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Selenocompounds and Sepsis: Redox Bypass Hypothesis: Part B- Selenocompounds in the Management of Early Sepsis

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Abstract

Significance: Endothelial barrier damage, in part caused by excess production of reactive oxygen, halogen and nitrogen species (ROHNS), especially peroxynitrite ONOO⁻, is a major event in early sepsis and, with leukocyte hyperactivation, part of the generalized dysregulated immune response to infection, which may even become a complex maladaptive state. Selenoenzymes have major antioxidant functions. Their synthesis is related to the need to limit deleterious oxidant redox cycling by small selenocompounds, which may be of therapeutic cytotoxic interest. Plasma selenoprotein-P is crucial for selenium transport from the liver to the tissues and for antioxidant endothelial protection, especially against ONOO⁻. Above micromolar concentrations, sodium selenite (Na₂SeO₃) becomes cytotoxic, with a lower cytotoxicity threshold in activated cells, which has led to cancer research.

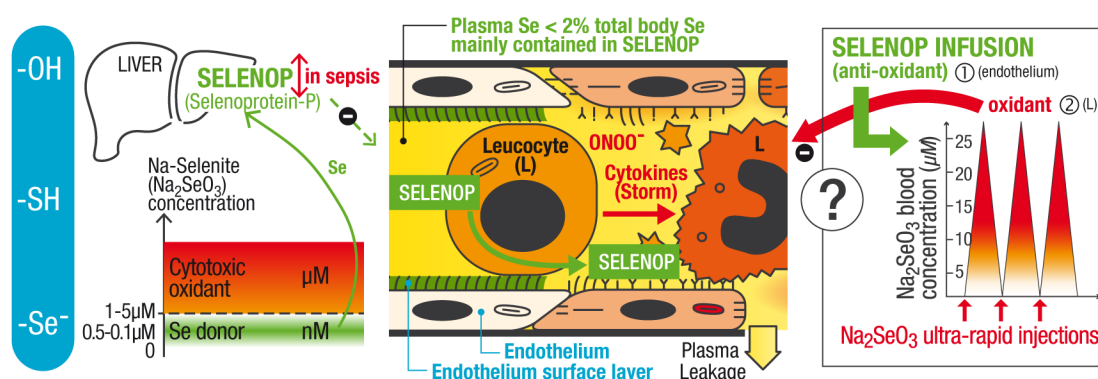
Recent advances: Plasma selenium (<2% of total body selenium) is mainly contained in selenoprotein-P, and concentrations decrease rapidly in the early phase of sepsis, because of increased selenoprotein-P binding and downregulation of hepatic synthesis and excretion. At low concentrations, Na₂SeO₃ acts as a selenium donor, favoring selenoprotein-P synthesis in physiology, but probably not in the acute phase of sepsis.

Critical issues: The cytotoxic effects of Na₂SeO₃ against hyperactivated leukocytes, especially the most immature forms that liberate ROHNS, may be beneficial, but may also be harmful for activated endothelial cells. Endothelial protection against ROHNS by selenoprotein-P may reduce Na₂SeO₃ toxicity, which is increased in sepsis.

Future Direction: The combination of selenoprotein-P for endothelial protection and the cytotoxic effects of Na₂SeO₃ against hyperactivated leukocytes may be a promising intervention for early sepsis.

References 318; **Tables** (2): 1-Acute cytotoxic effects of sodium selenite, 2-Reference values for plasma Se selenoprotein-P;

Figures (8): 1-Selenocysteine; 2-General Metabolism (+ oxidant antioxidants effects selenite), 3-Plasma Se selenoprotein-P concentration in ICU, 4-Concentration decrease in animal models, 5-Liver selenoprotein-P downregulation, 6-Cytotoxicity of selenite on leucocytes, 7-Schematic view of potential action, 8-Major intervention required to interrupt complex sepsis state.



Introduction

Sepsis is the result of a generalized, dysregulated immune response to infection, leading to organ failure (251). Sepsis is a leading cause of death with a 30-50% mortality rate in the intensive care unit (ICU), and is a continuous threat worldwide, as witnessed during the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (67,90,286). Moreover, sepsis survivors frequently experience long-term effects on health and quality of life (67,90).

As previously developed in part A of this 2-part article (90), the early phase of sepsis is characterized by deleterious redox situation leading to (i) extensive endothelium surface layer (ESL) damage (10,72,104,135); (ii) opening of inter-cellular gap junctions (143,144); (iii) modification of the vascular endothelial wall which evolves into a pro-coagulant, adherent, vasoconstrictor phenotype (134,143,164,204); (iv) increase in nitric oxide (NO•) excretion from *nM* to *μM* concentrations at the vascular wall (148,270); and (v) extensive endothelial barrier dysfunction in various organs, a first step toward multiple organ failure (MOF) (69,70,95,136,144,188,204,278) (see (90), especially Figs. 2, 3 and 4 and Tables 1 and 2). Neutrophil production and activation increase dramatically, with release of immature forms that have an increased lifespan in the circulation and may be more aggressive, increasing oxidative stress. Oxygen consumption by hyperactivated leukocytes increases by a factor of 20 to 100%, leading to release of superoxide anion (O₂^{-•}) in phagosomes and in the plasma, known as a respiratory burst (140,153,220,230,243,246,302,303). NET - DNA structures released with adherent bactericidal proteins, such as myeloperoxidase (MPO), participate in the trapping and killing of bacteria but also in endothelial damage (25,71,153). The hyperactivated leukocytes could be considered as an acute, transient, benign hematological tumor (90). As a result of the extensive interaction between activated leukocytes and the endothelium, widespread endothelial damage occurs within hours, mainly related to the overproduction of reactive oxygen, halogen and nitrogen species (ROHNS), especially peroxynitrite (ONOO⁻). A quantitative description of the multiple RHONS involved in the early phase of sepsis is provided in part A, especially in Tables 1 and 2 (90). Among these RHONS, NO• and O₂^{-•} rapidly react non-enzymatically to form the bactericidal but also cytotoxic by-product, ONOO⁻ (80,90,146,180,215,271). Although NO• is relatively stable and can diffuse across cell membranes, O₂^{-•} has a much shorter half-life and restricted diffusion across membranes (part A, Table 1) (90,271). Conditions for ONOO⁻ formation are notably fulfilled at the inner surface of the endothelial wall (Part A, Fig. 4 and corresponding text) (90,146,271). The ROHNS damage the inner surface of the endothelial wall, especially the ESL, and the endothelial cells, especially their mitochondria. These events lead, within hours of the start of sepsis (part A) (90), to disseminated, shock-induced endotheliopathy (SHINE), the first step toward MOF and ultimately death (69,70,95,136,144,188,204,278).

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock as a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities associated with a greater risk of mortality despite supportive care provided in an intensive care unit (ICU) (251). In nature, sepsis is often rapidly lethal and even more so for septic shock.

