenic acid intermediate of ebselen could spontaneously regenerate ebselen. It is more plausible to suppose that, in analogy to that occurs in the active center of native seleno-glutathione peroxidase, selenenic acid intermediate reacts successively with two thiol equivalents to regenerate the selenol intermediate of ebselen.

It is important to point out that contrasting to the reaction catalyzed by the enzyme, which contains binding sites conferring substrate specificity, ebselen and other organoselenium compounds can utilize a variety of thiols (Wendel et al. 1984; Müller et al. 1984; 1985; Fischer and Dereu 1987; Engman et al. 1992; Iwaoka and Tomoda 1994; Mugesh et al. 2001), in addition to GSH, as a substrate (Cotgreave et al. 1987; Maiorino et al. 1988; Haenen et al. 1990).

On the other hand, a set of points of evidence have indicated that ebselen displays relative catalyst activity in the reduction in hydroperoxides with aryl and benzylic thiols (Back and Moussa 2002, 2003; Back et al. 2004). Back has demonstrated that alkylselenenyl sulfides undergo a deactivation pathway that competes with the main catalytic cycle (Fig. 8). Thus, this figure can help explain the reduction in the catalytic property of ebselen (Back and Moussa 2003).

The fact that the glutathione peroxidase mimetic activity of ebselen depends on the reduction of the selenenic acid to selenol by thiols motivated Mugesh and collaborators to study the effect of the nature of the thiols on peroxidase

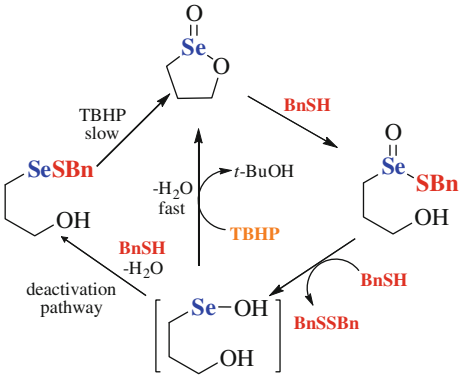

Fig. 8 Alkylselenenyl sulfides undergo a deactivation pathway that competes with the main catalytic cycle, reducing the catalyst property. Modified from Back and Moussa (2003)

activity of ebselen. The Mugesh's study was the first experimental evidence that any substituent that is capable of enhancing the nucleophilic attack of thiol at sulfur in the selenenyl sulfide intermediate would enhance the antioxidant potency of ebselen and other organoselenium compounds. It was demonstrated that the use of thiol having an intramolecular coordinating group would enhance the biological activity of ebselen. According to Fig. 9, S–N interactions modulate the attack of an incoming thiol at the sulfur atom in ebselen selenenyl sulfide (Sarma and Mugesh 2005).

In an extension of this research, Bhabak and Mugesh further revealed that the nature of the peroxide has little effect on the catalytic efficiencies, while the nature of thiols shows a dramatic effect on the catalytic activity of ebselen and its analogues (Bhabak and Mugesh 2007).

The influence of electronic and steric effects on the GPx-like activity of ebselen has been also reported. The incorporation of a substituent ortho to the selenium atom sterically hinders the attack of a nucleophile at selenium, prevents thiol exchange reactions, and promotes the production of selenol, the GPx-active form, and thus, the GPx-like activity is greatly enhanced. This study further demonstrated that the electronic nature of the substituents is less important than their steric effects to the peroxidase-like activity (Pearson and Boyd 2008).

In 2008, Sarma and Mugesh postulated a revised mechanism for the GPx-mimetic activity of ebselen. Considering the complications associated with the catalytic mechanism of ebselen and that none of the intermediates other than the selenenyl sulfides have been confirmed, a reversible cyclization pathway was demonstrated (Fig. 10). This study shows the first structural evidence that the seleninic acid, which was never proposed as an intermediate in the catalytic mechanism of ebselen, is the only stable and isolable product in the reaction of ebselen with peroxides. Cycle A shows that ebselen could be oxidized to the selenoxide derivative **a** by the reaction with hydrogen peroxide (Cycle A, step 1). In the presence of excess thiol, under physiologically relevant conditions, the Se-N bond in ebselen selenoxide **a** is readily cleaved by the thiol to produce the corresponding thiolseleninate **b** followed by the formation of selenenic acid **c** (Cycle A, step 3). The nitrogen nucleophilic attack to the selenium atom regenerates ebselen and water (Cycle A, step 4). On the other hand, the thiol group could cleave ebselen to give selenyl sulfide **d** which reacts with the thiol group and gives the ebselen selenol **e** (Cycle B, step 2). Ebselen selenol **e** could be oxidized to selenenic acid **c** (Cycle B, step 3), participating in cycle A. The disproportionation of the selenenyl sulfide **d** to produce the corresponding diselenide **f** (Cycle C, step 2) was demonstrated to be more important than the generation of selenol. Finally, the authors suggest that the regeneration of ebselen by cyclization of the selenenic acid under a variety of conditions protects the selenium moiety from irreversible inactivation (Sarma and Mugesh 2008).

The decade of the 1990s was characterized by an enormous development in the field of small synthetic organoselenium compounds that mimic glutathione peroxidase catalytic activity, such as benzoselenazinones (Jacquemin et al. 1992), benzoselenazolinones (Galet et al. 1994), camphor-derived selenenamide (Back and Dick 1997), 2-phenylselenenyl-naphthol (Engman et al. 1995), alfa-(phenylseleny)ketones (Engman et al. 1994), and oxygen-containing diselenides (Wirth 1998).

Moreover, a number of attempts have been made to design and synthesize ebselen-related GPx mimics based on substituent effects or isosteric replacements, most of them met with limited success. Ebselen derivatives, benzisochalcogenazolones, contain intramolecular interactions as Se-O increased the catalytic activity of ebselen. For instance, benzisoselenazolones *N*-alkyl substituted were more active than ebselen. However, benzisoselenazolone *N*-phenyl substituted showed lower peroxidase activity than ebselen, which could be attributed to its poor solubility.

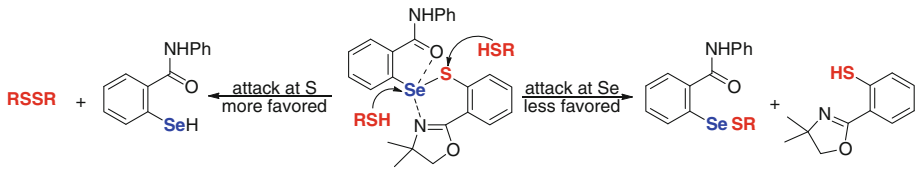

Fig. 9 The attack of an incoming thiol at the sulfur atom in ebselen selenenyl sulfide is modulated by S–N interactions. Modified from Sarma and Mugesh (2005)

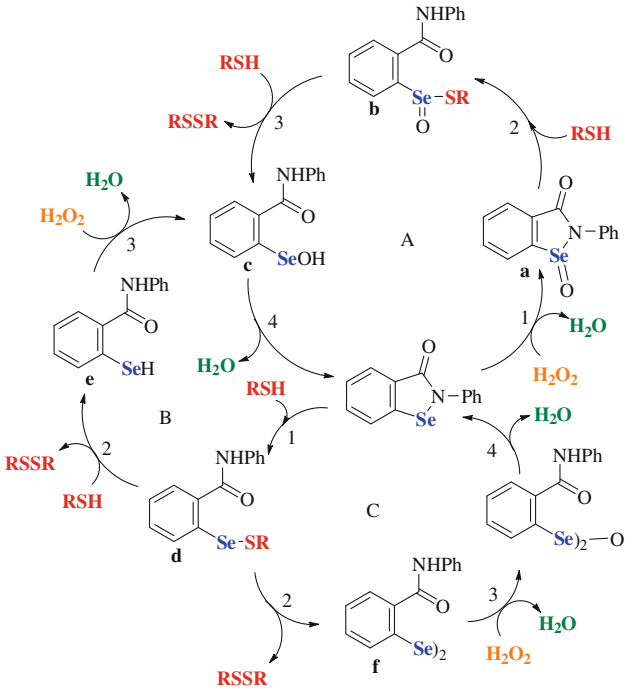

Fig. 10 A revised mechanism for the GPx-mimetic activity of ebselen proposed by Sarma and Mugesh (2008). *Cycle A* shows that ebselen could be oxidized to the selenoxide derivative **a** by the reaction with hydrogen peroxide (*Cycle A*, step 1). In the presence of excess thiol, the Se-N bond in the ebselen selenoxide **a** is readily cleaved by the thiol to produce the corresponding thiolseleninate **b** followed by the formation of selenenic acid **c** (*Cycle A*, step 3). The nitrogen nucleophilic attack to the selenium atom regenerates ebselen and water (*Cycle A*, step 4). The thiol group could cleave ebselen to give selenyl sulfide **d** which reacts with the thiol group and gives the ebselen selenol **e** (*Cycle B*, step 2). Ebselen selenol **e** could be oxidized to selenenic acid **c** (*Cycle B*, step 3), participating in *cycle A*. The disproportionation of the selenenyl sulfide **d** produces the corresponding diselenide **f** (*Cycle C*, step 2)

Following the rule that reactivity toward hydroperoxides increases as one descends the chalcogen group, benzisotellurazolone was 1.5 times more active than the selenium analogue (Zade et al. 2004).

In this context, it has been reported that the synergistic effect of selenium and pyrroline substituents greatly enhances the GPx-like activity of ebselen (Kalai et al. 2005).

Attempts have been made to improve the water solubility of organochalcogen compounds. Thus, organochalcogens with an *o*-hydroxy function in close proximity to the selenium atom have been tested as glutathione peroxidase mimetic. The results demonstrated that hydroxybenzyl diselenide and cyclic seleninate ester were more efficient catalysts in comparison with ebselen and have comparable activity to that of aliphatic seleninate ester. Allyl and hydroxybenzyl selenides have a poor GPx-like activity. A spirocyclic compound, containing selenium in oxidation state IV, was less active than the cyclic seleninate ester. It is important to point out that although the introduction of an *o*-hydroxy function close to the selenium atom of diselenides improved the GPx-like activity, in the case of selenides, the enhancement of catalytic activity was not observed (Tripathi et al. 2005).

Additionally, the GPx-like activity of tertiary- and secondary-amide-substituted diaryl diselenides has been investigated. Thus, tertiary-amide-substituted diselenides showed higher activity than the corresponding secondary-amine-based compounds (Bhabak and Mugesh 2009a). The authors also showed that different catalytic mechanisms may account for the lower GPx-mimetic activity of the secondary-amine-based compounds as compared to that of the tert-amide-substituted diselenides (Bhabak and Mugesh 2008).

A series of *sec*-amine-substituted diselenides were reported as GPx-mimetic compounds. *N*-methyl derivative and *N*-alkyl-based compounds were significantly more active than the corresponding *N*,*N*-dimethyl derivative and *N*,*N*-dialkyl derivatives. The replacement of the *tert*-amino groups in *N*,*N*-dialkyl benzylamine-based diselenides by *sec*-amine moieties increased the GPx-like activity, for generating the catalytically active selenols. Taken together, the authors concluded that the absence of thiol exchange reactions in the selenenyl sulfides may account for the highest catalytic activity of *sec*-amine-based diselenides (Bhabak and Mugesh 2009b).

Recently, a series of chiral amino acid derivatives containing selenium were investigated with respect to their GPx-mimetic activity. Thereupon, concluding that diselenides derived from L-phenylalanine, containing carbon chains with three and four atoms, exhibited higher peroxidase catalytic activity than diphenyl diselenide. By contrast, diselenide containing a short chain length, one carbon atom, was a poor catalyst. It was clearly demonstrated that the increase in the chain length between the selenium atom and the carbonyl group of the amino acid increases the GPx catalytic activity (Alberto et al. 2009).

Furthermore, a previous study from our laboratory indicated that *p*-chlorodiphenyl diselenide, diphenyl diselenide, and diethyl diselenide were more catalytic than ebselen. Diselenides, *p*-aminodiphenyl diselenide, and dibutyl diselenide had poor GPx-like activity, while *p*-methoxyldiphenyl diselenide and dipropyl diselenide had no effect (Meotti et al. 2004; Wilson et al. 1989). Additionally, we have demonstrated that dicholesteroyl diselenide, which has a bulky organic moiety, markedly decreased GPx-like activity when compared with diphenyl diselenide (Kade et al. 2008).

Dihydro quinoline, an antioxidant used to protect polyunsaturated fatty acids in fishmeal and various animal feeds (de Koning 2002), has been used as prototype drug to

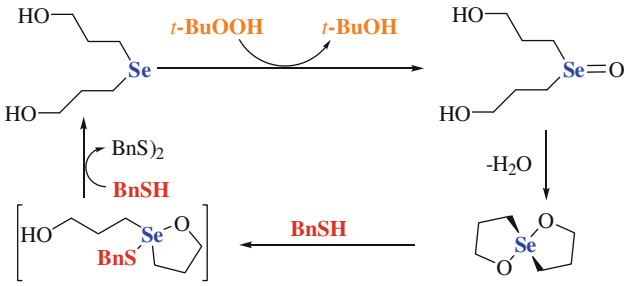

Fig. 11 The mechanism for peroxidase catalytic activity of di(3-hydroxypropyl) selenide is distinct from that employed by GPx enzyme and involves a spirodioxaselenanonane, as an intermediate. Modified from Back et al. (2004)

synthesize selenide analogues with the perspective to obtain GPx-mimetic compounds. Ethylseleno analogue was more catalytic than diphenyl diselenide, while phenylseleno analogue had peroxidase activity similar to diphenyl diselenide, a reference compound in this study. The corresponding telluro analogues were the most efficient catalysts (Kumar et al. 2007).

Allyl 3-hydroxypropyl selenide after a series of oxidation and [2,3] sigmatropic rearrangement steps in situ generated the corresponding cyclic seleninate, which has higher GPx-mimetic activity than ebselen. Results from Bach group reflect that O–Se compounds can be even more effective catalysts than the more widely studied N–Se analogues (Back and Moussa 2002, 2003). The exceptional GPx-mimetic activity of di(3-hydroxypropyl) selenide was also reported by Back and collaborators. Of particular importance, the mechanism for peroxidase catalytic activity of di(3-hydroxypropyl) selenide is distinct from that employed by GPx enzyme and by many of its small-molecule mimetics and involves a spirodioxaselenanonane, as an intermediate (Fig. 11) (Back et al. 2004).

