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COMMENTARY

SELENO-ORGANIC COMPOUNDS AND THE THERAPY OF HYDROPEROXIDE-LINKED PATHOLOGICAL CONDITIONS

MICHAEL J. PARNHAM* and ERICH GRAF
A. Nattermann Research Laboratories, D-5000 Cologne 30, Federal Republic of Germany

The rapid growth in recent years in our understanding of the roles of reactive oxygen species in pathology has brought with it new ideas for the therapy of a variety of diseases. To a large extent, the therapeutic use of superoxide dismutase (SOD†), particularly for inflammatory disorders [1], has been an incentive to the development of similar drugs. SOD is an enzyme, which inactivates the superoxide anion (O_2^-), and as such has limitations in its clinical application. Based on the knowledge that SOD is a copper-containing enzyme, an extensive literature has developed on the properties of copper-containing compounds, not only as anti-inflammatory agents, but also as antiulcer, anticonvulsant, anti-cancer and anti-diabetic agents [2]. These postulated applications all arise from the proposed role of O_2^- in these pathological conditions. An alternative approach is based on the selenium-containing enzyme, glutathione peroxidase (GSH-Px), which reduces hydroperoxides, the selenium-containing active centre being amenable to chemical modification. We discuss here the role of selenium and GSH-Px in the homeostasis of oxygen metabolism, the evidence for imbalance of this system in hydroperoxide-linked pathological conditions, and the prospects for their therapy with organoselenium compounds.

BIOCHEMISTRY OF SELENIUM AND GLUTATHIONE PEROXIDASE

Despite many similarities with sulfur, selenium occupies a special position between metals and non-metals, and its strong tendency to change its oxidation levels has been utilized for some time in organic chemical synthesis in which redox-reactions are involved.

Today we know that it is precisely this quality of selenium-containing enzymes that also plays an important part in biology. Until 1957 only the toxic effects of the element and its compounds were known. The work of Schwarz and Foltz [3] and others [4, 5] has since demonstrated the importance of selenium in the enzyme (GSH-Px). The enzyme, the four sub-units of which (each with a molecular weight of 21,000) each contain one atom of selenium in the form of selenocysteine [6], catalyses the reduction of H_2O_2 and organic hydroperoxides according to the reaction cycle shown in Fig. 1.

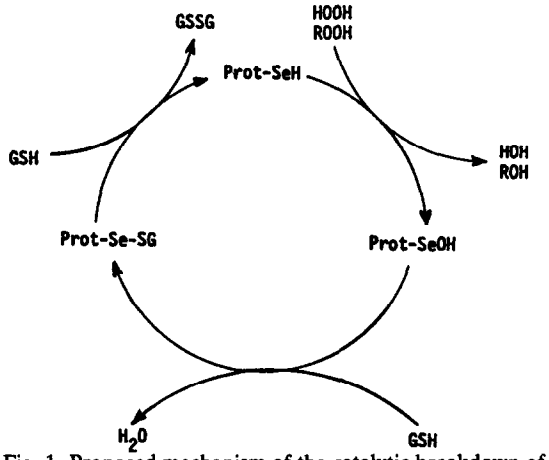

Fig. 1. Proposed mechanism of the catalytic breakdown of hydroperoxides by GSH-Px.

In this way, GSH-Px plays an important role in the protection of the cell from oxidative stress such as that represented by H_2O_2 and organic hydroperoxides [7–9]. It is therefore equally important as catalase (catabolism of H_2O_2), SOD (catabolism of (O_2^-) and probably the non-selenium-dependent GSH-*S*-transferase (catabolism of organic hydroperoxides only), in this respect [10]. During the selenium deficiency states discussed below, these other enzymes probably play an increased role, though the importance of GSH-*S*-transferase in man is unclear [11].

Although six non-GSH-Px seleno-enzymes have been isolated from micro-organisms—with one exception all involved in redox-reactions (for review see Ref. [8])—GSH-Px so far is the only such enzyme discovered in the higher organisms and is distributed throughout many human and animal organs [7]. Its activity (e.g. in erythrocytes or platelets) normally correlates well with dietary selenium uptake and plasma concentrations [12–15] and acute symptoms of selenium deficiency can be ascribed to

* Send all correspondence to: Dr. Michael J. Parnham, Nattermann Research Laboratories, P.O. Box 350120, D-5000 Cologne 30, F.R.G.