Organ support provided to patients with sepsis in the ICU, and especially to patients with septic shock, creates an unnatural, human-made situation. Without the artificial support, patients would die as a result of single or multiple organ failure linked to cellular dysfunction and damage, especially to mitochondria (11,34-36,99,151). This situation, in which the dysregulated cascades of the innate sepsis response are able to continue to develop and expand, could not have been anticipated by evolutionary adaptive mechanisms (77,251,284,285). Especially in the most severe form, i.e., septic shock, a complex maladaptive regulation state may thus be observed, in which otherwise appropriate processes and responses now have detrimental or disadvantageous effects (1,5,29,184,207,290,291) (see part A (90) especially Fig. 1, and the corresponding text). In this context, reference values for biochemical variables obtained from healthy individuals may not be appropriate for sepsis patients hospitalized in the ICU (288).

This complex maladaptive state may require a major intervention to shut it down in the early phase of sepsis (part A (90)). Numerous phase III studies performed over the last few decades, including of antioxidant agents, have failed to demonstrate decreased mortality rates in the intervention arm, probably because of the

complexity of the pathophysiology of sepsis. It has been suggested more recently that early therapeutic interventions targeting the microcirculation or mitochondrial dysfunction may be more effective and help disrupt the immune response early in sepsis (90).

In this article, we consider the role of selenocompounds, defined as compounds containing an atom of selenium (Se), as potential therapeutic agents for sepsis. Selenocompounds are involved in antioxidant defense in physiological conditions and, particularly selenoprotein-P, in the early phase of sepsis and the acute phase response (APR). Selenocompounds, especially sodium selenite (Na_2SeO_3), have been studied in cancer research for many years as oxidant cytotoxic compounds. In sepsis, because plasma Se and selenoprotein-P concentrations are low, Na_2SeO_3 has been proposed as a pharmacconutrient to supplement a presumed Se deficiency and restore Se status (22,193); however, there are no preclinical data to support this approach, and clinical results are inconclusive (27,182,225). Indeed, experimental data do not support such a deficiency, as developed later, in the section “The early stages of sepsis and the acute phase response are characterized by very low plasma selenium and selenoprotein-P concentrations”. Moreover, experimental data show that the hepatic synthesis and secretion of selenoprotein-P are downregulated by multiple mechanisms in the acute phase of sepsis.

Based on the promising preclinical data developed in the final section of this article, we propose rather a combined therapeutic redox intervention aimed at (i) first protecting the endothelium by using the antioxidant selenoprotein-P, which may also reduce endothelial activation and thus its susceptibility to Na_2SeO_3 toxicity, and then (ii) reducing the hyperactivity of leukocytes, especially neutrophils, by using Na_2SeO_3 as an oxidant cytotoxic molecule. Such an approach may reduce in large part the complex early sepsis response. Preliminary experimental results need to be confirmed to ensure safety and effectiveness.

Selenocompounds have both oxidant and anti-oxidant properties

The properties of selenocompounds arise from the position of Se in the periodic table. Se, the third atom of the VI-A column, situated below oxygen and sulfur, belongs to the chalcogens (or oxygen family). Se has a lower electronegativity than oxygen (Fig. 1) and a lower stability than sulfur because of greater polarizability (68,157). Consequently, at cellular pH (redox potential of about -230 mV), selenohydril groups are strongly dissociated (R-Se^-), in contrast to the corresponding sulfhydryl groups (RSH) (Fig. 1). This results in thiol oxidation by some selenocompounds (Fig. 2) (68,120,130). The polarizability of Se compared to sulfur accounts for the oxidant properties of selenocompounds, especially small inorganic chemicals, such as Na_2SeO_3 , which is highly cytotoxic above a micromolar (μM) concentration threshold. This cytotoxic concentration threshold depends on the specific cell and its degree of activation (see Table 1 for quantitative values and Fig. 2): more active cells have a lower threshold than quiescent cells and are more susceptible to the cytotoxic effects of oxidant selenocompounds (85,191,203,210). At low concentration –below the cytotoxic μM concentration threshold– (and dose), Na_2SeO_3 has an antioxidant action by the induction of antioxidant selenoenzymes (56,121,126,174). This effect requires the release of its Se followed by its incorporation into the antioxidant selenoenzymes (Fig. 2). Strictly speaking, Na_2SeO_3 should be considered as a pro-antioxidant molecule. The lower electronegativity of Se compared to oxygen, makes Se an essential antioxidant trace element when it is included in the 21st amino acid, selenocysteine (Sec), which is present at the active site of the 25 known selenoproteins in humans (Fig. 1 and 2). These selenoproteins have crucial anti-oxidant functions and play a major role in controlling the intracellular redox potential, mainly by decreasing the peroxide tone. They therefore affect many intracellular metabolic functions in an opposite direction to that of oxidant selenocompounds (39,102,255,257). In summary, as a result of interactions between Se, sulfur, and oxygen, selenoproteins exhibit antioxidant actions whereas some chemical selenocompounds have oxidative properties (Fig. 3) (39,102).

General Se metabolism

Selenium was identified as an essential micronutrient in 1954, initially in bacteria, especially *Escherichia coli* and anaerobic *Clostridia*, and later in mammals (212,255). Since the discovery in 1973 of glutathione peroxidase (GPX1), one of the major selenoenzymes in humans (83,228), more than 25 selenoprotein genes have been identified in humans, most of them selenoenzymes (37,39,101,102,115,201). Selenoenzymes are essential in mammals, as shown by the lethal effect of deletion of the gene that encodes Sec transfer

ribonucleic acid (tRNA) in mice (30). In humans, Se deficiency is associated with a lethal cardiomyopathy called “Keshan disease” (201,218).

Selenoprotein synthesis

Hydrogen selenide (HSe^-) – mainly bound to proteins – is a checkpoint molecule for the insertion of Sec into the active site of antioxidant selenoenzymes. With the exception of selenoprotein-P, selenoproteins contain only one Sec at their active enzyme site (44,102). In the liver, HSe^- is formed by the reduction of selenomethionine (SeMet), the principal form of Se in the human diet, and by protein catabolism, to Sec via the transsulfuration pathway (48,78,115,126); in other cells it is derived from selenoprotein-P (48,78). Sec is reduced to HSe^- by selenocysteine β -lyase in the presence of pyridoxal 5'-phosphate (PLP) with liberation of alanine (Fig. 2, upper-left) (189). Other small selenocompounds, such as selenite, can lead to HSe^- formation by another pathway, which is not active in physiological conditions except in the liver in the breakdown of ingested selenite (Fig. 2, upper right) (48,78,126). Because of its potential oxidative toxicity, free Sec concentrations are kept low by the action of selenocysteine β -lyase (SCLY). The cytotoxicity threshold of Sec can be deduced from cancer cell studies comparing selenite with Sec or with selenocystine (2 Sec bound via a Se-Se bridge, SeCys_2), a Sec donor. The cytotoxicity threshold seems to be about 2-40 μM of selenocystine (126,191,295). L-selenocystine is more toxic than D-L selenocystine, with a toxicity threshold less than that of Na_2SeO_3 (126). As for Na_2SeO_3 , this threshold depends on the cell, its degree of activation, and also the duration of exposure. Cellular concentrations are likely to be much lower than these toxicity thresholds of selenocystine, because Sec, given its low pKa value, is highly nucleophilic, rendering it highly unstable and reactive (98,191). The complex Sec insertion machinery is probably an evolutionary adaptation to insert Sec into selenoproteins taking into account this instability (Fig. 1) (44,191). The same evolutionary adaptation is probably also the case for HSe^- , which is transferred via the insertion complex acting as a molecular chaperone (48). The insertion of a Se atom to Sec requires a multistep process with four enzymatic conversions:

- (i) selenoprotein selenophosphate synthetase 2 (SPS2), which is both a selenoenzyme and an enzyme of Sec insertion (44,126,275);
- (ii) phosphoseryl tRNA kinase (PSTK);
- (iii) Sec synthase (SEPSECS) for co-translational Sec insertion, which is genetically regulated and requires energy; and
- (iv) the Sec insertion sequence (SECIS)-binding protein SBP2 factor, which is present in the nucleus and the cytoplasm.

The SBP2 factor shuttles between the two intracellular compartments via the chromosome region maintenance 1 (CRM1) (44,175,205,206,221) (Fig. 2, middle and right). Sec insertion uses a UGA codon, which is normally used by the cellular protein translation machinery as a stop signal, but used for Sec insertion in the presence of a SECIS element (44,115,118,205,248). Oxidative stress and Se availability increase selenoprotein synthesis (78,82,105,126,189,206,276,281,289). However, oxidative stress, as occurs during the early phase of sepsis with increased $\text{NO}\bullet$ excretion from $n\text{M}$ to μM concentration at the vascular wall (148,270), and a 20 to 100% increase in oxygen consumption by hyperactivated leukocytes, leading to a marked release of $\text{O}_2^{\bullet-}$ (140,153,220,230,243,246,302,303) and ONOO^- formation that could diffuse across bacterial and cell membranes (90,146,271) (see part A (90)), may reduce selenoprotein synthesis, especially by oxidation of the SBP2 factor, leading to increased nucleus localization at the expense of cytoplasm localization. Decreased cytoplasmic SBP2 is one of the limiting factors for Sec insertion (44,205,206,221,276).

Body Se content and regulation of the metabolism of selenocompounds

Total body Se content (TBSe) is about 10 to 15 mg in a healthy 70 kg man (48) (Table 2, Figs. 2 and 3). It has two components: a regulated Sec pool and an unregulated, non-biologically active SeMet pool (48). The TBSe is mainly linked to the lean mass, with the ratio of SeMet to Sec depending on the tissue and on Se intake (24). When Se intake increases, SeMet concentrations increase in muscle and Sec concentrations increase in the liver (24).

The liver is the central organ for Se regulation because of (i) its metabolism of the ingested Se within

selenocompounds (see below for ingested selenocompounds), and also of SeMet provided by hepatic protein catabolism, and (ii) the secretion of selenoprotein-P, which controls the delivery of Sec to the tissues (Fig. 2). Liver Se content is estimated at 3-4 mg according to Favier and represents 29% of mouse and 32% of rat TBSe (Figs. 3, 4 and 5) (20,48,78,92). In Se-replete mice, about 50% of the liver Se is contained within GPX1, concentrations of which decline sharply in Se starvation (48). The liver transsulfuration pathway is more active than in other tissues, allowing Se derived from SeMet to enter the Sec pool (48). In Figure 2, an absorption of 80 µg Se/day is shown, corresponding to ingestion of 100 µg Se/day; this value reflects US intake and is lower in Europe (78,84,217,306). SeMet accounts for the major part of Se incorporated in standard diets, followed by Sec, and to a lesser extent selenite (SeO₃²⁻) and selenate (SeO₄²⁻) (48,68,78,82,199).

A daily physiological turnover of about 0.4 mg Se/day can be extrapolated to: (i) the 11 kg protein content of a 70 kg man, with a total Se content of 12.5 g in the form of Sec and SeMet (42,48); and (ii) the physiological stable protein turnover rate of 300 g/day (4 g/kg/day) in reference to the lean mass (28,74,108,300). Muscle contains an important proportion of the TBSe, with about 4-6 mg of Se, because it comprises a high proportion of the body's lean mass, at about 40 to 45% of the total body weight (TBW) in rats and humans (Figs. 3 and 5) (20,93,179). Se turnover is markedly increased in sepsis and patients with severe burns (190,304) as a result of increased protein catabolism (Fig. 2 upper-left corner).

Plasma selenoprotein-P

Selenoprotein-P is expressed mainly by the liver (90% in mice (123)), but also in lesser amounts by other tissues, such as the kidney, muscle, heart, testis and brain (41,48,123,221,223,239,248) (Fig. 5). The amount of Se delivered to the liver in the form of Sec within selenoprotein-P can be extrapolated to between 0.6-0.8 mg Se/day (about 6% of TBSe) in a Se-replete person based on: (i) a plasma selenoprotein-P content of 0.2 mg for 2.7 L plasma (see table 2) (Fig. 3); and (ii) assumption of a similar 3-4 hour half-life of selenoprotein-P in humans as in rats (54). The liver excretion of selenoprotein-P regulates tissue Se hierarchy in physiological conditions – from the brain, thyroid, kidney, bone marrow and other tissues – by binding to specific receptors (see later in plasma selenoprotein section) (Fig. 2, lower-right corner) (48,240).

Pathophysiological actions of intracellular selenoenzymes

Selenoenzymes have a crucial role, acting as ubiquitous oxido-reductases inside cells, including endothelial cells (37,115,174). They play an important role in redox signaling, and in protection against ROHNS (see part A) (90). The importance of the GPX family, which uses glutathione (GSH) in its catalytic reactions, and the thioredoxin reductase (TXNRD) family, which has a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction function, should be highlighted (21,37-39,101,158,247). GPX1 (cytoplasmic GPX) plays an important role in H₂O₂ detoxification and signaling as well as acting as peroxynitrite reductase (12). GPX4 (membranous, phospholipid hydroperoxide GPX) is involved in membrane protection and mitochondrial protection against necroptosis or pyroptosis (145). It ranks near the top of the selenoprotein hierarchy (48). However, both GPXs rank among the “stress related selenoproteins”, more sensitive to Se availability than TXNRDs, which are conserved in Se deficiency (275). TXNRD1 (cytoplasmic and nuclear) and TXNRD2 (mitochondrial) have redox active lipid hydroperoxide detoxifying and protein denitrosylation functions and broad substrate specificity (8,21). These selenoproteins act especially against peroxides and, therefore, control the redox potential, catalyzing various thiol-dependent reactions and participating in the protection against ROHNS (21,38,39,101,158,247). The antioxidant action of selenoproteins, especially TXNRDs, and GPXs, is of particular importance in the protection against ROHNS and the adequate functioning of endothelial cells in the early phase of sepsis (see part A, (90)) (8,21,38,149).