GPx-like catalytic activity of *trans*-3,4-dihydroxyselenolane, a water-soluble cyclic selenide, was reported. Cyclic selenide exhibited higher GPx-mimetic catalytic activity than linear analogue. The increased catalytic activity is attributed to the cyclic structure, which elevates the highest occupied molecular orbital (HOMO) energy level and makes the selenium atom more exposed to the surroundings (Kumakura et al. 2010).

Lipid peroxidation and radical-scavenging activity

In the last two decades, the antioxidant activity of ebselen (Hermenegildo et al. 1990; Gustafson and Pritsos 1991; Pritsos et al. 1992; Geiger et al. 1993; Miyazawa et al. 1993; Christison et al. 1994; Li et al. 2000; Rossato et al. 2002a; Tiano et al. 2003) and other organoselenium compounds (Andersson et al. 1994; Ostrovidov et al. 2000; Rossato et al. 2002b; Meotti et al. 2004) has been reported in different experimental models. A number of studies emphasize that organoselenium compounds can effectively scavenge and eliminate reactive oxygen species.

A series of newly synthesized analogues of ebselen (2-(5-chloro-2-pyridyl)-7-azabenzisoselenazol-3(2*H*)-one, 2-phenyl-7-azabenzisoselenazol-3(2*H*)-one, 2-(pyridyl)-7-azabenzisoselenazol-3(2*H*)-one, 7-azabenzisoselenazol-3(2*H*)-one, and bis(2-aminophenyl) diselenide) were screened for antioxidant activity in human blood platelets. Among these compounds, only bis(2-aminophenyl) diselenide inhibited lipid peroxidation and this antioxidant effect was higher than that of ebselen. Bis(2-aminophenyl) diselenide was also effective in preventing the generation of oxidized low-molecular-weight thiols (GSH, cysteine CSH, cysteinylglycine CGSH) in platelets (Saluk-Juszczak et al. 2006).

Ebselen and its related derivatives were investigated on horseradish peroxidase (HRP) activity as well as on the antioxidant activity in terms of GPx-like, oxygen singlet, and lipid peroxidation. a good negative correlation between GPx-like and the HRP activities of ebselen and its tellurium derivative has been demonstrated. By contrast, Se-methyl and Se-benzyl derivatives of ebselen showed GPx-mimetic activity but did not inhibit HRP activity. As discussed in the above section, the GPx-mimetic activity of organoselenium compounds not only depends on the reactivity of the selenol intermediates toward hydrogen peroxide but also depends on the reactivity of the selenenyl sulfide intermediates toward thiols. Since in the Mugesh's study there was no addition of thiol in the HRP assay, the reactivity of ebselen and its tellurium derivative toward hydrogen peroxide may account for their inhibitory action in the HRP activity. Moreover, ebselen was the most potent in protecting against γ-radiation-induced lipid peroxidation, while ebselen diselenide was the least effective (Mishra et al. 2006).

A simple, stable, and water-soluble diselenide derivative of selenocystine, 3,3′-diselenodipropionic acid, was examined for in vitro antioxidant activity, free radical reactions, GPx-mimetic activity, and cytotoxicity. 3,3′-Diselenodipropionic acid and ebselen were equally effective in protecting red blood cells from hemolysis. 3,3′-Diselenodipropionic acid was an excellent scavenger of peroxyl radicals and showed GPx-like activity with higher substrate specificity toward peroxides than toward thiols. Although the peroxidase catalytic activity of ebselen is much higher than that of 3,3′-diselenodipropionic acid, the diselenide of selenocystine is a non-toxic water-soluble molecule that could be used as a model for the synthesis of more active and potent selenium antioxidants (Kunwar et al. 2007).

Simple diaryl diselenides have been screened for in vitro antioxidant activity (Meotti et al. 2004). Thereupon, concluding that diaryl diselenides, diphenyl diselenide and *p*-chlorodiphenyl diselenide, and dialkyl diselenides

such as diethyl, dipropyl, and dibutyl diselenides, were the most potent antioxidants in the brain homogenate of mouse in vitro (Meotti et al. 2004). Although there are few published studies on molecular mechanisms involved in diphenyl diselenide antioxidant property, diphenyl diselenide is generally thought to exert its antioxidant action by mimicking glutathione peroxidase. It is possible to hypothesize that the formation of stable selenolate ions increases the reducing property of this molecule and its antioxidant property. Therefore, the effect of pH on GPx-mimetic activity and other possible mechanisms involved in the diphenyl diselenide antioxidant activity were investigated. On the one hand, diphenyl diselenide had neither free radical-scavenging nor Fe^{2+}-chelating ability. However, diphenyl diselenide exhibited increasing ability to reduce Fe^{3+} with increasing pH. On the other hand, the GPx-like activity of diphenyl diselenide was maximum at physiological pH and totally abolished in the acidic medium. Furthermore, irrespective of the pH of the medium, diphenyl diselenide significantly inhibited both deoxyribose degradation under hydrogen peroxide and Fe^{2+} assault as well as lipid peroxidation; suggesting that the antioxidant mechanism of diphenyl diselenide in the acidic medium may not be related to its generally accepted GPx-mimetic activity (Ogunmoyole et al. 2009; Hassan et al. 2009a, b, c, d).

In support to the in vitro evidence of diphenyl diselenide antioxidant activity, a number of studies revealing its antioxidant action in different models of oxidative stress in brain, kidney, and liver of rodents and platelets of humans have been reported (Posser et al. 2006; Puntel et al. 2007; Luchese et al. 2007, 2009a, b; Kade et al. 2009c; Dalla Corte et al. 2009; Prigol et al. 2009c). In this context, the antioxidative property of disubstituted diaryl diselenides has been also demonstrated. From experiments with diphenyl diselenide, *m*-trifluoromethyldiphenyl diselenide, *p*-chlorodiphenyl diselenide, and *p*-methoxyldiphenyl diselenide, it was possible to conclude that all diselenides were able to protect against oxidative damage caused by sodium nitroprusside in the brains of mice (Prigol et al. 2009b).

Further, a series of alkynylselenoalcohols were screened for in vitro antioxidant activity. The results revealed that the antioxidant activity of selenides depends on their chemical structures. For instance, alkynylselenide containing a butyl group bonded to the selenium atom showed better antioxidant profile than alkynylselenoalcohol with a hydroxypropyl group. The substitution of phenyl for butyl group in alkynylselenoalcohol did not modify the effect of the former compound on lipid oxidation. Alkynylselenide containing a butyl group bonded to the selenium atom showed DPPH radical-scavenging activity. Alkynylselenoalcohol having a hydroxypropyl group and its tellurium analogue inhibited isocitrate-mediated oxidation of Fe^{2+} (Acker et al. 2009a).

Peroxynitrite scavenging activity

In addition to the recognized efficiency of organoselenium compounds in reacting with hydroperoxides, an increasing amount of evidence shows that ebselen and other organoselenium compounds can also protect against peroxynitrite, a potent inflammatory mediator (Sies et al. 1998; Woznichak et al. 2000; Masumoto and Sies 1996; Masumoto et al. 1996; Roussyn et al. 1996; Filipovska et al. 2005).

In fact, peroxynitrite ($ONOO^-$) is a strong oxidizing and nitrating agent that is produced by the diffusion-limited reaction of nitric oxide and superoxide anion. The formation of peroxynitrite may be beneficial in inflammatory reactions in terms of an oxidative destruction of intruding microorganisms. Higher concentrations and an uncontrolled generation of peroxynitrite, however, may result in an unwanted oxidation and the consecutive destruction of host cellular constituents.

Taking this into account, ebselen reacts with peroxynitrite efficiently, exhibiting one of the highest second-order rate constants for a low-molecular-weight compound (Masumoto and Sies 1996).

The mechanism proposed to explain the catalytic reduction of peroxynitrite by ebselen, in analogy with the glutathione peroxidase catalytic cycle, is depicted in Fig. 12. According to Fig. 12, ebselen acts catalytically in reducing peroxynitrite to nitrite, giving the ebselen selenoxide, as the sole selenium-containing product at 1:1 stoichiometry (Masumoto et al. 1996), followed by the reduction of this selenoxide back to ebselen in two consecutive one-electron reduction steps via the selenodisulfide, utilizing reducing equivalents in the form of glutathione. Ebselen selenoxide can also be reduced by the mammalian selenoprotein thioredoxin reductase at the expense of NADPH (Arteel et al. 1999).

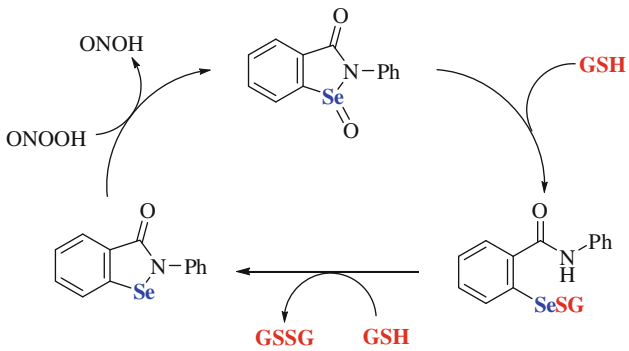

Fig. 12 Peroxynitrite is an oxidizing and nitrating agent and may result in an unwanted oxidation and the consecutive destruction of host cellular constituents. Modified from Masumoto et al. (1996)

Diaryl diselenides, diphenyl diselenide and *p*-chlorodiphenyl diselenide, and ebselen were reported as inhibitors of lipid peroxidation induced by sodium nitroprusside, a NO and ferricyanide generator, which is a redox-active compound (Rossato et al. 2002b). The results clearly demonstrated that ebselen was more effective than diselenides in scavenging NO generated by lipid peroxidation. Thus, further studies are necessary to establish whether diselenides can react directly with NO in addition to NOO^- or whether the antioxidant effects of these organoselenium compounds against sodium nitroprusside-induced lipid peroxidation are mediated by an interaction with lipids from brain and not related to NO itself.

Evidence has been found to suggest that organoselenides are able to catalytically reduce peroxynitrite. Phenylaminoethyl selenides protected plasmid DNA from peroxynitrite-mediated damage by scavenging this powerful cellular oxidant. The protective effect of phenylaminoethyl selenide was potentiated by GSH-mediated redox cycling of selenium forming phenylaminoethyl selenoxide as the sole selenium-containing product (Fig. 13) (De Silva et al. 2004).

The in vitro effect of bis(2-aminophenyl)-diselenide was compared with ebselen on the level of carbonyl group formation, tyrosine nitration, and lipid peroxidation induced by peroxynitrite in plasma. From this study, a similar protective effect of bis(2-aminophenyl)-diselenide and ebselen against peroxynitrite-induced oxidative/nitrative damage to human plasma proteins and lipids was revealed (Nowak et al. 2006).

The protection against peroxynitrite-mediated nitration reaction by diorganoselenides has been investigated. The data presented by the authors clearly demonstrated that selenides, having basic amino groups with weak intramolecular Se-N–C single bond interaction, were more active than the selenides having imino groups with strong Se-N–C double bond

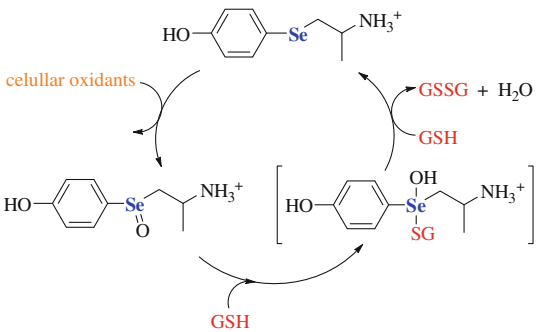

Fig. 13 The mechanism proposed to explain the catalytic reduction of peroxynitrite by phenylaminoethyl selenide. Phenylaminoethyl selenide acts catalytically in reducing peroxynitrite to nitrite, giving the phenylaminoethyl selenoxide, followed by the reduction of this selenoxide back to phenylaminoethyl selenide in two consecutive one-electron reduction steps via the selenodisulfide, utilizing reducing equivalents in the form of glutathione. Modified from De Silva et al. (2004)

interaction against peroxynitrite-mediated nitration reactions. The selenoxides of diorganoselenides, which can be reduced back to selenides, showed better protective action in the peroxynitrite assay than diorganoselenides. Intramolecularly, coordinated diaryl selenoxides, aryl benzyl selenoxides, and aryl alkyl selenoxide, lacking a β-hydrogen, did not undergo any selenoxide elimination reaction (Kumar et al. 2006).

Selenomethionine protects against peroxynitrite (NO_3^-) more effectively than methionine, the sulfur analogue (Briviba et al. 1996). This selectivity is attributed to a more easily oxidation of the selenium than sulfur atom. The oxidized selenomethionine is effectively reduced to selenomethionine by GSH, which involves the formation of a transient species of Se-N important for the reduction process (Fig. 14) (Assmann et al. 1998, 2000).

Organoselenium compounds can be substrates of mammalian thioredoxin reductase

The mammalian selenium-containing protein thioredoxin reductases have wide range of substrate specificity (Holmgren 1985), reducing not only different thioredoxins but also sodium selenite (Kumar et al. 1992), selenodiglutathione (Björnstedt et al. 1992), selenocystine (Björnstedt et al. 1997), selenenyl iodides (Mugesh et al. 2002, 2003), ebselen (Sies and Masumoto 1997; Zhao and Holmgren 2002; Zhao et al. 2002; Lu et al. 2009), diphenyl diselenide, and some analogues (Freitas et al. 2010). Thiredoxin reductase can reduce the selenenyl sulfide complex of serum albumin–ebselen and release free ebselen (Arteel et al. 1999).

Strong evidence from the Zhao group indicates that the antioxidant and other pharmacological properties of ebselen are, to a large extent, due to its reactions with the thioredoxin system (Zhao and Holmgren 2002). The thioredoxin system consists of NADPH, thioredoxin (Trx), and thioredoxin reductase (TrxR). Thioredoxin reductase is a dimeric FAD-containing enzyme that catalyzes the NADPH-dependent reduction of the active-site disulfide in oxidized thioredoxin to give a dithiol in reduced thioredoxin ($Trx(SH_2)$) (Tapiero et al. 2003).