† Abbreviations used: GSH-Px: glutathione peroxidase; HETE: hydroxy eicosatetraenoic acid; HPETE: hydroperoxy eicosatetraenoic acid; IgG: immunoglobulin G; LT: leukotriene; MDA: malonaldehyde; O_2^-: superoxide anion; PG: prostaglandin; PMNL: polymorphonuclear leucocytes; SOD: superoxide dismutase.

loss of this enzyme activity [14], although it is still uncertain whether the biological significance of selenium is totally restricted to GSH-Px [15–17].

Our increasing understanding of the role of oxidative stress in pathology [18] represents a challenge to search for direct and objective treatment of excessive, uncontrolled oxidative and radical processes—a form of treatment which should exceed unspecific supplementation in often questionable selenium deficiency.

PATHOLOGICAL PROCESSES INVOLVING HYDROPEROXIDES

Hydroperoxide generation may be the result of endogenous biochemical processes, usually associated with enzymatic redox reactions, or due to the toxic effects of drugs, chemicals or radiation on the organism. Consequently, with regard to hydroperoxide involvement, pathological conditions may be considered as those in which a physiological reaction becomes excessive or those elicited by toxic agents. Many of the former conditions are associated with leucocyte infiltration into an organ or tissue, these inflammatory cells becoming the major source of oxidative stress. Inflammation and/or its sequellae is thus an important factor in hydroperoxide-related tissue damage, not only for obviously inflammatory diseases, but also for diseases in which an inflammatory aetiological factor is only now becoming apparent.

Inflammation and related conditions

The major mechanism for the generation of reactive oxygen species by leucocytes, including both polymorphonuclear leucocytes (PMNL) and macrophages, is the "respiratory burst". This response, resulting from the stimulation of the leucocytes by soluble or phagocytic stimuli, involves enzymatic generation of superoxide anion (O_2^-) from molecular oxygen, hydrogen peroxide (H_2O_2) being formed from O_2^- either by spontaneous or superoxide dismutase (SOD) catalysed dismutation [19]. In addition to H_2O_2, PMNL and particularly macrophages generate lipid peroxides as products of the enzymatic metabolism of arachidonic acid. These include the cyclic endoperoxide intermediates in the cyclooxygenase-mediated biosynthesis of prostaglandins (PGs), PGG_2 and PGH_2 and the hydroperoxyeicosatetraenoic acids (HPETESs) formed by lipoxygenases, including the 5-lipoxygenase responsible for leukotriene (LT) biosynthesis (see Fig. 2). HPETEs can also be formed by non-enzymatic autooxidation of arachidonic and other polyunsaturated fatty acids [20]. In many tissues, Fe^{2+} ions are thought to play an important role in the initiation of lipid peroxidation. However, the generation of reactive oxygen species via the respiratory burst of leucocytes is likely to play a significant role in the peroxidation of fatty acids at inflamed sites (Fig. 2). According to this process, diene conjugates of the fatty acids are formed during the initiation of peroxidation, hydroperoxides being generated during the propagation phase and ethane, pentane and aldehydes, such as malondialdehyde (MDA), being products of the termination phase [20].

The demonstration of any or all of the above products at sites of inflammation is an indication of the possible involvement of lipid peroxidation in the inflammatory response, though the biological activities of the various compounds must inevitably be considered before attributing to any individual product a role in inflammation. With regard to the products of the enzymatic oxidation of arachidonic acid, PGE_2, the vasodilatory, hyperalgesic and oedema-enhancing cyclooxygenase product, and LTB_4, the chemotactic, leucocyte-activating 5-lipoxygenase product, are clearly more important as inflammatory mediators than their hydroperoxide intermediates [21, 22]. Nevertheless, where HPETEs and HETEs are formed in large amounts, their weak inflammatory properties may contribute to the inflammatory response [23].