The brain, a privileged organ for intracellular antioxidant selenoenzymes, has a specific cycle of selenoprotein-P from the astrocytes to the neurons, in addition to the main cycle of selenoprotein-P from the liver to the tissue. Parvalbumin-expressing (PV+) cortical and striatum as well as hippocampal gamma-aminobutyric acidergic (GABAergic) interneurons seem especially affected by impaired brain selenoprotein expression (39,48,239,242).

There is a time delay between Se intake and the increase in intracellular selenoenzymes. In some studies, 1 to 3 days were necessary to obtain a maximum TXNRD increase (8), restoration of GPX activities

(178) and corresponding inhibition of nuclear factor-kappa B (NF-κB) activation in a hepatoma cell line (177). Moreover, for most organs, an additional delay between Se supply and intracellular selenoenzyme expression is required to transfer Sec from the liver to the tissue by plasma selenoprotein-P (39,239) (Fig. 2). Such delays are not compatible with the rapid response required within the first hours of sepsis for the protection of endothelial cells (64) (see part A, especially Fig. 2) (90).

Physiological actions of plasma selenoproteins

In human plasma, there is almost no free Se or small chemical selenocompounds. Selenoprotein-P accounts for about 60% of the plasma Se, and GPX3 for about 30%. The rest of the plasma Se is incorporated into proteins – mainly albumin – as the non-biologically active form, SeMet (38,47,87,239). With an average of 0.3 mg, plasma Se constitutes only about 2% of the TBSe in a Se-replete person (Table 2) (Fig.3) (48,84,93,200,217).

Plasma selenoprotein-P

As previously mentioned, selenoprotein-P is expressed particularly in the liver. Selenoprotein-P ranks high in the hierarchy of selenoprotein production in hepatic cells (240,275). In all mammals, selenoprotein-P accounts for the major part (60 to 80%) of plasma Se with considerable homogeneity in its structure – especially for the N terminal part – in mice, rat, ox, and humans (116,124,173,195). Selenoprotein-P is an extracellular protein with a short half-life (46,54,122,198), which belongs to the group of heparin-binding proteins and has 6 glycosylation sites for a weight of 61 kDa (280). Nine of the 10 Sec residues of human selenoprotein-P are located in the C-terminal part and one in the N terminal part (47,195,208). These nine residues have a transport function and the Sec of the N terminal part has extracellular peroxidase antioxidant activity (47,208). Regardless of its toxicity, selenite is one of the best Se donors for selenoprotein-P synthesis and excretion by the liver (126).

Plasma selenoprotein-P binds to specific receptors (apolipoprotein E receptor-2 -ApoER2) in the endothelium of brain, testis, bone marrow and placenta and, to a lesser extent, of other organs (48,123,239). Selenoprotein-P also binds to another receptor (megalin) in the proximal tubule, preventing urinary loss and leading to the excretion of GPX3 (48,156,239). The heart, skeletal muscle, the brain and the kidney, can take up other forms of plasma Se than selenoprotein-P (54,125,137).

In the muscle, the low pH favors the non-specific binding of selenoprotein-P to heparin sulfate proteoglycans through heparin binding of the N-terminal domain and the histidine rich region (38,47,48,128).

In mice, selenoprotein-P causes exercise resistance during sustained effort, with increased ROS production: after exercise, selenoprotein-P deficient mice had a relative intensity of phosphorylated adenosine monophosphate-activated protein kinase (pAMPK) normalized to AMPK-α about twice as large as that of wild type mice and a concentration of thiobarbituric acid-reactive substance (TBARS) in the muscle also twice that of wild type mice (192). Moreover, increased concentrations of plasma selenoprotein-P predicted a lack of effect of training on endurance capacity in humans (192). In athletes, a significant decrease in serum Se concentration has been observed after anaerobic exercise with no change in urinary Se excretion (76,187). This finding suggests that the half-life of selenoprotein-P might be markedly shortened in case of non-specific binding to heparin sulfate proteoglycan exceeding the liver excretion capacity of selenoprotein-P.

GPX3

Plasma GPX3, which contains about 30% of plasma Se is synthesized in the kidney and is dependent on plasma selenoprotein-P (125,241). In rats, GPX3 has a longer half-life than selenoprotein-P (54). GPX3 seems to have no function in Se delivery (48).

Low selenoprotein-P in chronic disease and malnutrition

Low plasma Se and selenoprotein-P concentrations are observed in liver disease, especially in the most severe forms of cirrhosis (45,53). In a US study of patients with liver cirrhosis, plasma selenium concentrations were lower in patients with Child-Pugh class C (the worst severity) ($1.1 \pm 0.2 \mu\text{mol/L}$) than in those with class B ($1.2 \pm 0.2 \mu\text{mol/L}$) or A ($1.4 \pm 0.2 \mu\text{mol/L}$) and healthy control subjects ($1.7 \pm 0.2 \mu\text{mol/L}$) (45). The largest part of this difference concerned selenoprotein-P, which represented 47% of plasma Se content in the

control group and only 37% in the class C cirrhosis patients. In parallel to this decrease, there was an increase in GPX3 from 13% in controls to 31% in class C patients (45). In patients who underwent liver transplantation, plasma selenium increased from $1.2 \pm 0.2 \mu\text{mol/L}$ before transplant to $1.7 \pm 0.3 \mu\text{mol/L}$ after transplant, with a doubling of selenoprotein-P concentration from 0.4 ± 0.1 to $0.8 \pm 0.1 \text{ mU/mL}$ whereas GPX concentration remain unchanged (45). Cirrhosis, as previously indicated, is a condition associated with a low selenoprotein-P concentration, probably because of low levels of selenoprotein-P synthesis. Cirrhosis and sepsis share similarities in term of organ dysfunction, hemodynamic, metabolic, and immunological features (287). Sepsis prognosis is worse in cirrhotic patients (110,287), possibly in part favored by the reduced selenoprotein-P synthesis in these patients (46,167). Taking into account the role of selenoprotein-P within the microcirculation, which is developed in the next section, this deficiency may contribute to the exacerbated innate response in sepsis in cirrhotic patients compared with that observed in non-cirrhotic patients (110,287).