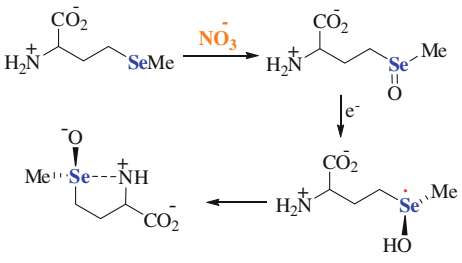

Fig. 14 Selenomethionine protects against peroxynitrite. The oxidized selenomethionine is effectively reduced to selenomethionine by GSH, which involves the formation of a transient species of Se–N. Modified from Assmann et al. (2000)

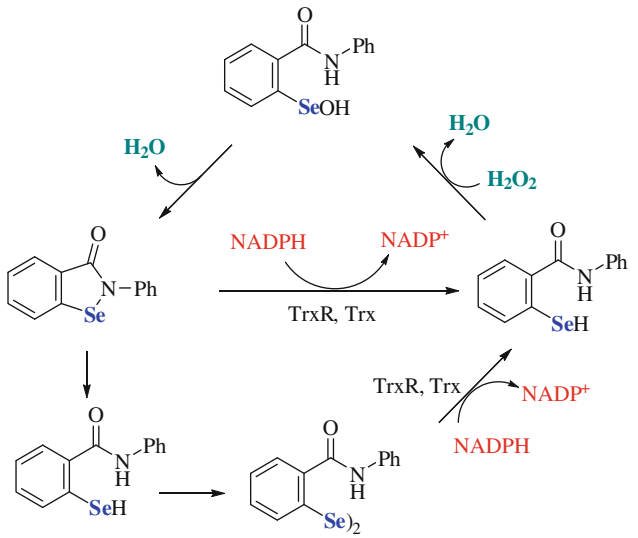

Fig. 15 The peroxiredoxin mimic activity of ebselen. Ebselen can be rapidly reduced by both TrxR in the presence of NADPH or by reduced Trx to form the ebselen selenol, which reacts with hydroperoxide yielding an ebselen selenenic acid derivative. Ebselen selenol can also undergo a rapidly oxidation to form the ebselen diselenide that acts as a substrate for the mammalian TrxR, forming the active selenol as a final product. Modified from Nogueira et al. (2004)

According to Fig. 15, ebselen is a highly efficient peroxiredoxin mimic catalyzing the hydroperoxide reduction by the mammalian Trx system. Ebselen can be rapidly reduced both by TrxR in the presence of NADPH or by reduced Trx to form the ebselen selenol, which reacts with hydroperoxide yielding an ebselen selenenic acid derivative. Ebselen selenol can also undergo a rapidly oxidation to form the ebselen diselenide that acts as a substrate for the mammalian TrxR, forming the active selenol as a final product (Zhao and Holmgren 2002; Zhao et al. 2002). Recently, it was also demonstrated that diphenyl diselenide and some of its analogues 4,4′-bistrifluoromethyldiphenyl diselenide, 4,4′-bismethoxydiphenyl diselenide, and 4,4′-bischlorodiphenyl diselenide could also be substrates for rat hepatic TrxR. Of particular pharmacological significance, diphenyl diselenide and 4,4′-bischlorodiphenyl diselenide were reduced more efficiently by the hepatic TrxR than ebselen (Freitas et al. 2010). In this study, a dissociation between two pathways for peroxide degradation was also observed (either via substrate for TrxR or as a mimic of GPx) for some of the studied disubstituted diphenyl diselenide. For instance, bismethoxydiphenyl diselenide had no GPx activity and was a good substrate for reduction by TrxR, whereas bistrifluoromethyldiphenyl diselenide had a good GPx activity and was a relative weak substrate for reduction by TrxR (Freitas et al. 2010).

The mammalian thioredoxin system is a dehydroascorbic acid (DHA) reductase recycling ascorbic acid essential for cell functions (May et al. 1997). In a similar way, ebselen and ebselen diselenide have been reported as able to recycle ascorbic acid. There has been revealed that in the presence of ebselen, the mammalian TrxR and Trx rapidly form ebselen selenol, which efficiently reduces dehydroascorbic acid in view of the high nucleophilicity and leaving character of the arylselenolate moiety (Fig. 16) (Jung et al. 2002; Zhao and Holmgren 2004).

The mimetic activity of tocopherol-quinone reductase has been also attributed to ebselen. Holmgren and collaborators have clearly shown that alphatocopherol-quinone can be reduced by ebselen in the presence of TrxR and NADPH. According to the mechanism depicted in Fig. 17, ebselen gives ebselen selenol that partly dissociates in pH 7.5 forming the selenolate anion. The selenolate anion, a high nucleophilic species, attacks tocopherol-quinone effectively, and the better leaving character of organoselenium group produces tocopherol hydroquinone, regenerating ebselen. Therefore, tocopherol-quinone reductase mimetic activity could help explain the effects of ebselen as an antioxidant in vivo (Fang et al. 2005).

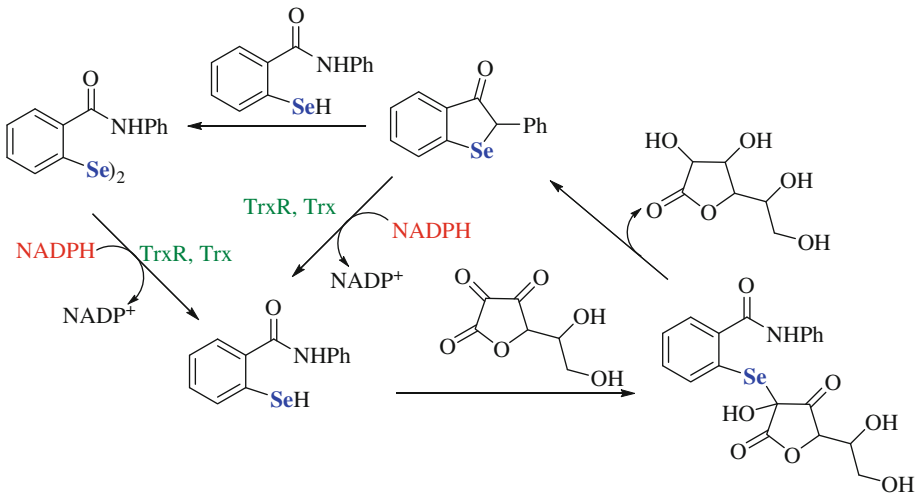

Fig. 16 The dehydroascorbic acid (DHA) reductase activity of ebselen. Ebselen in the presence of the mammalian TrxR and Trx reduces dehydroascorbic acid. Modified from Zhao and Holmgren (2004)

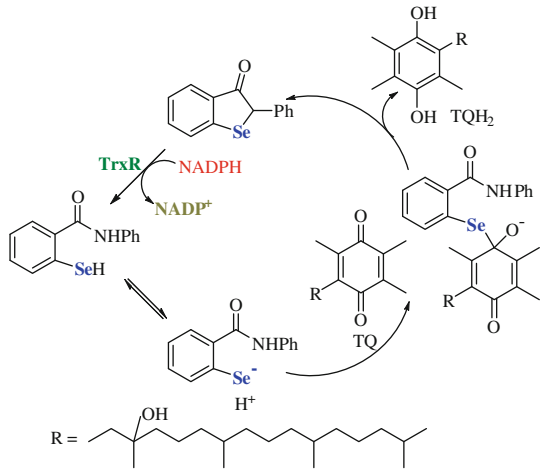

Fig. 17 The mimetic activity of tocopherol-quinone reductase of ebselen. Ebselen gives ebselen selenol which partly dissociates in pH 7.5 forming the selenolate anion. The selenolate anion attacks tocopherol-quinone (*TQ*) effectively and produces tocopherol hydroquinone (TQH_2), regenerating ebselen. TrxR (thioredoxin reductase). Modified from Fang et al. (2005)

In addition to the catalytic mimetic activities, ebselen is capable of potently inducing the cysteine-target oxidation of cellular proteins. Sakurai and his colleagues elegantly showed the ebselen electrophilic potential of mediating the formation of selenenyl sulfide and intra- and intermolecular disulfide linkages within Trx, a representative redox-active protein. By taking advantage of ebselen antioxidant and eletrophilic property, a translational modification of Kelch-like ECH-associated protein 1 (Keap 1), an electrophile sensor protein, which represses the ability of the transcription factor NF-E2-related factor 2(Nrf2) upon induction of the phase 2 detoxification response, was demonstrated (Sakurai et al. 2006). Previously, the increase in ebselen antioxidant activity or indirect induction of cellular antioxidant defenses by inducing Nrf-2 transcription was reported in cell line culture (Tamasi et al. 2004).

Even though data regarding the dehydroascorbic acid (DHA) reductase mimetic activity of simple diaryl diselenides and selenides are yet scarce in the literature, the DHA reductase-like activity of diphenyl diselenide was reported by our research group (Luchese and Nogueira 2010). We proposed the mechanism shown in Fig. 18 to explain the DHA reductase-like activity of diphenyl diselenide. In this proposed mechanism, diphenyl diselenide is reduced to its selenol form, phenylselenol, at the expense of GSH, giving the oxidized form, glutathione disulfide, GSSG. Phenylselenol reacts with DHA to generate phenylseleno-hemiketal, which reacts with another molecule of GSH to release ascorbic acid and the intermediate, phenylseleno-glutathione sulfide. Finally, phenylseleno-glutathione sulfide reacts with another GSH to regenerate diphenyl diselenide and GSSG. Based on the stoichiometry of the reaction and the detection of diphenyl diselenide after DHA reductase-like assay, we suggest that this is a catalytic cycle (Luchese and Nogueira 2010).

Anti-inflammatory and antinociceptive activities

Oxidants play a significant role in causing oxidative stress, which has been implicated in the pathogenesis of a wide range of human disorders, particularly in inflammatory disorders (Emerit et al. 2004; Wang et al. 2004; Gill et al. 2010). Thus, enormous efforts have been made to search scavengers and inhibitors of reactive oxygen species with low toxicity. One of the approaches taken in this search has been to investigate synthetic organoselenium compounds

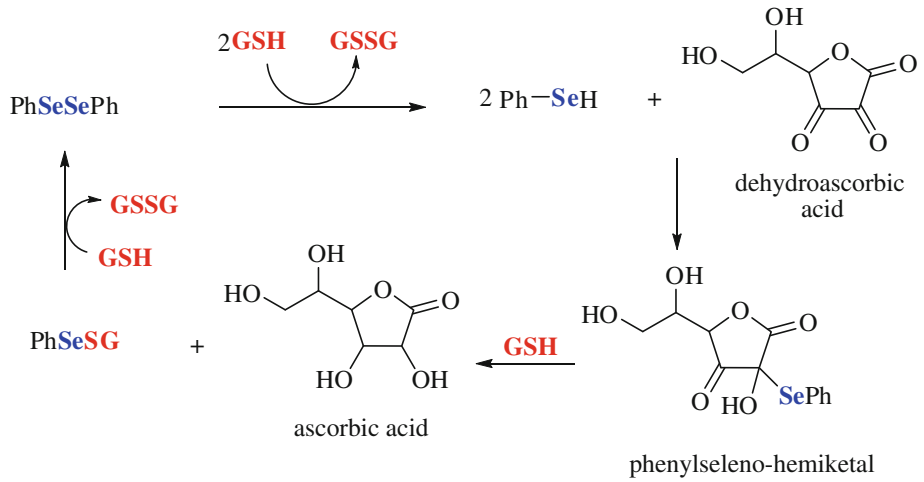

Fig. 18 The dehydroascorbic acid (*DHA*) reductase activity of of diphenyl diselenide. Diphenyl diselenide is reduced to phenylselenol, at the expense of GSH, giving the oxidized form, glutathione disulfide, GSSG. Phenylselenol reacts with DHA to generate phenylseleno-hemiketal, which reacts with another molecule of GSH to release ascorbic acid and the intermediate, phenylseleno-glutathione sulfide. Phenylseleno-glutathione sulfide reacts with another GSH to regenerate diphenyl diselenide and GSSG. Modified from Luchese and Nogueira (2010)

Table 2 Anti-inflammatory effect of ebselen in different experimental models

Experimental model	Animal species	Reference
Cobra venom paw edema	Rats	Jozsef and Filep (2003)
Glucose oxidase-induced monoarthritis	Mice	Schalkwijk et al. (1986)
H_2O_2-induced foot pad edema	Rats	Griffiths et al. (1992)
Alveolitis and bronchiolits	Rats	Cotgreave et al. (1988)
Allergic neuritis	Rats	Hartung et al. (1986)
Airway inflammation	Guinea pigs	Zhang et al. (2002)
Compound 48/80-induced histamine release	Rats	Tchoumkeu-Nzouessa and Rebel (1998)
Lung-transplanted	Rats	Hamacher et al. (2009)

Table 3 Anti-inflammatory effect of diselenides against carrageenin-induced paw edema in rats

Diselenides	Maximal inhibition (%)	Dose (mg kg^{-1})	Reference
2-Amine-5acetyl diaryl diselenide	45	3	Galet et al. (1994)
Diphenyl diselenide	63	100	Nogueira et al. (2003)
p-Chloro-diphenyl diselenide	37	100	Nogueira et al. (2003)
p-Methyl-diphenyl diselenide	10	100	Nogueira et al. (2003)

Table 4 The half maximal inhibitory concentration (IC_{50}) of diaryl diselenides against nitric oxide production in lipopolysaccharide-activated macrophage cells

Diselenides[a]	IC_{50} (μM)
Bis(2-hydroxyphenyl) diselenide	7.9
Bis(3-hydroxyphenyl) diselenide	5.0
Bis(4-hydroxyphenyl) diselenide	5.3
Dipyridyl diselenide	15.9

[a] Kyung-Min et al. (2009)

that may be therapeutically beneficial in the treatment of inflammatory diseases. The anti-inflammatory activity of organoselenium compounds was previously reviewed elsewhere (Nogueira et al. 2004; Nogueira and Rocha 2010).

In this way, ebselen and other organoselenium compounds able to mimic the GPx activity have been shown to be efficient anti-inflammatory agents in a variety of in vitro (Parnham and Kindt 1984; Kuhl et al. 1986; Ichikawa et al. 1987; Leurs et al. 1989; Cotgreave et al. 1989; Issekutz and Lopes 1992; Patrick et al. 1993; Aruoma 1997) and in vivo models of inflammation. Table 2 illustrates a wide range of experimental models in which ebselen was demonstrated to be an effective anti-inflammatory agent in different species.