H_2O_2, formed by the respiratory burst, is essential for the bactericidal activity of PMNL, but also induces inflammatory responses, such as oedema, leucocyte infiltration and tissue damage, as demonstrated when H_2O_2 is generated by glucose oxidase injected into rat lung or the mouse knee joint [19, 24]. The specificity of these actions for H_2O_2 is demonstrable by their inhibition with catalase, a specific inactivator of H_2O_2. Additional products of non-enzymatic lipid peroxidation that may play a role in inflammation are the aldehydes (see Fig. 2), since compounds such as 4-hydroxynonenal, 4-hydroxytetradecanal and 4-hydroxyoctenal are chemotactic for PMNL [25]. Quite apart from these inflammatory actions of individual oxidation products, the whole process of lipid peroxidation is damaging in that the peroxidation of fatty acids and the free radical attack of proteins and nucleic acids during the propagation phase result in loss of cellular integrity and function [19, 25].

Based on the presence of biologically active products of enzymatic and nonenzymatic hydroperoxide generation at inflamed sites or in the serum or plasma of patients, a number of clinical diseases may be proposed as "hydroperoxide-linked conditions" (Table 1). For some of these conditions (e.g. inflammatory joint diseases) the evidence for a role of hydroperoxides based on levels of these compounds is relatively strong. For others, such as shock and acute lung injury and post-ischaemic reperfusion injury, the scarce clinical data are strengthened by a large amount of experimental data demonstrating the generation of hydroperoxides under these conditions [26–28].

In addition to the presence of hydroperoxides and their products, significant decreases in the activities of the hydroperoxide-scavenging enzymes, GSH-Px and/or catalase, further support the proposal that hydroperoxide-overproduction is involved in the aetiology of some of these inflammatory conditions. For instance, synovial catalase and GSH-Px activities have been shown to be insufficient to protect against hydroperoxide damage in rheumatoid arthritis patients, while erythrocyte GSH-Px activity is reduced in severely burned patients [29–31]. The conditions listed in Table 1 thus represent potential therapeutic indications for organoselenium compounds.

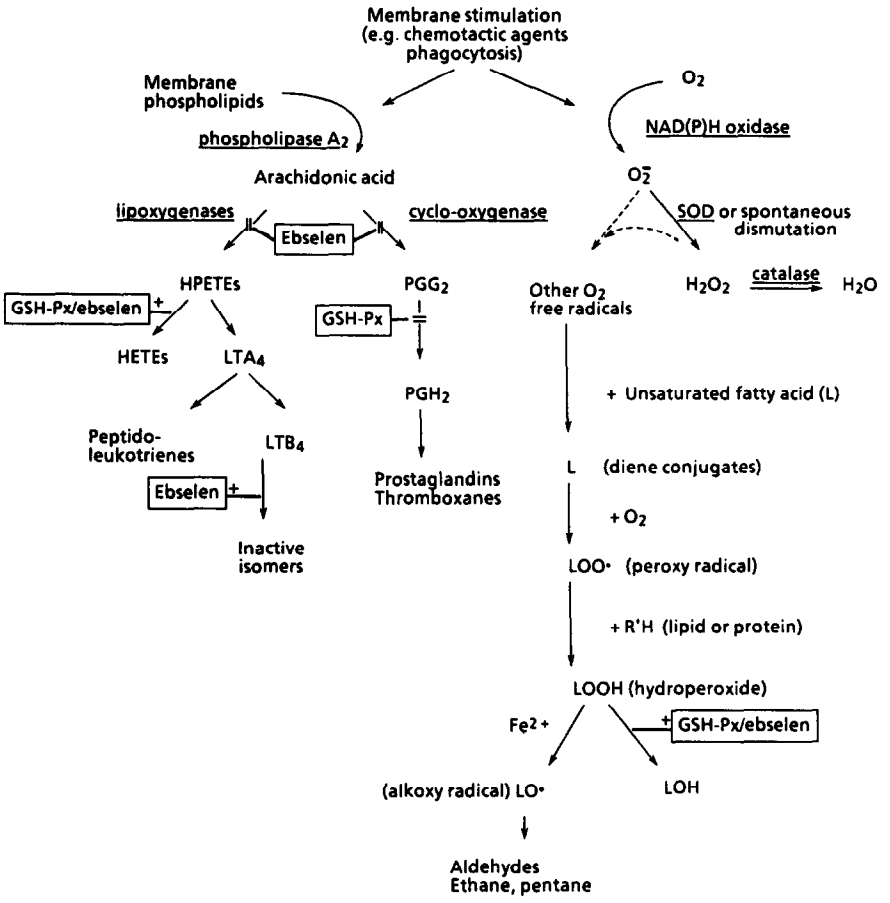

Fig. 2. Formation of hydroperoxides and their breakdown products by leucocytes and sites of action of GSH-Px and ebselen.