Low plasma Se and selenoprotein-P concentrations are also observed in dietary Se deficiency because of low soil Se bioavailability (e.g., northern Europe, New Zealand, and some areas of China), long-term parenteral nutrition without Se intake, or severe malnutrition (124,163,194,217). Plasma Se concentrations in the Deshang area of China were reported to be $0.56 \mu\text{mol/L}$, i.e., 36% of the reference US control value of $1.8 \mu\text{mol/L}$. The lowest concentrations of selenoprotein-P were observed in 8-12 year boys, with a selenoprotein-P concentration of 0.10 ± 0.04 , compared to 1 U/L in the US controls. After a 2 week period of supplementation with $100 \mu\text{g Se/day}$ as selenate, selenoprotein-P concentration increased to $0.5 \pm 0.1 \text{ U/L}$ in the Chinese boys (124). In Tibet, an area with endemic Kashin-Beck disease (osteoarthropathy related to Se deficiency), plasma Se concentrations may be less than $0.065 \mu\text{mol/L}$ (194). (see Table 2 for reference plasma Se concentrations in the US and Europe). Low plasma Se and selenoprotein-P concentrations are also observed in individuals with chronic inflammatory bowel disease, particularly Crohn's disease. In a Japanese study, the concentration of selenoprotein-P in patients with Crohn's disease was almost half the value observed in healthy individuals, whereas no difference was observed in patients with ulcerative colitis vs healthy individuals (7). In patients with Crohn's disease, the serum Se concentration was 1.2 ± 0.3 vs. $1.7 \pm 0.3 \mu\text{mol/L}$ in controls ($p < 0.01$). The difference in serum Se was more pronounced in patients with Crohn's disease receiving a long-term elemental diet containing a small amount of Se ($1.6 \mu\text{g}/1000 \text{ kcal}$), with a value of $1 \pm 0.3 \mu\text{mol/L}$ (7). A relationship between serum Se and selenoprotein-P concentrations was observed. Serum selenoprotein-P concentration were $3.4 \pm 0.8 \mu\text{g/ml}$ in healthy controls, $3 \pm 1 \mu\text{g/ml}$ in patients with ulcerative colitis, $1.8 \pm 0.5 \mu\text{g/ml}$ in patients with Crohn's disease, and also significantly lower $1.4 \pm 0.4 \mu\text{g/ml}$ in patients with Crohn's disease receiving an elemental diet vs. those without non-elemental diet ($p < 0.01$)(7). Low plasma Se and selenoprotein-P concentrations are also observed in renal failure, especially in patients receiving chronic dialysis (274,312). Before renal transplantation, a plasma Se concentration of $0.8 \pm 0.2 \mu\text{mol/L}$ was measured, vs. 1 ± 0.1 in healthy controls; the concentration returned to baseline 180 days after transplantation (312). Low plasma Se and selenoprotein-P concentrations are also observed in some cancers, especially aggressive ones (152,162,176,318). In a study in Poland, patients with pancreatic cancer had a mean plasma Se concentration of $0.8 \mu\text{mol/L}$ (range 0.4 to $1.6 \mu\text{mol/L}$) compared to $1 \mu\text{mol/L}$ (range 0.6 to $1.4 \mu\text{mol/L}$) in matched healthy subjects (162). Similar results are obtained in patients with human immunodeficiency virus (HIV) infection, especially at advanced stages (17,94,261). In a US study, low plasma Se concentration ($< 1.1 \mu\text{mol/L}$) was the only independent predictor of survival in patients with HIV infection, even when controlling for CD4 counts (18). Low plasma Se concentration was also an independent predictor of mortality in children with a mean age of 4 years infected with HIV prenatally (59).

Apart from these situations, plasma selenoprotein-P concentrations are very stable in the general population of a country (46,208,209,216,240).

Plasma selenoprotein functions in the acute phase of sepsis: major role of selenoprotein-P

Protection of the ESL and endothelium

As developed in part A (90), the ESL, which includes the glycocalyx, covers all endothelial cells and is highly fragile. In sepsis, ROHNS, especially ONOO⁻, damage the inner surface of the endothelial wall, especially the ESL. They also damage the endothelial cells, especially their mitochondria. As an anti-oxidant, plasma

selenoprotein-P could therefore have beneficial effects in sepsis, especially against the deleterious effects of ONOO⁻.

The hippocampal region of the brain, which physiologically has a thicker glycocalyx than the cortex, seems to be especially susceptible to damage, making it one of the first organs to suffer in sepsis (58). Similarly, early damage to the thicker glycocalyx present in the pulmonary vasculature compared to that in the systemic vasculature may be an important first step towards acute respiratory distress syndrome (ARDS) (58). Endothelial barrier dysfunction also impacts macromolecule transit and fluid extravasation (58,90,251).

Increased selenoprotein-P adhesion to the endothelium in sepsis via non-specific adhesion

In addition to binding to the previously cited specific receptors, selenoprotein-P binds non-specifically to heparin-binding sites (3,13,47,121,156). The heparin binding domain of selenoprotein-P enables it to bind to endothelial cells, especially within the ESL, which contains heparin sulfates and chondroitin sulfates (12,13). This binding to endothelial cells is favored by the acidic pH present at sites of inflammation, with pH decreases as large as 1 unit in acidosis or anoxia, as indicated by the increased fixation of selenoprotein-P in muscle during exercise (38,47,48,128). The binding is also sensitive to ionic strength (13). Two sites of fixation may exist, one with great affinity and a second with lower affinity for heparin, which may be due to an interaction with lysine residues (13,128).

Direct antioxidant action and endothelial protection by selenoprotein-P

In vitro studies

Selenoprotein-P has an extracellular phospholipid GPX4-like activity in vitro (232). However, thioredoxin (TRX) is a highly preferential substrate for selenoprotein-P, leading to the conclusion that selenoprotein-P should be considered as an extracellular TXNRD (48,272). A protective action of selenoprotein-P against ONOO⁻ has been observed in human plasma in vitro (14,15). Bound selenoprotein-P may have a protective function against ONOO⁻ at the surface of the endothelium (14,15,46,195,260). Other studies demonstrate further direct antioxidant effects of selenoprotein-P (38,52,272,277). In addition, purified selenoprotein-P inhibits lipopolysaccharide (LPS) by interacting with its histidine-rich regions at pathophysiologically relevant concentrations (313). Further in vitro sepsis studies are needed to confirm whether selenoprotein-P can protect endothelial cells in sepsis.