The anti-inflammatory effects of ebselen can be partially mediated by its selenol intermediate via the modulation of the peroxide tonus or via inhibition of the pro-inflammatory enzymes, 5- and 15-lipoxygenases, even in the absence of GSH (Schewe et al. 1994). Moreover, an investigation into the molecular mechanisms by which ebselen and methylselenocysteine may affect the inflammatory response demonstrates that both attenuate $ONOO^-$-mediated nuclear accumulation of the transcription factors $NF\text{-}_kB$ and activator protein (AP-1) and suppress IL-8 gene expression and production in human leukocytes (Jozsef and Filep 2003).

The inhibitory effect of ebselen on ATP and ADP hydrolysis in the platelets of rats was also reported and may represent an important approach for the use of ebselen as an anti-inflammatory agent (Fürstenau et al. 2004). However, the inhibition of nucleotides hydrolysis was obtained only at non-pharmacological concentration of ebselen (about 500 μM).

The screening of anti-inflammatory activity of simple disubstituted diaryl diselenides revealed that they are effective compounds against carrageenin-induced paw edema in rats (Table 3). It is interesting to note that 2-amine-5-acetyl diaryl diselenide has an anti-inflammatory activity at a very low dose and that the substitution of the diaryl diselenide molecule with an electron-withdrawing (chloro) or an electron-donating (methyl) group reduced considerably the anti-inflammatory action of a non-substituted diaryl diselenide, diphenyl diselenide (Table 3).

Diaryl diselenides substituted with a hydroxyl group have been found to be potential anti-inflammatory compounds in an in vitro model of inflammation (Shen et al. 2004). As a result, bis(3-hydroxyphenyl) diselenide was demonstrated to be the most potent of diselenides against nitric oxide production in lipopolysaccharide-activated macrophage cells (Table 4). Dipyridyl diselenide was less potent than all other diselenides tested (Table 4).

Kyung-Min et al. (2009) reported that bis(3-hydroxyphenyl) diselenide acts at the transcriptional level by blocking nuclear factor ($NF\text{-}_KB$) activation in RAW 264.7 macrophages.

2-Alkylselenyl benzoic acid derivatives and *p*-alkylselenobenzamides have been screened as anti-inflammatory agents on granuloma induced by subcutaneous implantation of cotton pellets in rats. Thus, it was found that 2-alkylselenyl benzoic acid derivatives decreased the inflammatory process, while selected alkylselenobenzamides did not have anti-inflammatory activity (Martinez-Ramos et al. 2008).

Antinociceptive activity

Diphenyl diselenide administered by both subcutaneous and oral routes was demonstrated to be an antinociceptive

Table 5 Minimal effective dose of subcutaneously ebselen and diphenyl diselenide administered in mice in different experimental models of nociception

Experimental model	Ebselen (mg kg^{-1})	Diphenyl diselenide (mg kg^{-1})
Formalin		
First phase	Non-effective[a]	5
Second phase	10	5
Capsaicin	100	10
Acetic acid	100	5
Tail-flick	Non-effective[a]	50

[a] Doses tested up to 100 mg/kg

compound, due to its effective action on experimental models such as tail-flick, formalin, acetic acid-induced abdominal writhing, and capsaicin (Nogueira et al. 2003; Savegnago et al. 2008c). Interestingly, at subcutaneous route, diphenyl diselenide was more effective than ebselen (Table 5) (Nogueira et al. 2003).

Investigating the mechanisms by which diphenyl diselenide elicits its antinociceptive action in the formalin test, the participation of NO/cyclic GMP/Ca^{2+} and K^+ channel pathways (Savegnago et al. 2008c) and 5-HT_3 receptor (Zasso et al. 2005) was demonstrated.

Diphenyl diselenide and ebselen have a significant antinociceptive local action in the late phase of the formalin test (Zasso et al. 2005). Additionally, intraplantar administration of diphenyl diselenide produced an antinociceptive effect when co-injected with glutamate in mice (Savegnago et al. 2007c). In contrast, ebselen produced nociceptive behavior and had a synergistic effect with glutamate. The pronociceptive effect of ebselen was blocked by buthionine-sulphoximine (BSO), a reduced glutathione (GSH)-depleting agent (Meotti et al. 2009).

Considering the reported findings on diphenyl diselenide's anti-inflammatory and antinociceptive actions, this compound was investigated as a candidate for relieving neuropathic and inflammatory pain as well as acute thermal hyperalgesia. Oral administration of diphenyl diselenide inhibited tactile allodynia induced by persistent models of pain: sciatic nerve partial constriction and chemical CFA-induced inflammation in mice (Savegnago et al. 2007a).

The evidence that the antinociceptive action of diphenyl diselenide depends on its selective interaction with NMDA receptor was reinforced by the demonstration that diphenyl diselenide prevents glutamate and NMDA-induced biting response. The interaction with vanilloid and peptidergic receptors as well as with pro-inflammatory cytokines has also been demonstrated (Savegnago et al. 2007d).

In an attempt to understand the mechanisms behind diphenyl diselenide antinociceptive action in a thermal model of nociception, this organoselenium compound was evaluated in the hot-plate test. Therefore, A_{2B} receptors were demonstrated to be involved in the antinociceptive effect caused by diphenyl diselenide in the hot-plate in mice (Savegnago et al. 2008a).

The substitution of an H at the aryl group of diaryl diselenide by an electron-donating substituent did not alter the pharmacological action of *p*-methoxydiphenyl diselenide when compared with diphenyl diselenide but ameliorated its effect in the acetic acid test (Pinto et al. 2008). Similar to the mechanisms related to the diphenyl diselenide antinociceptive effect, an interaction with glutamatergic system, nitrergic system, $5HT_3$, D_1, B_1 and B_2 receptors is involved in *p*-methoxydiphenyl diselenide antinociceptive action (Jesse et al. 2009).

The presence of an electron-withdrawing functional group, trifluoromethyl, at the aryl group of diaryl diselenide did not alter the antinociceptive profile of a non-substituted diaryl diselenide, diphenyl diselenide. However, different from diphenyl diselenide, m-trifluoromethyldiphenyl diselenide antinociceptive action in different models of pain involves an interaction with the central opioid system, more specifically μ-opioid and δ-opioid receptors (Bruning et al. 2010).

Bis selenide alkene derivatives were antinociceptive agents in different models of pain (acetic acid, capsaicin, and tail-flick) without altering motor performance in mice (Savegnago et al. 2006a). Bis selenide alkene derivatives inhibited neurogenic and inflammatory pain induced by formalin and the nociceptive response and edema caused by intraplantar injection of glutamate, serotonin, histamine, and compound 48/80 in mice (Jesse et al. 2007, 2008). Bis selenide produced antinociception at spinal sites through multiple sites such as the activation of ATP-sensitive and voltage-gated K^+ channels, the interaction with kainate and trans-ACPD receptors and vanilloid and pro-inflammatory cytokines (Jesse et al. 2008).

Antidepressant-like and anxiolytic activities

Considerable evidence suggests that a low selenium status leads to depressed mood and anxiety (Sher 2000, 2007; Rayman 2000), while high dietary or selenium supplementation could improve mood and depression status (Benton 2002; Benton and Cook 1991). Therefore, it is plausible that organoselenium compounds could improve mood and reduce anxiety.

In this context, different organoselenium compounds have been evaluated in the experimental models predictive of depressant activity. It is clearly depicted in Table 6 that the minimal effective dose to elicit antidepressant-like activity varies depending on the chemical structure of compounds, the route of administration, and the animal species investigated. Ebselen reduced the immobility time in the

Table 6 Minimal effective dose of different organoselenium compounds evaluated in experimental models predictive of depressant activity

Compound	Test	Dose (mg kg^{-1})	Route	Species	Reference
Ebselen	FST	10	s.c	Mice	Posser et al. (2009)
	TST	Non-effective*	s.c	Mice	Posser et al. (2009)
Diphenyl diselenide	FST	0.1	Oral	Rats	Savegnago et al. (2007b)
	FST induced by malathion	50	Oral	Rats	Acker et al. (2009b)
	TST	5.0	Oral	Mice	Savegnago et al. (2008b)
Bis selenide[a]	FST	0.5	Oral	Mice	Jesse et al. (2010a)
	TST	0.5	Oral	Mice	Jesse et al. (2010b)
	FST induced by CCI[b]	1.0	Oral	Mice	Jesse et al. (2010c)

* Dose up to 30 mg/kg, forced swimming test (FST), tail suspension test (TST), subcutaneous (s.c.)

[a] Bis selenide -[(Z)-2,3-bis(4-chlorophenylselanyl)prop-2en-1-ol]

[b] Depressant-like behavior induced by chronic constriction injured (CCI)

forced swimming test (FST) but did not cause any effect in the tail suspension test (TST) (Table 6).

The involvement of noradrenergic (α1 and α2-adrenoceptors) and dopaminergic (D1 and D2 receptors) systems in ebselen antidepressant-like action was pharmacologically demonstrated. It is important to point out that the ebselen action was independent of interaction with serotonergic system (Posser et al. 2009).

Regarding the mechanisms involved in diphenyl diselenide antidepressant action, the involvement of the serotonergic (5-HT_{1A}, 5-$HT_{2A/C}$, and 5-HT_3), noradrenergic (α_1 and α_2), and dopaminergic (D_1, D_2 and D_3) receptors was demonstrated (Savegnago et al. 2007b). In an extension of this study, the inhibition of L-arginine-NO-cGMP pathway and modulation of K+ channels and PPARγ receptors were also reported (Savegnago et al. 2008b; Wilhelm et al. 2010).

Diphenyl diselenide has also been proposed to have anxiolytic action in different animal models. In fact, diphenyl diselenide had anxiolytic action in the elevated plus-maze, light–dark box, and open-field tests in complete absence of adverse effects, such as alterations in locomotor activity or memory (Ghisleni et al. 2008a; Savegnago et al. 2008b). The potential mechanisms underlying the anxiolytic-like action of diphenyl diselenide were reported to be 5-HT_{1A}, 5-$HT_{2A/C}$, and $GABA_A$ receptors (Ghisleni et al. 2008a).

It is important to point out that although most of the mechanisms involved in diphenyl diselenide, ebselen, and biselenide actions were indirectly demonstrated, using pharmacological tools, these organoselenium compounds appear to have multiple sites of action rather than a very specific target (Table 7).

One important set of pharmacological and neurochemical evidence supports a role of 5-HT_{1A}, 5-$HT_{2A/C}$, and 5-HT_3 receptors in the anxiolytic action of *m*-trifluoromethyl-diphenyl diselenide in two well-consolidated models of anxiety, the elevated plus-maze and the light–dark choice tests, without modifying the locomotor and exploratory activities of mice. This study also indicated that *m*-trifluoromethyldiphenyl diselenide may be a selective inhibitor of mono amino oxidase A (MAO-A) activity in the cerebral cortex of mouse (Brüning et al. 2009).

Table 7 Multiple sites of action involved in the antidepressant-like activity of organoselenium compounds

Receptor	Ebselen	Diphenyl diselenide	Bis selenide[a]
Serotonergic		1A, 2A/C, 3	2A/C, 3
Adrenergic	α1, α 2	α1, α2	
Dopaminergic	D1, D2	D1, D2, D3	

[a] Bis selenide -[(Z)-2,3-bis(4-chlorophenylselanyl)prop-2en-1-ol]

Hepatoprotective activity

The recognition of selenium as nutritionally important trace element came with the discovery of its ability to prevent liver pathology (Schwarz and Fredga 1969). Therefore, selenorganic compounds have been extensively studied against liver damage and the various clinical conditions in which hydroperoxides play a role. Table 8 shows some organoselenium compounds with hepatoprotective action in different experimental models in rodents.

With respect to the mechanism by which ebselen acts as a hepatoprotective agent, Shimohashi and collaborators have reported that ebselen suppresses TNF-α and NO production by lipopolysaccharide-activated Kupffer cells by the modulation of Jun-N-terminal kinase and the NF_kB signaling pathway (Shimohashi et al. 2000). This pharmacological profile suggests that ebselen has a promising potential in the therapy of diseases that are characterized by an initial overactivation of the immune system.

According to Table 8, diphenyl diselenide has hepatoprotective activity against 2-nitropropane, cadmium, and acetominophen-induced hepatic damage in rats. By contrast,

Table 8 Protective effect of different organoselenium compounds against experimental models of hepatic damage in rodents

Compounds	Experimental model	Reference
Ebselen	Galactosamine	Wendel and Tiegs (1986)
	Paracetamol	Li et al. (1994), Rocha et al. (2005)
	CCl_4	Wasser et al. (2001)
	Lipopolysaccharide/ *Propionibacterium acnes*	Koyanagi et al. (2001)
	Ethanol	Oshita et al. (1994), Kono et al. (2001), Pivetta et al. (2006)
	Ischemia–reperfusion	Ozaki et al. (1997)
Diphenyl diselenide	2-Nitropropane	Borges et al. (2005a, 2006)
	Cadmium	Borges et al. (2008)
	Paracetamol	Wilhelm et al. (2009a)
m-Trifluoromethyl-diphenyl diselenide	2-Nitropropane	Wilhelm et al. (2009c)
p-Methoxyldiphenyl diselenide	Lipopolysaccharide/galactosamine	Wilhelm et al. (2009b)
Binaphthyl diselenide	2-Nitropropane	Ibrahim et al. (2010)
Diselenole[a]	2-Nitropropane	Wilhelm et al. (2011)

[a] Diselenole—(E)-2-benzylidene-4-phenyl-1,3-diselenole

hepatotoxicity caused by CCl_4 was potentiated by repeated administration of diphenyl diselenide in rats. It has been accepted that inhibitors of cytochrome P450s can impair the bioactivation of CCl_4 into their respective reactive species and thus provide protection against the hepatocellular damage (Janbaz and Gilani 2000). Thus, pharmacological evidence supports the hypothesis that diphenyl diselenide activates CCl_4 biotransformation by inducing hepatic cytochrome P450s, potentiating CCl_4-induced hepatic damage (Nogueira et al. 2009).

Gastroprotective activity

The most common side effect of all non-steroidal anti-inflammatory drugs (NSAIDS) is irritation of the gastric mucosa. In this regard, it appears relevant that organoselenium compounds have no irritant or damaging effect on the gastric mucosa.

In this context, ebselen prevents ulceration induced by aspirin, diclofenac (Leyck and Parnham 1990), HCl and acidified ethanol (Kurebayashi et al. 1989), 48/80 compound (Ohta et al. 2002), ethanol (Tabuchi et al. 1995), and water-immersion restraint stress (Tabuchi and Kurebayashi 1993).