Table 1. "Hydroperoxide-linked" inflammatory conditions in which hydroperoxides and/or peroxidation products have been detected in increased amounts

Disease	Peroxidation products detected	References
Rheumatoid arthritis and related inflammatory joint diseases	Synovial PGs and LTs, diene conjugates and fluorescent IgG; plasma MDA; enhanced synovial PMNL respiratory burst	21, 22, 32–35
Burn injury	Plasma PGs, TxB_2, LTB_4, MDA	31, 36–38
Shock and acute lung injury (e.g. ARDS)	Plasma PGs, TxB_2, LTs and probably other leucocyte products	26, 27, 39
Post-ischaemic reperfusion damage	Platelet MDA	40
Psoriasis	LTs and 12-HETE in plaque; increased oxidative burst of peripheral blood PMNL incubated with psoriatic serum	41, 42
Obstructive airways diseases	LTs, MDA and diene conjugates in sputum	43, 44

Other pathological conditions

A number of central nervous system (CNS) diseases have been proposed to be associated with increased lipid peroxidation. These include Parkinson's disease, in which H_2O_2 generated by monoamine oxidase may cause neurone degeneration and in such patients lower brain GSH levels are found; epilepsy, since cerebrospinal fluid from patients with this disease contains increased aldehyde levels; and neuronal ceroid lipofuscinosis and encephalopathy associated with accumulation in the brain of iron and fluorescent products of lipid peroxidation [45–47]. A decrease in GSH-Px activity is also detectable in the latter condition [48].

A large number of experimental studies indicate that lipid peroxidation is induced in the liver by a wide variety of hepatotoxic chemicals and drugs [49, 50]. Recently, the diene conjugate, 9,11-linoleic acid, has been identified in the serum of alcoholics, providing an indication that in man lipid peroxidation

can be detectable, at least when alcohol is the hepatotoxic agent [51].

Finally, radiation and cancer are two related conditions in which, at least experimentally, lipid peroxidation has been shown to occur and probably plays a role in tissue damage and DNA alteration [52]. Once again clinical data are scarce, but in human colon carcinoma, for instance, MDA levels are enhanced in comparison to healthy colonic tissue, whereas catalase activity is reduced markedly, indicating that, in this form of carcinoma, H_2O_2 may be an important noxious agent [53].

Consequently, in addition to inflammation and inflammation-related conditions, a variety of other clinical diseases represent possible targets for hydroperoxide-inactivating therapy.

DISEASES ASSOCIATED WITH LOW OR DEFICIENT SELENIUM LEVELS

Given the fact that a variety of diseases are associated with increased peroxidation products and occasionally with decreased GSH-Px activities, evidence for a regulatory role of selenium in the control of hydroperoxide generation under similar conditions would clearly add further support to the proposal for therapy of hydroperoxide-related conditions with seleno-organic compounds. This evidence is provided by a number of selenium deficiency diseases and by reports of low levels of selenium in other diseases.

The clearest association between selenium deficiency and disease is observable in certain muscular diseases. In man cardiac myopathy with arrhythmias and cardiac enlargement results from dietary selenium deficiency. This condition, known as Keshan disease from the Chinese province in which the disease is most prominent, affects children in particular and is essentially prevented by dietary supplementation with sodium selenite, though a partial viral aetiology may play a role [54]. Interestingly, in acute myocardial infarction patients, the platelet GSH-Px activity is also reduced significantly [55], suggesting that several forms of heart disease may be associated with selenium deficiency.

The association of selenium with cancer has a long history, initial investigations having been carried out at the turn of the century [14]. Since then a large number of clinical and experimental studies have confirmed that increased selenium uptake, in a variety of forms, results in a non-specific enhancement of resistance to tumours of all types [14]. Epidemiological studies, particularly in the United States, clearly indicated a direct correlation between low dietary selenium intake and incidence of cancer, though this has not been observed in all studies in endemically selenium-deficient countries, probably because other dietary and environmental factors may play a role in the aetiology of cancer [14, 56]. It is also possible that, in selenium deficiency, enhanced activities of other oxygen radical scavenging enzymes than GSH-Px (e.g. SOD, catalase, GSH-*S*-transferase) may compensate for the reduced mutation-preventing effects of hydroperoxide-scavenging by GSH-Px.