Animal studies

Although the effectiveness of selenoprotein-P in protecting the endothelium during the early phase of sepsis has not been tested in animal models to our knowledge, studies have been conducted in a rat model of oxidative damage of the liver with overproduction of ONOO⁻, which could be extrapolated to sepsis (16,46,49,50,55). Intoxication with diquat, a compound close to paraquat, induces lethal hepato-renal toxicity. In the rat model, massive liver necrosis occurs within 2 to 3 hours (55). In this model, Atkinson, Hill and Burk suggested that, in well-oxygenated hepatocytes, diquat, a redox-cycling compound, received an extra electron from NADPH-cytochrome P-450 reductase and became a free radical, diquat• (16). This electron was further donated to molecular oxygen (O₂), producing superoxide anion (O₂^{-•}), which was efficiently removed by superoxide dismutase within the hepatocyte (16). In areas with low O₂ tension, the diquat• may diffuse across the hepatocyte membrane to the extracellular space and be available to react with O₂ in the space of Disse to form O₂^{-•}. In this space, superoxide dismutase activity is low and NO• produced by endothelial relatively abundant. O₂^{-•} together with nitric oxide (NO•), leads to ONOO⁻ production (16). As a result, ONOO⁻ induces its hepatotoxic effects from the lumen of the vessels to the internal hepatic structure, especially the sinusoids of the centrilobular region (16). The overproduction of ONOO⁻ is considered as the key event leading to endothelial injury (16). Endothelial damage starts as early as 20 minutes after diquat injection, and sinusoids are devoid of endothelial cells in 2 h. Hepatocyte lesions occur 1 h before disruption of the plasma membrane, with mitochondrial swelling and necrosis (16) (see part A for sepsis-related endothelial lesions, especially Fig. 2) (90). Within minutes, massive lipoperoxidation occurs (16,49,55). In this model, the injection of 50 µg Se as Na₂SeO₃ at 6 and 10 h before diquat intoxication in Se-deficient animals did not increase GPX activity in liver, kidney, and lung, but protected against lipid peroxidation and mortality (55). Selenoprotein-P concentration

increased in these rats 6 h after the Na₂SeO₃ injection, with rapid ⁷⁵Se turnover (54). Subsequent experiments confirmed the contribution of selenoprotein-P to endothelial protection against ONOO⁻ in the liver, but also in the microcirculation (49). This protection did not involve intracellular GPX1 or plasma GPX (GPX3), which remained at less than 2% of the values measured in control rats. There was only a slight increase in intracellular liver GPX4, leading to the conclusion that the protection of the liver was selenoprotein-P dependent (49). The authors demonstrated, by immunohistochemical staining, that selenoprotein-P was bound to endothelial cells in the liver, especially in the centrilobular regions (50). Selenoprotein-P is therefore likely involved in protection of the endothelium against diquat toxicity in this model by detoxification of ONOO⁻ (16,46). In sepsis, as previously noted, among all the RHONS, ONOO⁻ formation at the surface of endothelial cells is considered deleterious against the ESL and endothelial mitochondria (see part A Fig. 4) (90).

In a mouse model of African trypanosomiasis (*T. congolense* and *T. brucei*), Bosschaerts et al. showed that the gene for selenoprotein-P was IL-10 dependent and part of the cytokine-associated myeloid M2 response (ability to antagonize the prototypic inflammatory response especially in situations of prolonged inflammation inducing, e.g., immunoregulation, encapsulation of parasite, matrix deposition and remodeling) (31,185,244). The N-terminal part of selenoprotein-P, which has peroxidase capacity, was crucial for an effective response against *T. congolense* (31). This N-terminal part of selenoprotein-P seems to be involved in the decrease in oxidative lesions in hepatocytes and in apoptosis in the liver immune cells (31). Through its antioxidant properties, selenoprotein-P may thus limit the concentrations of ROS via its N-terminal domain-mediated peroxidase enzymatic function (32).

Antioxidant action of GPX3

The antioxidant function of GPX3 in plasma is unlikely to be because of the low plasma GSH concentration (26,112). Plasma GSH concentrations are in the μ M range (about 20-30 μ M) but the K_m of GPX3 for GSH is in the mM range, which is the case within cells (112). GPX3 may exert its antioxidant action after specific binding to some basement membranes or to the extracellular matrix (ECM) (57,236). Its antioxidant function may therefore participate in the protection of the double endothelial barrier after ESL damage, as the endothelial oxidative damage expands from the vascular luminal surface to the tissue side in the acute phase of sepsis (see part A) (90).

Selenocompounds, especially sodium selenite, as oxidant cytotoxic chemotherapeutic agents

Small chemical selenocompounds have been studied as cytotoxic drugs in cancer because their cytotoxicity is more pronounced in active cells that have a lower threshold than in quiescent ones, as previously mentioned (85,191,203,210) (Fig. 2). Cytotoxicity varies greatly among selenium compounds, with Na₂SeO₃ being among the most oxidative (23,75,126,154,201,203,262,273), but also one of the most efficient Se donors for Se incorporation into selenoproteins (126,171,253,262) (Fig. 2). Hence, the toxicity of Na₂SeO₃ is transient and reversible over several hours or days as observed in animal intoxication, in Se poisoning, and in a phase I cancer dose-response study (23,40,60,89,154,203,238,254,273). This is most probably due to the rapid incorporation of the Se contained in Na₂SeO₃ into antioxidant selenoenzymes, which have the opposite action to the oxidant cytotoxic effects of high Na₂SeO₃ concentrations and doses (23,40,60,89,154,203,238,254,273).

In vitro studies on cancer cells

Attachment of malignant cells to the extracellular matrix or the endothelium is a crucial early step for the spread of cancer. Likewise, leukocyte to endothelium binding is a crucial step of the local response to tissue infection and to the early phase of sepsis (129). In HeLa cells, Na₂SeO₃ reduced cell adhesion, an effect that preceded its cytotoxic effects (311), and may involve a decrease in integrin-mediated adhesion (316). The same mechanism may be involved in the adhesion of activated leukocytes to the endothelium in oncological lymphedema (211).

The oxidant cytotoxicity of Na₂SeO₃ has been observed in various types of neoplastic cells, including from prostate, colon, liver, lung, bladder, glioblastoma, leukemia, and lymphoma (79,107,113,169,191,308,309,317). Selected studies on prostate cancer cells and immune cells are shown in