Diphenyl diselenide has also been effective in preventing and reversing gastric ulcers induced by ethanol and indomethacin, as well as inhibiting gastric acid secretion in pylorus-ligated rats (Savegnago et al. 2006b; Ineu et al. 2008). Similarly, ebselen can inhibit gastric acid secretions in pylorus-ligated rats (Tabuchi and Kurebayashi 1993) and H^+, K^+ ATPase in parietal cells (Tabuchi et al. 1994; Beil et al. 1990), indicating that this antisecretory action is involved in the antiulcer effect of this compound in rats.

The inhibition of H^+, K^+ ATPase sulfhydryl groups has been associated with ebselen and diphenyl diselenide protective action on mucosal damage. This effect on the enzyme responsible for acid secretion can counteract the undesirable side effects caused by non-steroidal anti-inflammatory drugs. Thus, from the point of view of anti-inflammatory drugs, organoselenium compounds are versatile with regard to gastric ulcers, because not only do they block the inflammatory cascade, which can impair gastric endogenous protective factors against HCl, but also do they inhibit the HCl secretion. Since the therapeutic approach toward a variety of diseases is changing from a single to a multi-target one, it would be very useful to evaluate the possible synergism of the association of organoselenium compounds with other non-steroidal anti-inflammatory drugs with respect to the anti-inflammatory response and the antagonism of gastric ulcer development.

Renoprotective activity

There are only a few published studies dealing with organoselenium action on renal damage. In this way, ebselen protected against ischemic acute renal failure injury by improving renal function due to the suppression of peroxynitrite production or its scavenging activity, consequently preventing lipid peroxidation and oxidative DNA damage (Noiri et al. 2001). The scavenging peroxynitrite activity of ebselen has also been associated with the amelioration of microvasculopathy and angiogenesis of nephropathy in Zucker diabetic fat rats (Gealekman et al. 2004).

The nephrotoxicity of cisplatin, a highly effective antineoplastic DNA alkylating agent, has been well documented. Therefore, ebselen alone or combined with allopurinol significantly reduced cisplatin-associated nephorotoxicity (Yoshida et al. 2000; Lynch et al. 2005).

Despite beneficial effects of gentamicin, a widely used amino glycoside antibiotic, it has considerable nephrotoxic effects. In this context, ebselen protected against gentamicin-induced oxidative and nitrosative renal damage (Dhanarajan et al. 2006).

Recently, diphenyl diselenide and binaphthyl diselenide were tested and proved to be effective against acute renal failure induced by glycerol in rats (Brandao et al. 2009; Ibrahim et al. 2011).

Cardioprotective activity

Keshan and Kashin–Beck diseases, endemic cardiomyopathies, are the best-documented examples of extreme dietary selenium deficiencies (Navarro-Alarcon and López-Martínez 2000). Therefore, selenium status has been associated with cardiovascular disorders. Hypercholesterolemia has also been associated with selenium deficiency (Huang et al. 2002; Lee et al. 2003), which lead to an increased HMG-CoA reductase activity, the rate-controlling enzyme in the cholesterol biosynthesis, that in turn resulted in increased endogenous cholesterol synthesis (Nassir et al. 1997). Moreover, inorganic selenium supplementation is responsible for upregulation of both low-density lipoprotein receptor activity and mRNA expression in experimental hypercholesterolemia in rats (Dhingra and Bansal 2006).

In this way, organoselenium compounds have been studied in different models of cardiovascular damage. Ebselen was effective against daunorubicin-induced cardiomyopathy in rats. In fact, ebselen can normalize serum cardiac enzymes creatine kinase, lactate dehydrogenase, and glutathione peroxidase (Saad et al. 2006).

Considering that atherosclerosis affects vascular wall and leads to coronary artery diseases and that lipoprotein oxidation is a key early stage in the development of atherosclerosis, the potential beneficial effect of diphenyl diselenide in protecting low-density lipoprotein (LDL) oxidation in vitro was investigated. Thereupon, concluding that diphenyl diselenide inhibited lipid peroxidation and prevented the oxidation of protein moieties in human isolated LDL in vitro (de Bem et al. 2008). Of particular pharmacological significance, we have demonstrated that low doses of diphenyl diselenide reduced the formation of atherosclerotic lesion in hypercholesterolemic LDL receptor knockout (LDLr−/−) mice, which was accompanied by improved endothelium-dependent vasorelaxation and lowered nitrotyrosine and MDA levels. Furthermore, there was a decrease in vessel wall infiltration by inflammatory cells and the upregulation of the proatherogenic monocyte chemoattractant protein-1 (MCP-1) in hypercholesterolemic LDL receptor knockout (LDLr−/−) mice was blunted by diphenyl diselenide (Hort et al. 2011).

Based on the fact that hyperlipidemia is one of the major risk factors for atherosclerosis, the hypolipidaemic potential of diphenyl diselenide was investigated in cholesterol-fed rabbits. Thus, supplementation with 10 ppm diphenyl diselenide reduced total cholesterol levels (de Bem et al. 2009). From experiments with Triton WR-1339 model of hyperlipidemia, the hypolipidemic potential of diphenyl diselenide was further confirmed. The hypolipidemic action of diphenyl diselenide was characterized by the reduction in the total cholesterol, non-high-density lipoprotein cholesterol, and triglycerides levels. One important finding of this investigation is that oral administration of diphenyl diselenide increased the levels of high-density lipoprotein cholesterol in Triton WR-1339-treated mice (da Rocha et al. 2009).

Additionally, ebselen attenuates H_2O_2-induced endothelial cell death through the inhibition of signaling pathways mediated by p38 MAP kinase, caspase-3, and cytochrome c release, suggesting ebselen as a potential drug for the treatment of atherosclerosis (Ali et al. 2004). Ebselen also reduces nitration and restores voltage-gated potassium channel function in small coronary arteries of diabetic rats. Therefore, ebselen may be beneficial for the therapeutic treatment of vascular complications (Bubolz et al. 2007).

Insulin mimetic activity

The selenate form of selenium has been known for a number of insulin-like actions and potential antidiabetic agent. This has been adequately revised by Stapleton and will not be dealt with further here (Stapleton 2000). However, the current knowledge concerning the hypoglycemic action of selenium compounds is limited to inorganic derivatives. On the topic of organoselenium compounds, a few studies dealing with insulin mimetic activity have appeared in the literature in recent years.

In this way, chronic treatment with diphenyl diselenide, but not with ebselen, caused a significant reduction in blood glucose levels, glycated proteins, and some parameters of oxidative stress of streptozotocin-treated rats (Barbosa et al. 2006). Supplementation with diphenyl diselenide contributed to the prevention of diabetic complications associated with oxidative stress (Barbosa et al. 2008c; Kade et al. 2009a, b).

Selenium in the diet exists mainly as selenoaminoacids; therefore, hypoglycemic properties of methylselenocysteine in alloxan diabetic rats were investigated. As a result, methylselenocysteine normalized blood glucose concentration and renal function in diabetic rats (Kiersztan et al.

2009). Similarly, diphenyl diselenide treatment reduced the blood glucose and fructosamine levels, which were increased in alloxan-treated adult rats (Barbosa et al. 2008b). These results are somewhat in contrast with the recent epidemiological studies demonstrating that overexposure to dietary selenium can increase the incidence of diabetes type II in human populations (Vinceti et al. 2009; Stranges et al. 2010).

Neuroprotective activity

Neuroprotection may be defined as an attempt to maintain the highest possible integrity of cellular interactions in the brain resulting in an undisturbed neural function. The search for neuroprotective agents aims at identifying compounds that can be translated into therapeutic strategies in humans. With this idea in mind, organoselenium compounds have been investigated as potential neuroprotective drugs.

In this regard, ebselen was used in clinical trials about 10 years ago for the treatment of neuropathological conditions associated with oxidative stress (Saito et al. 1998). The use of ebselen in human clinical studies was supported by successful results of this organoselenium compounds in diverse experimental models. Ebselen has been proved to protect against brain damage from different models of permanent focal ischemia (Johshita et al. 1990; Takasago et al. 1997), transient focal ischemia (Dawson et al. 1995), and hypoxia/ischemia-induced neuronal damage (Knollema et al. 1996). It was also demonstrated that ebselen ameliorated cerebral vasospasm in a canine two-hemorrhage model (Watanabe et al. 1997), inhibited cerebral vasospasm after subarachnoid hemorrhage in rats and primates (Handa et al. 2000; Gul et al. 2010), protected against cerebral ischemia, and accelerated the recovery during reperfusion (Kondoh et al. 1999). Moreover, ebselen can protect against cerebral injury in stroke-prone spontaneously hypertensive rats. The inhibition of inducible nitric oxide synthase (iNOS) protein expression was associated with neuroprotective effect of ebselen (Sui et al. 2005; Yamagata et al. 2008).

Oxidative DNA damage has been proposed to be a major contributor to focal cerebral ischemic injury. Therefore, the role of oxidative damage in the degeneration of the thalamic ventroposterior nucleus after focal cerebral cortical infarction in hypertensive rats was investigated. Thereupon, concluding that ebselen attenuated oxidative DNA damage, enhanced its repair activity, and protected the thalamus against the secondary damage (He et al. 2007).

Additionally, *N*-acetylcysteine was effective in potentiating the neuroprotective effect of ebselen against hydroxynonenal-induced neurotoxicity in cerebellar granule neurons. These data further suggest that ebselen exerts a neuroprotective effect under the conditions of increased glutathione production, a consequence of N-acetylcysteine pretreatment (Arakawa et al. 2007).

In an in vitro ischemic model, ebselen protected the brain against oxygen and glucose deprivation (Porciúncula et al. 2003). As ischemic insults decrease cellular glutathione levels, Shi and co-workers have investigated the role of glutathione in ebselen-induced cell death under ischemia, providing persuasive evidence that depletion of cellular glutathione plays an important role in ebselen-increased C6 glioma cell damage under ischemic condition (Shi et al. 2006).

Furthermore, ebselen attenuated, in a concentration-dependent manner, the degeneration caused by an in vitro model of ischemia and simultaneous depletion of glutathione in astrocytes (Gabryel and Malecki 2006). In an extension of this study, Malecki demonstrated that ebselen normalized neuronal viability and increased glutathione levels in normoxia and ischemia (Pawlas and Malecki 2007).

The mechanism behind the neuroprotective effect of ebselen against ischemic damage in the hippocampal CA1 region was disclosed. A set of evidence was reported demonstrating that GABA shunt enzymes are involved in the neuroprotective effect of ebselen. Treatment with ebselen increased the expression of glutamic acid decarboxylase (GAD), GABA transaminase (GABA-T), and succinic semialdehyde dehydrogenase (SSADH) in the hippocampal CA1 region (Seo et al. 2009).

Although a discrete line of evidence for the absence of ebselen neuroprotection arises from the data obtained with rats subjected to severe focal ischemia (Salom et al. 2004), data from clinical trials have consistently demonstrated that ebselen reduced brain damage in patients with delayed neurological deficits after aneurismal subarachnoid hemorrhage (Saito et al. 1998) and improved the outcome of acute ischemic stroke, suggesting that ebselen may be a promising neuroprotective agent (Yamaguchi et al. 1998).

It has been clearly indicated that ebselen protects neuronal cells from injury induced by glutamate by blocking lipid peroxidation and inhibiting the synaptosomal release of glutamate (Porciúncula et al. 2001; Nogueira et al. 2002). However, ebselen displayed a dual effect on vesicular glutamate uptake. In fact, low concentrations of ebselen increased, while high concentrations inhibited, the vesicular glutamate uptake (Porciúncula et al. 2004).

The mechanisms underlying the protective actions of ebselen on glutamate-induced neurotoxicity have been explored. Excitotoxic concentrations of glutamate resulted in an increase in Bax protein expression and a decrease in Bcl-2 protein expression. The neuroprotective effect of ebselen was associated with the regulation of Bcl-2 and Bax proteins, antiapoptotic effect, but unrelated to

glutamate-mediated increase in intracellular calcium (Xu et al. 2006).

In addition, neuronal differentiation induced by ebselen has been attributed to the activation of the classical Ras/MAPK (mitogen-activated protein kinase) cascade rather than to regulation of the redox state (Nishina et al. 2008; Satoh et al. 2004).

Consistent with these findings, studies in vivo have found that ebselen has neuroprotective effect against spinal cord injury in rats. Ebselen has neuroprotective and restoring effects on secondary pathochemical events after spinal cord injury, suggesting that ebselen treatment might have potential benefit in spinal cord tissue damage on clinical grounds (Kalayci et al. 2005). In view of the well-reported antioxidative and neuroprotective properties of ebselen, the hypothesis tested by Liu and co-workers is that the covalent attachment of the biologically active ebselen moiety to C_{60}-fullerene may lead to the formation of a new C_{60}-based ebselen derivative. The results showed that the antioxidative and protective activities of C_{60}-based ebselen derivative against H_2O_2-mediated neuronal injury were significantly higher than those of C_{60}-derivative, ebselen derivative, and the equimolar mixture of both (Liu et al. 2007a, b).

Besides the neuroprotective effect of ebselen in several experimental models of excitotoxicity (Moussaoui et al. 2000; Farina et al. 2003b, c; Satoh et al. 2004; Centurião et al. 2005; Moussaoui et al. 2000; Porciúncula et al. 2001; Rossato et al. 2002a, b), it has been tested and proved to be effective against noise-induced hearing loss (Yamasoba et al. 2005), immobilization stress (Lee et al. 2006), superoxide dismutase 1 (SOD1)-related familial motor neuron degeneration (Wood-Allum et al. 2006), alcohol-induced rat hippocampal stress (Johnsen-Soriano et al. 2007), and demyelination lesion caused by ethidium bromide (Mazzanti et al. 2009).

Despite the well-documented neuroprotective effect of ebselen in different experimental in vitro and in vivo conditions, this organoselenium compound does not appear to exhibit neuroprotective effects against dopaminergic toxicity induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the nigrostriatal tract of mice (Dhanasekaran et al. 2006).

Regarding selenomethionine, the major component of dietary selenium, there have been few studies of its neuroprotective action. A study performed by Lovell demonstrated that pretreatment of primary cortical neurons with selenomethionine decreased free radical production by β-amyloid and Fe^{2+}/H_2O_2 and increased glutathione peroxidase activity, suggesting its potential use as a therapeutic agent in neurodegenerative diseases (Xiong et al. 2007).