With the growing appreciation of the role of dietary selenium in cardiac disease and cancer, a considerable number of reports have appeared in which low (usually plasma) selenium levels have been correlated with a wide variety of diseases. However, as described above in relation to the inflammatory response in general, decreases in selenium levels and GSH-Px activities may be general responses to injury. Consequently, if a fall in selenium concentration and the associated GSH-Px activity is likely to be an aetiological factor in any particular disease, it should be expected that selenite supplementation will reverse at least some of the disease symptoms. Diseases in which both low selenium levels and a beneficial effect of selenite supplementation have been reported include psoriasis, several other skin diseases [57, 58], and rheumatoid arthritis [59, 60]. In the Chinese province in which Keshan's disease is prevalent, a rheumatic disease called "Big-Joint Disease" or Kashin–Beck's disease has also been observed in both children and sheep, characterised by marked enlargement of the knee joints and other articulations [14]. Dietary selenium supplementation has been reported recently to be effective in preventing and treating this inflammatory joint disease [61*]. In rheumatoid arthritis, selenite administration together with either vitamin E [59] or allogeneic lymphocyte infusion [60] relieved joint pain and morning stiffness in a significant proportion of the patients. The lowered plasma selenium levels and erythrocyte GSH-Px activities were restored by the treatment in the former study. Other authors have confirmed that serum selenium concentration is low in severe rheumatoid arthritis, though a significant correlation with serum selenium was only found for a number of selected disease parameters [61], indicating that selenium and presumably hydroperoxides may play a role in certain aspects of this disease. In normal individuals living in a selenium-deficient area, selenium supplementation has been reported to decrease serum cholesterol levels, suggesting that atherosclerotic patients may respond to selenium therapy [62].

In view of the findings discussed earlier, that the activity of GSH-Px is decreased and lipid peroxidation enhanced during inflammation, it might be expected that inorganic selenium therapy would be beneficial in a variety of inflammatory conditions. While rheumatoid arthritis remains the only clinical inflammatory condition in which data exist on selenium supplementation, studies on laboratory animals indicate that selenite treatment exerts anti-inflammatory effects on acute inflammatory models, burn injury and ischaemic myocardial damage [63–65]. It would thus seem likely that in man such conditions may also be susceptible to organo-selenium therapy.

The assumption is generally made that the deleterious effects of selenium deficiency and the beneficial effects of selenite supplementation are due to enhanced (lipid) peroxidation and its inhibition respectively. However, *in vivo* or *ex vivo* data supporting this assumption are relatively scarce. In the

*L. Chongzhena, H. Jingrong and L. Caixia, in *Abstracts, Third International Symposium on Selenium in Biology and Medicine*, Beijing, p. 73 (1984).

studies on experimental burn injury and myocardial ischaemia, selenite supplementation inhibited plasma and myocardial MDA production, respectively [64, 65], while selenium deficiency enhances phagocytosis-induced H_2O_2 release by mouse macrophages *ex vivo* [66]. The metabolism of arachidonic acid is also affected by selenium deficiency, apparently due to effects on hydroperoxide intermediates [67, 68] (see Fig. 2).

BIOLOGICAL ACTIVITIES OF ORGANOSELENIUM COMPOUNDS

If one disregards ^{75}Se-radiolabelled products ([^{75}Se]-methionine, ROTOP, and tauro-23[^{75}Se],25-homocholic acid, Amersham Buchler), which serve diagnostic purposes, there is no chemically defined seleno-organic compound on the market, although Klayman [69] reviewed a large number of such compounds as potential chemotherapeutic agents as long ago as 1973. In view of toxicological considerations, some may consider this justified. At least it seems to be an expression of anxiety over such problems.

The majority of seleno-organic compounds that have been reported in the literature (see Refs. 63, 69–73) are direct selenium analogues of oxygen- or sulfur-containing compounds of known struucture and pharmacological activity. Such structural changes have not been reported to provide any therapeutic advantage or to improve hydroperoxide-reducing properties.