Table 1 (133,168,250,307,315), highlighting several factors relevant to the treatment of sepsis. Na_2SeO_3 oxidant cytotoxicity: (i) requires a concentration $> 2\text{--}4 \mu\text{M}$ to inhibit cell adhesion, preceding cytotoxicity; (ii) acts preferentially on detached rather than attached cells; (iii) specifically targets activated rather than quiescent cells (161,168,191,224). Na_2SeO_3 has complex cytotoxic effects – on mitochondria, endoplasmic reticulum, DNA and transcription factors – which lead to various cell death processes: apoptosis, necrosis, autophagy and necroptosis (79,224) (Fig. 2, upper-right corner). In glioblastomas implanted into nude mice, Na_2SeO_3 induced oxidative stress, and arrested cell growth in the G2M phase, from a concentration of $2.5 \mu\text{M}$. This effect preceded effects on necrosis and apoptosis that occurred from concentrations of $2.5 \mu\text{M}$, and especially from $5 \mu\text{M}$ via caspase 3 (23). This cytotoxicity results from interaction between RSe^- and R-SH in the presence of O_2 leading to thiol oxidation, formation of RS-Se-SR adducts, and protein $\text{RS-SR}'$ aggregation. The resulting redox cycling induces $\text{O}_2^{\cdot-}$ and hydrogen peroxide (H_2O_2) production in a dose-dependent manner (63,79,111,224,252,262,292) (Fig. 2, upper-right corner). In addition, HSe^- reacts with amino acids and induces toxic breaks in the DNA (161,191,210) (Fig. 2). In activated cells, such as cancer cells, the redox potential of which is already increased, the mitochondria seem to be a specific target of Na_2SeO_3 toxicity (111,183,308). Na_2SeO_3 induced mitochondrial swelling already at concentrations of $0.1 \mu\text{M}$, with a dose-dependent effect, and exerted a major effect at $10 \mu\text{M}$. At this concentration, exposure for 10 minutes induced an 80% decrease in the mitochondrial GSH concentration and release of cytochrome c. Na_2SeO_3 also induced opening of the mitochondrial permeability transition (MPT) pore complex, via thiol- and NADH/complex I-dependent reduction (249) and calcium release. This mitochondrial dysfunction increased the production of ROS and the intracellular redox potential in macrophages and T cells, leading to cell death with necrotic characteristics (250) (Table 1). In this study, Na_2SeO_3 at concentrations $\geq 5 \mu\text{M}$ for 72 h induced cell death of Jurkat T cells and macrophages (215). $\text{Na}_2\text{SeO}_3 > 10 \mu\text{M}$ increased $\text{O}_2^{\cdot-}$ production in isolated rat liver mitochondria. Pretreatment with *tert*-butyl hydroperoxide, a superoxide scavenger, protected Jurkat T cells and macrophages against Na_2SeO_3 -induced cell death ($10 \mu\text{M}$). This cell death was preceded by a rapid loss in the cellular capacity of Jurkat T cells and macrophages to generate ROS production. The authors suggested there was a shift in the cellular redox balance (increase in mitochondrial $\text{O}_2^{\cdot-}$ and decrease in hydrogen peroxide) under Na_2SeO_3 at concentrations greater than the toxicity threshold, and that one of the mechanisms of Na_2SeO_3 cytotoxicity in macrophages and T cells may be the targeting of mitochondrial manganese superoxide dismutase (250). Fig. 2 presents a schematic view of the oxidant or antioxidant metabolism induced by Na_2SeO_3 depending on its concentration above or below a micromolar threshold (upper-right corner to center right-hand box), and the general acute toxicity of Na_2SeO_3 (center-left box) (78,82,96,97,105,111,126,150,189,268,269,279).

Animal studies

As early as 1956, Weisberger and Suhrland, using cell, animal and human experiments, observed the cytotoxic effect of selenocystine against leukemic leukocytes, Murphy lymphosarcoma, and leukemia. They observed that DL- or L-selenocystine reduced the influx of S^{35} L-cystine into leukemic leukocytes (301). They suspected a competition between L-selenocystine and L-cystine for membrane permeability, which was demonstrated much later by the oxidative-stress-inducible cysteine/glutamate exchange system (65,165,202). Rats receiving intra-peritoneal (IP) administration of 1 mg/kg SeCys_2 per day for 14 days had markedly reduced tumor growth compared to controls (301). Nearly 60 years later, data suggested that $20 \mu\text{M}$ Na_2SeO_3 could induce cell cycle arrest at the G0/G1 phase, apoptosis and necrosis in acute promyelocytic leukemia NB4 cells, and reduce CD33 positive cells in spleen and liver in a mouse model (6).

Clinical trials in cancer patients

In the third step of the study by Weisberger and Suhrland, selenocystine was administered orally to two patients with acute leukemia and two with chronic myeloid leukemia at a dose of about 100 mg per day (from 50 to 200 mg/day) for 10 to 57 days. A striking decrease in total leukocyte count was observed within several days (301). The margin of safety for Na_2SeO_3 in cancer treatment is, however, a matter of concern, as was shown in a phase I clinical trial performed in 2015 patients with carcinoma who were refractory to cytostatic drug treatment. Doses higher than 10.2 mg/m^2 Se as Na_2SeO_3 (17 mg in a patient with a 1.72 m^2 surface area)

induced acute respiratory distress of cardiac or pulmonary origin or both, despite a slow 4 hour infusion (40) (Fig. 2, center-left box).

The early stages of sepsis and the acute phase response are characterized by very low plasma selenium and selenoprotein-P concentrations

Reference values for plasma Se and selenoprotein-P are given in Table 2 (46,48,54,84,93,195,200,217,219,231,299). At ICU admission, plasma Se concentration is low in patients with sepsis, at about 40 to 50% of reference values (Fig. 3; studies a, b and c) (27,93,233). Moreover the degree of decrease in plasma Se at admission to the ICU is directly related to the severity of sepsis (9,27,93,119,138,233). In hospitalized patients with coronavirus disease 2019 (COVID-19), especially non-surviving patients, plasma Se concentrations are also reduced (Fig. 3; study f and fd) (193). Patients with severe trauma, a situation of APR, have similarly low plasma Se concentrations (Fig. 3; study g) (33).

At ICU admission, plasma selenoprotein-P concentrations are also low in patients with sepsis, down to 30% to 40% of the reference value (Fig. 3; study d, n=11, study e, n = 318). Selenoprotein-P has even been reported to be undetectable in the plasma of patients with septic shock (Fig. 3; study d) (87,127). A low plasma selenoprotein-P concentration is also observed in hospitalized patients with COVID-19, especially in non-survivors (Fig. 3; study f, and fd), and in patients with severe trauma (Fig. 3, study g). A low selenoprotein-P concentration thus seems to be the main component involved in the observed decrease in plasma Se (Fig. 3, study e) (87).

ICU trials using intravenous Na₂SeO₃ in patients with sepsis, septic shock or APR

As a consequence of the low plasma Se and selenoprotein-P concentrations seen in patients with sepsis or an APR, reaching values similar to those observed in severe Se deficiency, several clinical intervention trials have been performed based on the hypothesis that these patients are Se deficient (4,9). However, this hypothesis is questionable (22,193) (Figs. 3, 4 and 5), as developed later, based on animal studies that are rarely cited. If such a deficiency does occur in sepsis or APR, situations of oxidative stress, it would be rational to consider that increased requirements of Se may be necessary to form selenoprotein-P (9). However, such a deficiency is unlikely in the absence of Se loss during sepsis, outside specific situations, such as extensive burns or previously existing deficiency (66,85). In addition, no preclinical studies have been carried out to validate the hypothesis of Se deficiency and the early induction of selenoprotein-P synthesis by large doses of Na₂SeO₃. The margin of safety of Na₂SeO₃ when given as an intravenous bolus injection has not been assessed in sepsis, to our knowledge, apart from in our preliminary study (developed further below (88)).