Diphenyl diselenide has been reported as a neuroprotector agent in a classical model of in vitro ischemia (Ghisleni et al. 2003). Interestingly, ebselen and diphenyl diselenide blocked the increase in inducible nitric oxide synthase (iNOS) overexpression caused by glucose and oxygen deprivation in rat brain slices. Thus, we can suppose that they inhibited the excessive NO production by iNOS, which occurs after brain ischemia in vitro. This inhibitory effect can be a common molecular mechanism underlying part of the neuroprotection afforded by these compounds after brain ischemia. Furthermore, since iNOS is involved in the inflammatory process (Bredt and Snyder 1994; Gross and Wolin 1995), it is possible that organoselenium compounds have part of their anti-inflammatory activity mediated by chemically decreasing iNOS overexpression. Regulation of this important molecular pathway can help injured tissues to more efficiently handle the oxidative stress. Thus, in addition to reacting and directly neutralizing NOO^- derived from NO, organoselenium compounds block an early complex molecular pathway that involves the repression of the synthesis of an important protein involved in cell death mechanisms. Although there is a scarcity of studies on the molecular mechanisms behind diphenyl diselenide neuroprotective action, a decrease in lipid peroxidation and inhibition of H_2O_2-induced MAPKs phosphorilation (ERK-1/2 activation) have been demonstrated (Posser et al. 2008). The prevention of ectoenzymes activation, essential for the maintenance of purinergic/glutamatergic signaling interaction, has also been reported as a mechanism by which diphenyl diselenide protects against glutamate toxicity in cultured neurons (Ghisleni et al. 2008b).

Considering that hyperphosphorilation of cytoskeletal proteins is associated with neuronal dysfunction and neurodegeneration, diphenyl diselenide and ebselen can prevent hyperphosphorylation of the high-salt Triton-insoluble neurofilament subunits (NF-M and NF-L), glial fibrillary acidic protein (GFAP), and vimentin induced by the neurotoxic agent diphenyl ditelluride (Moretto et al. 2005).

Tardive dyskinesia, a serious neurological syndrome characterized by involuntary orofacial movements, is most frequently found in older patients using typical antipsychotic agents. In this context, the neuroprotective action of diphenyl diselenide and ebselen in dyskinesia induced by antipsychotics in rats was tested (Table 9).

As demonstrated in Table 9, diphenyl diselenide showed modest protective effect against reserpine-induced orofacial dyskinesia in old rats (Burger et al. 2004), while ebselen was effective in this experimental model (Burger et al. 2003). It is important to note that the dose used of diphenyl diselenide was 3 times lesser than the effective dose of ebselen in reserpine-induced orofacial dyskinesia in old rats (Table 9). In addition, not only diphenyl diselenide but also ebselen attenuated dyskinesia induced by haloperidol (Burger et al. 2005, 2006). Diphenyl diselenide can also

Table 9 Neuroprotective effect of ebselen and diphenyl diselenide against dyskinesia—induced by antipsychotics in rats

Antipsychotic	Compound	Dose (mg kg^{-1}), route	Effect	Reference
Haloperidol	Ebselen	30, i.p.	Effective	Burger et al. (2005)
	Diselenide	5, s.c.	Effective	Burger et al. (2006)
Reserpine	Ebselen	30, i.p.	Effective	Burger et al. (2003)
	Diselenide	10, i.p.	Modest	Burger et al. (2004)
Fluphenazine	Diselenide	1, s.c.	Effective	Fachinetto et al. (2007)

Table 10 Neuroprotective action of diphenyl diselenide and its analogues in different experimental models in rodents

Compound	Model	Animal species	Reference
Diphenyl diselenide	Object recognition memory	Rats	Rosa et al. (2003)
	Spatial memory	Rats	Stangherlin et al. (2008)
p-Methoxyldiphenyl diselenide	Memory impairment induced by streptozotocin	Mice	Pinton et al. (2010)
m-Trifluoromethyldiphenyl diselenide	Apomorphine-induced stereotypy	Mice	Machado et al. (2006)
	Pentylenetetrazole-induced seizures	Mice	Prigol et al. (2009a)

decrease orofacial dyskinesia caused by fluphenazine (Fachinetto et al. 2007), and ebselen was not investigated in this model.

Low selenium concentrations in the eldery have been significantly associated with senility and cognitive decline (Berr et al. 2000). In this way, diphenyl diselenide and its analogues were reported as neuroprotective agents in different experimental models (Table 10).

Diphenyl diselenide, a non-substituted diaryl diselenide, has been demonstrated to be an inductor of facilitation of memory in rats (Rosa et al. 2003; Stangherlin et al. 2008; Table 10).

Although *p*-methoxyldiphenyl diselenide has been investigated in a different experimental model of neurotoxicidade if compared to diphenyl diselenide, the introduction of a methoxyl group into the aryl group of diaryl diselenide yields a compound with neuroprotective action. In fact, *p*-methoxyldiphenyl diselenide was able to reverse the learning and memory impairments induced by intracerebroventricular injection of streptozotocin, a model of sporadic dementia of Alzheimer's type, in mice (Table 10). The impairment of learning and memory was accompanied by increasing activity of cerebral acetylcholinesterase and diphenyl diselenide normalized the enzyme activity (Pinton et al. 2010).

Another substitution into the aryl group of diaryl diselenide, the introduction of a trifluoromethyl group, gives an organoselenium compound with neuroprotective profile. In a model of apomorphine-induced stereotypy in mice, *m*-trifluoromethyldiphenyl diselenide attenuated behavioral features associated with a mouse model of psychosis (Table 10). Of particular importance is the author's observation that at the highest dose (10 mg kg^{-1}) used *m*-trifluoromethyldiphenyl diselenide did not affect open-field behavior, habituation or aversively motivated memory (Machado et al. 2006).

Additionally, *m*-trifluoromethyldiphenyl diselenide has been tested and proved to be an anticonvulsant agent against pentylenetetrazole-induced seizures in mice (Table 10). The detailed mechanism behind the anticonvulsant action remains incompletely understood; however, it appears to involve an increase of GABA levels in the synaptic cleft by inhibiting GABA uptake (Prigol et al. 2009a).

Potential use of selenium

Chemopreventive activity

The dual faces of selenium are sharply identificable in cancer studies. In the early 1940s, a variety of selenium forms were reported as carcinogens in liver of rats (Nelson et al. 1943). Twenty some years later, Shamberger and Frost associated the selenium element with the cancer risk (Shamberger and Frost 1969). After that, a substantial body of research has established that selenium reduces experimental carcinogenesis. Besides, solid evidence based on epidemiological studies shows an inverse relationship between selenium intake and risk of cancers in humans (El-Bayoumy 1991, 1994, 2001; El-Bayoumy et al. 1995, 1997, 2001; Kelloff et al. 1996; Montoya and Wargovich 1997; Ip 1998; Combs and Gray 1998; Sugie et al. 2000; Reddy 2000; Raich et al. 2001; Combs 2001a, b; Combs et al. 2001; Gopalakrishna and Gundimeda 2002; Czeczot et al. 2006; Trumbo 2005; Wei et al. 2004; Donaldson 2004).

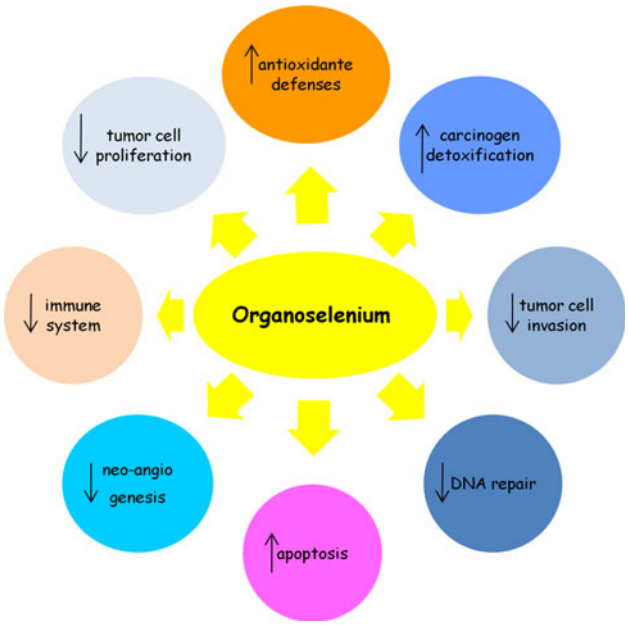

Fig. 19 Mechanisms involved in anticancer activity of organoselenium compounds

Several mechanisms have been proposed for the anticancer activity of selenium which include its effects on antioxidant defenses (selenoenzymes), programmed cell death, DNA repair, carcinogen detoxification, immune system, neo-angiogenesis, regulation of cell proliferation and tumor cell invasion (Fig. 19) (Whanger 2004; Zeng and Combs 2008). It is possible that selenium does not reduce tumorigenesis by a single mechanism, but instead by multiple ones.

In the 1980s, the research group of El-Bayoumy was the birth of synthetic organoselenium compounds as chemopreventive agents in laboratory animals. The chronology started with *p*-methoxybenzeneselenol, an effective inhibitor of benzo(a)pirene-induced forestomach tumors in mice (El-Bayoumy 1985) and azoxymethane-induced hepato (Tanaka et al. 1985; Reddy et al. 1985b) and colon carcinogenesis in rats (Reddy et al. 1985b). However, this compound was quickly abandoned in favor of benzylselenocyanate.

Benzylselenocyanate, a versatile organoselenium chemopreventive agent in several model systems (Foiles et al. 1993, 1995), has been reported to inhibit the development of colon (Reddy et al. 1987; Fiala et al. 1991) and mammary tumors in rats (Nayini et al. 1989). The potential genotoxic and antiproliferative activities of benzylselenocyanate were demonstrated as well (Khalil and Maslat 1990; Fiala et al. 1997, 1998).

Based on mechanistic and metabolic studies (Sohn et al. 1991; El-Bayoumy et al. 1991), the structure of benzylselenocyanate (Reddy et al. 1985a) was modified to develop a more effective and less toxic (Maslat and Khalil 1991) chemopreventive agent. As a consequence, *p*-phenylenebis(methylene)selenocyanate arose as a compound less toxic than benzylselenocyanate (Conaway et al. 1992). Thus, the efficiency of *p*-phenylenebis(methylene)selenocyanate in experimental models for carcinogenesis at both initiation and post-initiation stages in colon (Reddy et al. 1992, 1997; Narayanan et al. 2004), mammary glands (El-Bayoumy et al. 1992; Ip et al. 1994), lung (El-Bayoumy et al. 1992, 1993, 1996, 2006; Tanaka et al. 2000; Prokopczyk et al. 1997; Rosa et al. 1998; Prokopczyk et al. 1996, 2000; Richie et al. 2006), liver (Prokopczyk et al. 1996), intestine (Rao et al. 2000), tongue (Chen et al. 2009) and oral tissues (Tanaka et al. 1997; Von Pressentin et al. 2000), has been widely reported. No attempt is made here to thoroughly discuss the chemepreventive effects of *p*-phenylenebis(methylene)selenocyanate, as these have been adequately reviewed elsewhere (El-Bayoumy and Sinha 2004).

Ip has proposed the hypothesis that selenium compounds which directly generate monomethylated selenium are more effective chemopreventive agents than selenium compounds that are metabolized to H_2Se. The data on chemopreventive activity of selenobetaine and methylselenocysteine, which are metabolized to monomethylated selenium, compared to sodium selenite and selenomethionine further support this hypothesis since selenobetaine and methylselenocysteine were more effective as chemopreventive agents than the other two forms, which generate H_2Se (Ip 1998).

In this context, methylselenocysteine and selenocysteine have been extensively studied as chemopreventive agents. Methylselenocysteine holds effective potential as a chemopreventive agent especially against mammary tumorogenesis (Ip and Ganther 1992). Accordingly, an anti-angiogenic activity of methylselenocysteine has been demonstrated and characterized by the intratumoral vessel density and a vascular endothelial growth factor in mammary carcinoma (Jiang et al. 1999). In this way, Sinha convincingly demonstrated that the methylselenocysteine inhibitory effect on the growth of mouse mammary tumor epithelial cells coincides with a specific blocking of cdk2 kinase activity, with the increase of *gadd* gene expression and with apoptosis (Sinha and Medina 1997). A synchronized mouse mammary cell line TM6 has been used to demonstrate that methylselenocysteine increased caspases 3, 6 and 8 activities, leading to apoptosis in the methylselenocysteine-treated TM6 cells (Unni et al. 2001).

Based on the knowledge that phosphatidylinositol 3-kinase (PI3-K) regulates diverse cellular functions such as growth, survival and malignant transformation through its multiple enzymatic functions, namely lipid kinase and protein kinase activities (Krasilinikov 2000), and acts either synergistically with the Raf pathway or in opposition to it

(Hu et al. 1996; Rodriguez-Viciana et al. 1997), the effects of methylselenocysteine on the components of the PI3 K–Akt and signal-related kinase Raf–MEK–ERK pathways were investigated to gain a better understanding of the mechanisms of growth inhibition in the TM6 mouse mammary tumor cell line. Methylselenocysteine inhibited PI3-K activity and subsequently inactivated Akt, by dephosphorylation. The phosphorylation of p38 MAPK was also downregulated by methylselenocysteine. In parallel experiments methylselenocysteine inhibited the Raf–MEK–ERK signaling pathway. Therefore, methylselenocysteine blocks multiple pathways in mouse mammary tumor cells in vitro (Unni et al. 2005).

Lu and collaborators have demonstrated that selenite inhibits cell growth through predominantly non-specific genotoxic effects which are manifested by single-strand DNA breaks and cytotoxicity. In contrast, methylselenocysteine, which is metabolized predominantly to methylselenol, induced growth inhibition in the absence of DNA single-strand breakage. Consequently, these findings support the hypothesis that selenite and organoselenium compounds have different and distinct modes of action in the growth inhibition of cells in vitro (Lu et al. 1995; Sinha et al. 1999).