Ever since Schwarz first recognized the nutritional role of selenium in his experiments with selenium-deficient animals [3], the principle of nutritional supplementation [14, 74] since propagated has been steadily gaining ground—sometimes rather uncritically. Besides inorganic selenium compounds (sodium selenite, sodium selenate), organic natural products (e.g. yeast) are also being used for this purpose, the latter containing mainly seleno-amino acids (Se-cysteine, Se-cystine, Se-cystathione, Se-methionine). It is hard to assess the benefit of pure selenoamino acids in comparison to inorganic selenium, as there are no convincing comparative studies, neither with respect to pharmacokinetic data (for review see Ref. 70), nor with regard to their efficacy against the symptoms of selenium deficiency. Therefore, an advantage of these amino acids with regard to their efficacy/toxicity relation cannot be detected, a fact in line with our own unpublished data on animal models of inflammation. The most extensive studies with selenoorganic compounds were performed by Schwarz who, together with Fredga, synthesized about 850 substances and tested them for their biological efficacy in liver necrosis in rats after a "selenium deficient diet" (see Ref. 75).

These studies were started before GSH-Px was identified as a seleno-enzyme, and their aim had always been selenium substitution with maximum availability for "factor 3" (probably GSH-Px), with the lowest possible toxicity. Among other compounds, aliphatic mono- and diselenides were also included. As a result, considerable differences in the efficacy and toxicity of the compounds with remarkable variation in their therapeutic indices were observed, and selenodiacetylalanine and diseleno-dipropionic acid, for instance, proved to be exceptionally effective in preventing diet-induced liver damage.

These findings are hard to evaluate now, and a conclusive analysis is complicated by the fact that when estimating the therapeutic index the chronic effect was compared with acute toxicity using two different routes of administration. In addition, it is impossible to conclude whether the effects were based on a direct pharmacodynamic effect of the substances and/or their metabolites, or whether the biosynthesis of the GSH-Px was being promoted. Finally, the model of liver necrosis used by Schwarz was not induced solely by selenium deficiency. Nevertheless, it is clear from these studies that one cannot equate biological activity with toxicity when considering seleno-organic compounds.

In approximately half of the more recent papers (see Refs. 71 and 76) on seleno-organic compounds, an "anti-tumor effect" is claimed. In view of the possible role of hydroperoxides or radical mechanisms in oncogenesis, discussed earlier, this claim would appear to be related to the hydroperoxide-inactivating function of selenium in association with GSH-Px.

In addition, epidemiological evidence and results from *in vitro* and *in vivo* experiments involving both inorganic selenium supplementation and seleno-organic compounds such as selenodiglutathione, selenodicysteine [77] and selenomethionine,* support the possibility of influencing tumor growth by selenium (for review see Refs. 71 and 76). Most of the chemical structures published recently do not represent a novel approach but are related to well known antitumor compounds into which a selenium atom is inserted, such as selenopurines, selenoguanosines, selenoguanine–platinum complexes, selenourea derivatives or seleno-TEPA. It is unclear whether such compounds possess the required selenium specificity (redox-potential) on the one hand and an acceptable toxicity on the other in order to demonstrate an advantage over their oxygen or sulfur analogues.

With regard to inflammation, Roberts found as far back as 1963 [78] an inhibitory effect of organic and inorganic selenium by examining liver extracts and their ash in the granuloma-pouch-test. His findings on acute inflammation have been confirmed in principle with synthetic organic substances (e.g. selenocystine, diseleno-fatty acids) (for review see Ref. 63). However, later studies [72, 73] based on proven anti-inflammatory structures (salicylic acid, aspirin) failed because of toxicity. In accordance with the involvement of hydroperoxides in the pathophysiology of inflammation, as discussed previously, this indication would seem to be the most reasonable for seleno-organic compounds.

The reasons for the inclusion of selenium in the compounds developed for various indications have not always been clear. Obviously, assumption of a relation between selenium supplementation and conventional pharmacological expectations seems to

* H. J. Thompson and N. H. Durham, *Abstr. Am. Chem. Soc. 184 Meeting*, 10 (1982).