Combined with a chemotherapeutic agent, methylselenocysteine and selenomethionine provide protection against the toxicity of different chemotherapeutic agents. Chemotherapy with irinotecan, a topoisomerase I poison, alone and in combination with other anticancer drugs is limited by lack of therapeutic selectivity and resistance. The challenge in chemoprevention is to develop new drugs and treatment modalities that will significantly impact cure rates, but with minimal toxicity. In this context, there has been reported that the combination of methylselenocysteine and irinotecan significantly increased the cure rates of human head and neck xenografts and protected animals from irinotecan-induced death (Cao et al. 2004). To better understand the basis for the efficacy of methylselenocysteine in increasing the therapeutic index of irinotecan against human tumor xenografts a new study was performed. Methylselenocysteine in a dose-dependent manner enhances antitumor activities of irinotecan and protects from its toxicity. However, intratumoral total selenium concentration was not predictive of the combination therapy response rates (Azrak et al. 2007).

In contrast, some authors have described that rats supplemented with methylselenocysteine had more 3,2′-dimethyl-4-aminobiphenyl-induced colonic DNA adducts and greater aberrant crypt foci formation in the colon than those supplemented with inorganic selenium. These findings suggest that the supplementation of selenium in the form of methylselenocysteine in the diet does not inhibit the preneoplasic lesions in the colon (Reddy et al. 2000; Davis et al. 1999; Feng et al. 1999). Thus, even though methylselenocysteine has been shown to be the most effective organoselenium compound in the reduction of mammary tumorigenesis, it may not be able to reduce colon tumors.

The inhibitory capacity of selenocysteine conjugates toward seven of the most important human P450 was examined. The most potent inhibitor was benzylseleno-selenocysteine, but the majority of the selenocysteine conjugates produced inhibition of cytochrome 1A1 at μM range, suggesting that this effect may contribute to their chemopreventive activity (Venhorst et al. 2003). Additionally, promising results were observed with prodrugs of selenocysteine, selenazolidines, as potential selenium delivery agents for cancer chemoprevention. Of note, selenazolidines exhibited reduced toxicity to V79 cells (Short et al. 2003).

Selenocystine and selenodiglutathione have also been reported to inhibit phorbol ester-induced transformation of epidermal cells. Besides, these organoselenium compounds induce a redox modulation of protein kinase C, compartmentally independent from the cytosolic GSH, but intimately connected to an NADPH-dependent reductase system (Gopalakrishna et al. 1997).

A mechanistic study of in vitro anticancer activity of selenocystine further revealed that reactive oxygen species play a key role in the signaling pathway of selenocystine-mediated apoptosis in susceptible cancer cells (Tianfeng and Yum-Shing 2009). Apoptosis triggered by selenocystine involves caspase-independent apoptosis and activates reactive oxygen species-mediated mitochondrial pathway and p53 phosphorylation. Bcl-2 family members regulated the release of apoptosis-inducing factor from mitochondria to the cytosol, which translocated into nucleus and induced chromatin condensation and DNA degradation and finally resulted in apoptotic cell death (Fig. 20) (Chen and Wong 2009).

During the past few years, the mechanism of cytotoxicity proposed for the potential cancer therapeutic action of selenium has been the generation of reactive oxygen species (Drake 2006; Chen et al. 2007). To gain further insight into the cytotoxic mechanism for the chemoprevention the role of glutaredoxin (Grx), proteins with a central function in maintaining the redox balance within the cell, has been explored. Selenite, selenodiglutathione and selenocystine were shown to be substrates of human Grx1. According to Fig. 21a, selenodiglutathione and selenide, substrates for Grx1, are reduced to selenol, generating reactive oxygen species. By contrast, selenocystine is stoichiometrically reduced by Grx1 with 1:1 oxidation of NADPH, yielding its complete reduction and absence of reactive oxygen species formation (Fig. 21b). The authors suggest that citotoxicity caused by selenocystine may involve a different

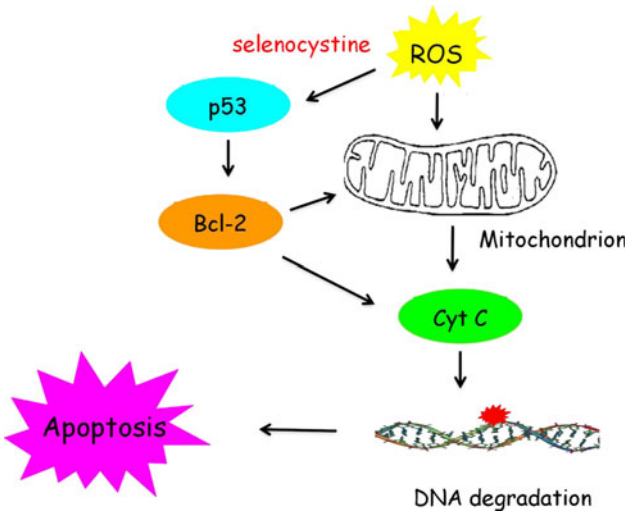

Fig. 20 Selenocystine induces caspase-independent apoptosis

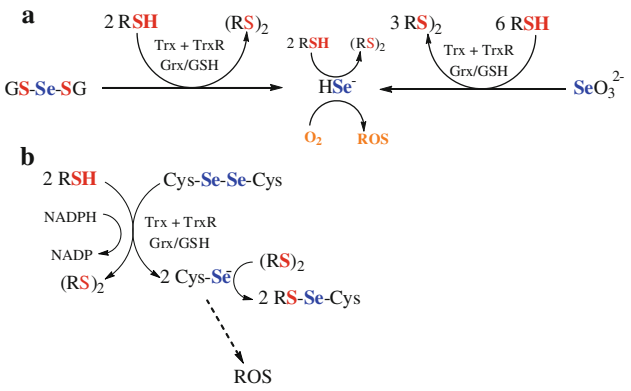

Fig. 21 **a** Selenodiglutathione (GS-Se-SG) and selenide, substrates for glutaredoxin (Grx), are reduced to selenol, generating reactive oxygen species (ROS). **b** Selenocystine (CysSeSeCys) is completely reduced by Grx with oxidation of NADPH without ROS generation. Modified from Wallenberg et al. (2010)

pathway independent on the reactive oxygen species generation (Wallenberg et al. 2010).

The study elegantly performed by Spallholz and co-workers investigated selenomethionine and methylselenocysteine for their toxicity and mutagenicity as well as potential detrimental effects on DNA yeast *Saccharomyces cerevisiae*. At equimolar concentrations, selenomethionine and methylselenocysteine were less toxic than inorganic selenium, sodium selenite, in *S. cerevisiae* and this was attributed to differences between sodium selenite and selenomethionine or methylselenocysteine in their ability to redox cycle and generate superoxide. Therefore the results demonstrated that sodium selenite but not selenomethionine and methylselenocysteine is toxic and may be mutagenic in yeasts (Letavayova et al. 2008). Further the genotoxic potential of selenomethionine as compared to sodium selenite against DNA damage induced by doxorubicin was investigated. Both selenomethionine and sodium selenite were able to prevent DNA damage induced by doxorubicin in peripheral blood cells of rats. The authors suggest that the antioxidant mechanism may account for the chemoprotective activity (dos Santos et al. 2007).

Previous studies show that selenomethionine exerts cancer chemopreventive properties by regulating ERK phosphorylation leading to cell-cycle arrest in human colon cancer cells (Goulet et al. 2005). Selenomethionine was described as a low-toxic chemotherapeutic agent able to inhibit tumor growth in a model of colorectal carcinoma by downregulating the expression of the protein Bcl-xL, increasing the expression of Bax and Bad and activating caspase-9 (Yang et al. 2009). Selenomethionine inhibits human prostate cancer cell viability; however, in contrast to 1,4-phenylenebis(methylene)selenocyanate, it is not active at physiologically relevant doses (Pinto et al. 2007).

The selenium supplementation in human trials revealed that selenomethionine as selenium-yeast reduced the incidence of colon, lung, and prostate cancer by nearly 50% (Clark et al. 1996). However, the selenium and vitamin E cancer prevention trial (SELECT) for the prevention of prostate cancer in men over 50 years of age (http://www.crab.org/select/) failed to show the efficacy of selenomethionine for prostate cancer prevention (Drudge-Coates 2009; Zhang et al. 2010). In human prostate cancer cells, selenomethionine was also reported as unable to inhibit androgen receptor and Akt signaling (Facompre et al. 2010).

As mentioned previously, methylselenol is postulated to be the selenium metabolite responsible for the dietary chemoprevention of cancers. The study of Spallholz further confirmed that methylselenol, a metabolite of methioninase catalysis of selenomethionine, generates superoxide in the presence of glutathione. Further, methylselenocysteine in vivo is very likely carcinostatic in like manner to selenomethionine by generating methylselenol from other enzymatic activity, i.e., beta-lyase or amino acid oxidases. Redox cycling, oxidative stress-induced apoptosis by methyl and other selenides appears to account for the carcinostatic attributes of selenium supplementation to animals and humans (Spallholz et al. 2004).

Seo and co-workers have reported that tumor suppressor p53 was activated by selenomethionine via the modulation of redox status. In an extension of their study, they were able to demonstrate that methyl methanesulfonate-induced base excision repair was enhanced under the modulation of p53 in the presence of selenomethionine. From this study emerges a possibility of a novel chemopreventive activity of selenomethionine to play a role in preventing mutagenesis in normal cells from various oxidative metabolites to induce base damages in DNA (Seo et al. 2002; Jung et al. 2009).

The hypothesis that selenomethionine protective effects against ionizing radiation, a widely employed therapy in the cancer treatment, are mediated by p53 pathway was tested. The activity of p53 was modulated by redox factor 1 in response to selenomethionine treatment (Rafferty et al. 2003; Jeong et al. 2009).

Cyclophosphamide, a widely used antineoplastic drug, causes myelosuppression in normal cells. Therefore, the possible protective effect of selenomethionine on cyclophosphamide-induced toxicity of the blood and bone marrow of rats was investigated. The data revealed that selenomethionine at a select dose range had hematoprotective effect against cyclophosphamide toxicity (Ayhanci et al. 2009).

There has been shown that the administration of daily selenomethionine starting 1 week before initiation of weekly irinotecan therapy reduces irinotecan-induced toxicity and improves antitumor activity in preclinical models (Cao et al. 2004; Azrak et al. 2005). Consequently, a phase I study to determine the maximum tolerated dose of irinotecan with fixed, non-toxic high dose of selenomethionine was performed. The dose of selenomethionine investigated on this study (2,200 μg Se) resulted in suboptimal concentrations of selenium on day 8 of treatment (<10 $\mu molL^{-1}$ in all patients on the first day of irinotecan), which may explain the lack of protective effects and the inability to escalate irinotecan beyond the previously maximum tolerated dose. The authors suggest that higher doses of selenomethionine are needed to test adequately for normal tissue toxicity protection. Based on the data obtained in this phase I trial, a new study designed to determine the recommended dose of selenomethionine in combination with irinotecan that consistently results in a protective plasma selenium concentration >15 μM after 1 week of SLM loading was carried out. It is evident from the data that a safe dose of selenomethionine for 1 week can produce a level of 15 μM selenium concentration in plasma. Although no major protection against irinotecan toxicity was established; minimal gastrointestinal toxicity was noted-supporting the investigation of this combination in future trials (Fakih et al. 2006, 2008).

In addition to methylselenocysteine, methylseleninic acid is also believed to be a direct precursor of methylselenol, the key metabolite responsible for selenium's anticancer activity (El-Bayoumy and Sinha 2004). Accordingly, methylseleninic acid has been reported to protect against prostate cancer by inhibiting cell proliferation, by modulating the expression of androgen receptor and androgen receptor-regulated genes and by inducing carcinogen defenses (Zhao et al. 2004). The increased expression of both prometastatic genes, matrix metalloproteinases, and antimetastatic genes, tissue inhibitor metalloproteinase, in HT1080 tumor cells has been attributed to methylselenol. The net effect of these increases is the inhibition of prometalloproteinase activation and of tumor cell migration and invasion capacity (Zeng et al. 2006).

In parallel to a number of pharmacological properties reported, ebselen has been studied as a chemopreventive compound. In this way, ebselen inhibits the cell growth in human breast and colon cancer cells (Engman et al. 1997), and induces apoptosis in the human hepatoma cell line HepG2 (Yang et al. 2000a). The apoptotic effect of ebselen involves its ability to deplete thiols and to alter the mitochondrial permeability transition (Yang et al. 2000b).

Evidences concerning the direct effect of ebselen on MAP kinase activity in neuronal cells arose from Yoshimuzi group. Thus, ebselen specifically inhibits H_2O_2-induced JNK activation but not ERK ½ and p38 activation in PC12 cells. Ebselen was also found to attenuate H_2O_2-induced PC 12 cell death including apoptosis (Yoshizumi et al. 2002).

In addition to its capacity to provoke cell death, ebselen has been shown to inhibit apoptosis (Kotamraju et al. 2000; Maulik and Yoshida 2000). In fact, ebselen was found to prevent nitrogen mustard-induced apoptosis in normal and transformed thymocytes (Holl et al. 2000) and to protect cells from radiation-induced apoptosis (Ramakrishnan et al. 1996).

Ebselen has been reported as able to induce cellular necrosis in the murine hybridoma cell line. In the same study, ebselen completely inhibits caspase activation induced by cycloheximide treatment, indicating that the cell death mechanisms triggered by ebselen interfere with the apoptotic death machinery (Guerin and Gauthier 2003).

The thioredoxin system has been described to be important for cancer cell growth and inhibition of apoptosis. The thioredoxin system was originally studied for its ability to provide reducing equivalents to ribonucleotide reductase, the first unique step in DNA synthesis (Laurent et al. 1964).

A number of investigators have been pursuing an approach to the development of chemepreventive agents, which targets the mammalian selenoenzyme thioredoxin reductase. In fact, inhibition of thioredoxin reductase would be expected to be highly detrimental to the growth of tumor cells, especially since the levels of both thioredoxin reductase and thioredoxin have been found to be elevated in tumor cell lines. However, it has been reported that thioredoxin stimulates the proliferation of at least some types of human tumor cells (Powis et al. 1994; Biguet et al. 1994; Gasdaska et al. 1995).

In an attempt to investigate new chemopreventive agents, ebselen has been evaluated as inhibitor of thioredoxin reductase. As a result, ebselen was an effective inhibitor of thioredoxin reductase (IC_{50} value of 4.2 μM). By contrast, supra nutritional levels of methylselenocysteine and methylseleninic acid did not affect thioredoxin reductase activity (Ganther and Ip 2001).