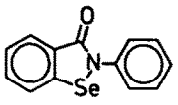

Fig. 3. Chemical structure of ebselen (PZ 51).

have played a role. No correlation between biological effects and the pseudo-GSH-Px activity of the substance itself was investigated, although even before the biological redox function of selenium in GSH-Px was revealed, Caldwell and Tappel [79] and Walter and Roy [80] had pointed out the anti-oxidative and catalytic activities of selenocystine and selenomethionine in the reductive catabolism of H_2O_2 and organic hydroperoxides as well as their possible biological significance. Yasuda *et al.* [81] have since confirmed this activity in a biological *in vitro* system for Se-cystine and for Se-cystamine and suggested a catalytic reaction cycle. The high toxicity of the substances used—LD_{50} values are in the range of a few mg/kg—has obviously blocked the medical development of such directly active compounds.

To protect the cell from an excessive oxidative stress, it is therefore necessary to present the known activity of seleno-organic compounds in a way that is tolerable to the organism. This means that during the whole process of absorption, distribution, biological action and complete excretion no interactions with critical sulfhydryl groups in functional proteins must occur, which is considered to be a reason for the high toxicity of many selenium compounds.

EBSELEN

The development of the seleno-organic compound ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one; PZ51) (Fig. 3) represents a distinct advance over other such compounds, since ebselen is an anti-inflammatory agent that does not release selenium from the molecule, which probably accounts for its relative lack of toxicity.

Ebselen is a unique example of a chemical structure in which the selenium is tightly bound but in a form which exhibits the desired redox activity. In the presence of GSH as a substrate, ebselen catalyses the degradation of H_2O_2 and organic hydroperoxides in a manner similar to that of GSH-Px [82] with a lower reaction velocity but with an activating energy which is only slightly higher than that of the endogenous enzyme [83]. The intermediate compounds formed during the catalytic redox cycle or ebselen represent different oxidation levels of selenium (diselenide, selenenic acid, seleninic acid). The inactivity of the sulfur analogue demonstrates the essential nature of the selenium moiety.

Direct inhibition of leucocyte 5-lipoxygenase by ebselen probably accounts for its inhibition of LT synthesis [84]. At lower concentrations, however, ebselen selectively inactivates LTB_4, converting it to its biologically inactive 6-*trans* isomer, once again in a manner totally dependent on the selenium content of the compound [85]. This represents a novel mechanism of action, previously not described for any other drug. The peroxidase activity of ebselen is clearly dependent on GSH, as shown with GSH-depeleted hepatocytes [86]. This activity of ebselen suggests that it may be effective in the treatment of inflammatory conditions, such as rheumatoid arthritis. This suggestion is supported by the findings *in vivo* that, while ebselen is a weak inhibitor of the classical inflammatory models, carrageenan paw oedema and adjuvant arthritis in the rat, it is considerably more effective than classical non-steroidal drugs as an inhibitor of cobra venom paw oedema in the rat and glucose oxidase-induced monoarthritis in mice [24, 87], models in which hydroperoxides play a more important role. In addition, ebselen given orally to mice is an effective inhibitor of galactosamine/endotoxin-induced liver damage, a model in which peptido-LTs are considered to play a role [88]. Consequently, liver damage is a probable therapeutic target of this compound, as well as the various clinical conditions described above in which hydroperoxides are thought to play a role.

CONCLUSIONS

A wide variety of clinical pathological conditions have been linked to lipid peroxidation and its products, formed either enzymatically or by auto-oxidation. These include inflammatory conditions such as rheumatoid arthritis, burns, shock, post-ischaemic necrosis, psoriasis and asthma, as well as CNS diseases such as Parkinson's disease, epilepsy and neuronal ceroid lipofuscinosis, liver damage, radiation damage and cancer. In several of these and related conditions, such as myocardial infarction and atherosclerosis, low selenium levels and/or GSH-Px activities have been reported, and beneficial effects of inorganic selenium supplementation have been described. Treatment with seleno-organic compounds has also been shown to produce beneficial effects on a number of pathological processes, but such compounds, together with dietary selenium, have the disadvantage that slight overdosing produces marked toxicity. Several selenoamino acids and synthetic seleno-organic compounds, which have been investigated during the last 20 years, have not offered any significant progress in this respect. The recently described compound, ebselen, has the advantage of low toxicity while exerting, itself, GSH-Px-like activity. Such compounds offer a promising approach to the therapy of hydroperoxide-linked pathological conditions.

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