Table 11 Cytotoxicity and mutagenicity of ebselen, diphenyl diselenide and its analogues in strains of *Saccharomyces cerevisiae*

	Cytotoxicity (μM)	Mutagenicity (μM)			Reference
		LYS[a]	HIS[b]	HOM[c]	
Ebselen	Non-toxic	Non-mut	Non-mut	Non-mut	Miorelli et al. (2008)
Diphenyl diselenide	100	100	100	1	Rosa et al. (2004)
m-Trifluoromethyldiphenyl diselenide	120	Non-mut	Non-mut	Non-mut	Machado et al. (2009)
p-Chlorodiphenyl diselenide	Non-toxic	Non-mut	Non-mut	Non-mut	Rosa et al. (2010)
p-Methyldiphenyl diselenide	10	Non-mut	Non-mut	Non-mut	Rosa et al. (2010)
p-Methoxyldiphenyl diselenide	1	0.1	1	0.1	Rosa et al. (2010)
Diphenyl ditelluride	10	100	50	5	Degrandi et al. (2010)

Treatment in stationary phase

Non-mutagenic—Non-mut (up to 100 μM), Non-toxic (up to 100 μM)

[a] LYS1 locus

[b] HIS 1 locus

[c] HOM 3 locus

A balance between therapeutic activity and toxic effects of a compound is an important parameter when evaluating its usefulness as a pharmacological agent. In this way, the cytotoxicity of organoselenium compounds could be employed in anti-proliferative therapy. Accordingly, one important set of evidence indicates that diphenyl diselenide has genotoxic potential (Rosa et al. 2004). In a model of yeast mutant strains defective in antioxidant defenses, diphenyl diselenide was reported as a pro-oxidant agent. The pro-oxidant effect was characterized by depletion of free glutathione, probably via direct coupling of the drug to the sulfhydryl group of the cysteine residue in glutathione and thus sensitizing the cell to reactive oxygen species (Rosa et al. 2005).

Table 11 illustrates that ebselen different from diphenyl diselenide (Rosa et al. 2004) was neither cytotoxic nor mutagenic in *Saccharomyces cerevisiae* (Miorelli et al. 2008).

The hypothesis that structural modifications into the aryl group of diaryl diselenide could achieve greater chemopreventive efficacy with minimal toxic side effects stimulated the investigation of antimutagenic potential of diaryl diselenide derivatives. As a result, genotoxic, mutagenic and protective effects of *m*-trifluoromethyl-diphenyl diselenide were reported. At high concentrations, *m*-trifluoromethyl-diphenyl diselenide was a weak cytotoxic agent and had genotoxic effects on V79 cells. Two mutagenic experimental models, bacteria and yeast, were used to evaluate the DNA damage induced by *m*-trifluoromethyldiphenyl diselenide, in contrast to the high level of frameshift mutation in *S. typhimurium* and in *S. cerevisiae* (Table 11) haploid strain caused by diphenyl diselenide, *m*-trifluoromethyldiphenyl diselenide was not mutagenic for these biological models. The authors demonstrated that *m*-trifluoromethyldiphenyl diselenide protective effect against hydrogen peroxide-induced mutagenesis involves catalase mimetic activity (Machado et al. 2009).

Additionally, other symmetrical diselenide derivatives, namely *p*-chlorodiphenyl diselenide, *p*-methyldiphenyl diselenide and *p*-methoxyldiphenyl diselenide, were screened for cytotoxicity and mutagenicity, using the yeast *Saccharomyces cerevisiae* as a model organism. *p*-Methoxyldiphenyl-diselenide was the most cytotoxic compound tested (Table 11).

Similar to diphenyl diselenide, the mutagenic potential of *p*-methoxyldiphenyl diselenide could be associated to its ability to deplete thiols and generates oxidative stress. Conversely, the introduction of a chloro or a methyl group into the aryl group of diaryl diselenide confers lower capacity than methoxyl to disturb the redox homeostasis and/or interact directly with DNA by intercalation, since frameshift mutations are not observed in yeast.

Taken these data together it is possible to conclude that the introduction of a methoxyl group into the aryl group of diaryl diselenide increases cytotoxic and genotoxicity of diphenyl diselenide (Table 11). It is also important to emphasize that *p*-methoxyldiphenyl diselenide was more cytotoxic and mutagenic than diphenyl ditelluride, a diphenyl diselenide analogous (Table 11) (Degrandi et al. 2010). Moreover, the introduction of a methyl group increases the cytotoxicity of the compound without affecting mutagenicity (Rosa et al. 2010) (Table 11).

Based on pro-oxidant and mutagenic properties of diphenyl diselenide in different cells (Rosa et al. 2007a), the threshold of dose at which the molecule presents genotoxic effects was investigated in mice. Thus, this study revealed that diphenyl diselenide induces DNA damage in brain, kidney, liver and testes of mice. The systemic genotoxicity was clearly dependent on the dose, ranging from 75 to 200 μmol kg^{-1} when administered by intraperitoneal route.

Table 12 Cytotoxicity and genotoxicity of amino acid derivatives and simple diaryl diselenides in human leukocytes cells

Compound	Genotoxicity (μM) Damage frequency	Cytotoxicity (μM) Cell viability
(*S*)-*Tert*-butyl 1-diselenide-3-methylbutan-2-ylcarbamate	40	10
(*S*)-*Tert*-butyl 1-diselenide-3-phenylpropan-2-ylcarbamate	10	10
(*S*)-2-Amino-1-diselenide-3-methylpropanyl	10	>40
(*S*)-2-Amino-1-diselenide-3-phenylpropanyl	10	>40
m-Trifluoromethyldiphenyl diselenide	40	10
p-Methoxyldiphenyl diselenide	10	40
p-Chlorodiphenyl diselenide	40	40
Hexamethyldiphenyl diselenide	40	>40

Santos et al. (2009a)

The study clearly demonstrated a correlation between the pro-oxidant effect and DNA damage (Rosa et al. 2007b).

The antigenotoxic and antimutagenic effects of diphenyl diselenide on Chinese hamster V79 cell line have been investigated. The experimental data revealed diphenyl diselenide as a potential chemopreventive agent using several mutagens. At low concentrations diphenyl diselenide protects against methyl methanesulfonate, UVC radiation and hydrogen peroxide-induced cytotoxicity, DNA damage, and clastogenesis in V79 cells by increasing glutathione peroxidase activity (Rosa et al. 2007c).

Using animal model of carcinogenesis, the chemopreventive effect of dietary diphenyl diselenide was reported in *N*-nitroso-*N*-methylurea (NMU)-induced mammary in rats. Supplementation with diphenyl diselenide promoted pronounced increase in the latency to the onset of tumor development and reduction in the incidence and frequency of tumors. The results indicated that diphenyl diselenide presents a protective effect against the tumor development, even when supplemented at a relatively low concentration (1 ppm) (Barbosa et al. 2008a).

Additionally, a new class of amino acid derivatives was investigated by comparing their cytotoxic and genotoxic properties to that of simple diaryl diselenides in human leukocytes cells. The exposure of leukocytes to (*S*)-*tert*-butyl 1-diselenide-3-methylbutan-2-ylcarbamate, (*S*)-*tert*-butyl 1-diselenide-3-phenylpropan-2-ylcarbamate, ditrifluoromethyl diphenyl diselenide, dimethoxy diphenyl diselenide, dichloro diphenyl diselenide induced a significant loss of cell viability (cytotoxic) (Table 12). All aminoacid derivatives and simple diaryl diselenides caused DNA damage (genotoxic) at low concentrations in human leukocytes cells (Table 12) (Santos et al. 2009a).

We have demonstrated that diphenyl diselenide and diphenyl diselenide as well as their organotellurium analogous, diphenyl telluride and diphenyl ditelluride, decreased at similar concentrations the osmotic stability of human erythrocytes in vitro (Schiar et al. 2009; Santos et al. 2009b) (Table 13). (S)-2-Amino-1-diselenide-3-methylpropanyl showed hemolytic effect at the concentration of 100 μM (Table 13). The hemolytic effect was strictly related to the presence of Se and Te atoms in their moieties, since the organic structure without these elements did not alter the effect. Indeed, diphenyl selenide which had the greatest hemolytic effect was genotoxic to leukocytes cells (Santos et al. 2009b).

Table 13 Minimal concentration of organoselenium and their analogous organotellurium required to cause hemolysis in human erithrocytes

Compounds	Minimal concentration (μM)
Diphenyl selenide	75
Diphenyl telluride	75
Diphenyl diselenide	100
Diphenyl ditelluride	100
(S)-2-Amino-1-diselenide-3-methylpropanyl	100

Santos et al. (2009b)

Induction of Phase II enzymes has emerged as an effective strategy for cancer chemoprevention. Thus Xiao and Parkin reported that among twenty-seven selenium and sixteen structurally related organosulfur compounds tested the most potent were dimethyl diselenide, 2,5-diphenyl-selenophene, dibenzyl diselenide, methylseleninic acid, diphenyl diselenide, benzeneseleninic acid, benzene selenol, triphenylselenonium chloride and ebselen, increasing quinone reductase and glutathione S transferase activities in murine hepatoma (Hepa IcIc7) cells, at low micromolar concentrations. The concentration-dependence of quinone reductase induction and cell growth inhibition were linearly correlated among the group of organoselenium compounds (dimethyl diselenide, dibenzyl diselenide, methylseleninic acid, diphenyl diselenide, benzeneseleninic acid, benzene selenol and ebselen) with putative selenol-generating potential, implying that both responses of Hepa IcIc 7 cells were based on these selenol metabolites (Xiao and Parkin 2006).

Conclusion

The biological narrative of the element selenium in the last century has been marked by a contrast between its toxic and its beneficial effects. Indeed, selenium was first described as an extremely toxic element to mammalian organisms, which has given rise to a lasting negative view of Selenium. Posteriorly, with the clear demonstration that selenium was essential to mammals, the perceptions about the element selenium started to change slowly and about a half a century after the publication of the classical paper of Schwarz and Foltz (1957), the awareness about the element has been changed from the negative toxic to an exaggerate positive view of selenium as an antioxidant. In fact, the use of selenium supplementation have been stimulated in the last decades without a scientific support and with a complete negligence about the dual chemistry of selenium in biology: inorganic selenium found in the environment and organic forms of selenium found in plants (e.g., selenomethionine and methylselenocysteine) can be potentially pro-oxidant and not anti-oxidant in vertebrate cells; whereas the amino-acid residue selenocysteyl found in some selenoproteins can perform antioxidant roles in biology. Of particular importance for animal and human health, cumulative and recent epidemiological observations have clearly indicated that dietary overexposure to selenium can increase the incidence of chronic degenerative diseases such as diabetes II, amyothrophic lateral sclerosis and some types of cancer (Vinceti et al. 2009, 2010).

The molecular bases for the long-term dietary toxicity of selenium are still obscure, but possibly involve the oxidation of thiols from specific proteins by inorganic and organic selenium compounds. From the toxicological point of view, we suggest that the study of interaction of inorganic and naturally occurring organic selenium compounds with specific thiol-containing proteins be stimulated. Based on the results of the recent epidemiological studies, we strongly recommend that the scientific community with expertise in the field of selenium biology call attention to the necessity of more cautionary and restrictive policies for the use of dietary selenium supplementation.

Otherwise, we are under the risk of having a silent outbreak of long-term selenium intoxication in the next few decades. Indeed, our knowledge about the precise nutritional biochemistry of inorganic and naturally occurring organic selenium compounds is still incipient. Consequently, to find the fine balance between the nutritional requirements and the long-term potential toxicological consequences of inadequate selenium intake (both under- or overexposure) much more detailed epidemiological, nutritional and toxicological studies will be needed. In this review we have also presented the toxicological and pharmacological effects of a variety of synthetic organoselenium compounds, giving a particular emphasis to the general molecular bases of their actions. Regarding their ample pharmacological effects without the identification of definite targets strongly suggest that most of their beneficial effects are related to the modulation of the redox status of the living cells. Consequently, we can deduce that the antioxidant activities of ebselen and diphenyl diselenide are linked to their reductive metabolism to intermediates that "can imitate" the natural role played by the selenol/selenolate groups found in selenoporteins. Accordingly, ebselen and diphenyl diselenide are mimetics of the native glutathione peroxidase and can be substrates of thioredoxin reductase, which metabolizes ebselen to ebselen selenol and diphenyl diselenide to selenophenol. On the other hand, the molecular toxicology of organoselenium is not known with detail. However, the ability to oxidize sulfhydryl groups from biological molecules can be involved both in their pharmacological and toxicological effects. In fact, organoselenium can induce thiol oxidation and apoptosis in vitro. Similarly, exposure to high doses of organoselenium can cause the depletion of endogenous reduced glutathione in a variety of tissues. However, the depletion of endogenous thiols by diphenyl diselenide and analogues does not strictly follow the in vitro reactivity of these organochalcogens toward low-molecular-weight thiols, emphasizing the necessity of more detailed studies about the potential in vivo oxidation of high-molecular-weight thiol-containing targets by a variety of promising simple organochalcogens.

We realize that in vitro properties of organochalcogens such as their thiol-peroxidase-like activity and their ability to be reduced by TrxR should guide future in vivo studies with rodents. Furthermore, computational simulation should be performed to identify those molecules that could interact with specific and biologically relevant proteins. From these studies, a rational chemical and biological hypothesis could be constructed about the tentative reactivity of organochalcogens toward widespread endogenous thiols, particularly glutathione and specific thiol-containing proteins. Thus, the design of compounds that could not oxidize glutathione and could react with specific targeted proteins to modulate therapeutically relevant pathways, would represent an important step for accelerating the development of new organoselenium compounds with therapeutic efficacy. The sporadic use of ebselen in 3 clinical trials in the 1990s and the abandonment of its clinical use without a clear explanation by the Japanese pharmaceutical company can be viewed either as a deterring or stimulating fact. Badly, it is possible that ebselen had been used in large trials without the confirmation of the results obtained in the preliminary small clinical trials or, alternatively, the efficacy observed initially could not be confirmed in the longitudinal following up of the patients engaged in the 3 clinical trials. Optimistically, we can say that ebselen was

apparently not toxic for humans after short-term intake schedules, which can indicate that other organoselenium compounds, such as diphenyl diselenide, could also be safe for acute therapeutic use.

Thus, the potential therapeutic use of simple organoselenium compounds has not yet been sufficiently explored and, consequently, we can not discard this class of compounds as promising pharmaceutical agents. In effect, the future of the organochalcogens as pharmacological agents with the capacity of imitating the natural chemistry of selenium in mammals and performing beneficial biological effects will depend on more detailed toxicological studies in the oncoming years.

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