Beneficial effects of Na₂SeO₃ were observed in a phase II study in patients with septic shock, using a 30 min intravenous (IV) bolus dose of 1 mg Se as Na₂SeO₃, followed by a continuous infusion of 1 mg Se as Na₂SeO₃ /day for 14 days (9). The negative results of the phase III trial in ICU patients with sepsis, with a similar design to that of the study by Angstwurm et al. (9), and the corresponding meta-analysis confirm that Se administration did not improve outcomes in sepsis (27,182,225), but did not exclude interest in the effect of the peak in Na₂SeO₃ achieved after rapid IV administration. Further studies have been conducted in patients with sepsis or an APR, and the authors of a meta-analysis in 2019 concluded that selenium supplementation may have beneficial effects on overall mortality but not on 28-day mortality, length of stay in the ICU or duration of ventilation (314).

In animal models

As previously indicated, several animal studies have been conducted that do not support the hypothesis of Se deficiency in the acute phase of sepsis but rather a marked downregulation of hepatic selenoprotein-P release.

In animal models of sepsis (mice, rat and sheep models), there is an early and profound decrease in plasma concentrations of Se and selenoprotein-P in the early phase (Fig. 4), making erythrocyte Se concentration more useful to diagnose prior Se deficiency (66,186,259) (Fig. 3, right part). In Figs. 4 and 5, animal studies in sepsis are numbered in chronological order according to their publication date. The sheep model (Fig. 4, study 2) is a model close to the clinical situation (296). These sheep undergo endotracheal intubation and mechanical ventilation and receive fluid loading based on arterial pressure and pulmonary artery catheter-derived data using an algorithm similar to that used for early patient resuscitation (266,296). A significant decrease in blood pressure occurs at 10 hours post-induction, and lactate concentrations increase significantly by 14 hours, 4 hours before death in control animals (266,296). In this model, plasma Se

concentration decreased rapidly after the onset of peritonitis, reaching 70% of the baseline value at 3 hours and 30% of the baseline value at 9 hours.

In a non-exudative, non-lethal burn model in rats (Fig. 4, study 3), the degree of the slope and the magnitude of decrease in plasma Se concentration in relation to the total body surface area were linked to the magnitude of the APR (2,109,197,213,234). A decrease in plasma selenoprotein-P may be an earlier marker of severity than an increase in plasma lactate, which forms part of the definition of septic shock (251). In a sublethal mouse model, GPX3 concentration and activity remained stable during the first 24 hours (Fig. 4, study 5), whereas selenoprotein-P concentration decreased (248).

Downregulation of selenoprotein-P expression and liver excretion, but not of GPX3, in the acute phase of sepsis (and APR)

Cellular mechanisms that may be involved in selenoprotein-P downregulation

First, selenoprotein-P promoter characteristics favor negative regulation by inflammatory acute phase cytokines involved in the cytokine-associated myeloid M1 phase response (prototypic inflammatory response such as innate activation with pro-inflammatory cytokines and NO•), including transforming growth factor- β_1 (TGF- β_1), secreted by activated macrophages, interferon gamma (IFN- γ), tumor necrosis factor- α (TNF- α) and interleukin (IL-1 β), the last of these having the strongest inhibitory effect (73,185,195,196,244). Conversely, positive regulation of selenoprotein-P has been observed in the M2 phase response by IL-10, and indirectly by IL-13, IL-4, and IL-4R α (31,100,185).

Second, in hypoxic conditions, selenoprotein biosynthesis is reduced, probably by a posttranscriptional regulatory mechanism (19,264). In this situation, synthesis of intracellular GPX4 instead of selenoprotein-P may be favored by hepatocytes, for protection against stress-induced death (19).

Third, in hepatocytes exposed to LPS, impaired selenoprotein-P secretion was reported despite increased selenoprotein-P expression (313). Selenoprotein-P was kept inside the hepatocyte, which may also be an adaptive mechanism for cell protection against hyperoxidation, especially within the endoplasmic reticulum (ER). This raises the possibility that increased intracellular selenoprotein-P provides cell protection (313).

Finally, liver mitochondrial dysfunction in sepsis may impair the highly energy-requiring synthesis of selenoprotein-P (34,36,117,131,181,214,227,229,283).

Animal studies

The hypothesis of downregulation of selenoprotein-P in the acute phase of sepsis is confirmed in vivo in rat and mouse models. Animal models highlight the downregulation of selenoprotein-P liver synthesis: reduced HSe⁻ synthesis, downregulation of Sec insertion, decreased selenoprotein-P mRNA and post-transcriptional selenoprotein-P synthesis inhibition (Fig. 2; Fig. 4 and Fig. 5, studies 4 and 5) (221,248). Selenoprotein synthesis and concentrations in various organs match the redistribution of Se from the liver to the tissues observed in septic rats (Fig. 4 and Fig. 5, study 1) (176), and in a less severe non-lethal burned rat model (2,234). In contrast with the hypothesis of acute Se deficiency, the liver Se content returned to baseline after resolution of the innate response in the non-lethal rat model (Fig. 4 and Fig. 5, study 1). In addition, the results from the sheep peritonitis model suggest difficulty in overcoming the downregulation of liver selenoprotein-P excretion in the acute phase of sepsis. In our study, despite a dose of about 1 mg Se as Na₂SeO₃ in a 25 kg animal given by continuous infusion (0.04 mg/kg - about a quarter of the sheep's TBSe content), it was not possible to restore the baseline plasma Se concentration. In human congenital deficiency of SBP2, which is implicated in the last step of the multistep process for Se insertion into selenoproteins, Se supplementation failed to restore plasma selenoprotein-P concentrations (237) (Fig. 2, middle and right of the figure). In the acute phase of sepsis, selenoprotein-P synthesis and Se insertion are downregulated, so that Se supplementation is unlikely to be effective.

The downregulation mechanisms of selenoprotein-P release by hepatocytes may be a defense mechanism against microorganisms, limiting their ability to acquire Se, which is required for their growth and antioxidant defense against ROHNS, from the systemic circulation (48,103,159,170,256,258) (see part A for Fe and Se) (90). One should remember that the use of life-sustaining supportive therapies creates an unnatural human-made state in ICU patients with sepsis and the innate response of early sepsis may be inadequate in these conditions (see part A) (90). Moreover, some interventions currently used in the initial

phase of sepsis, such as aminoglycoside antibiotics or insulin, have a negative impact on selenoprotein-P synthesis (222,293). As liver selenoprotein-P excretion is downregulated in the acute phase of sepsis, an infusion of recombinant selenoprotein-P may be a means of protecting the endothelium at this stage. Concomitantly, high concentrations of the oxidant Na_2SeO_3 might be required to reduce the activity of leukocytes that damage the endothelium by an overwhelming production of ROHNS, especially ONOO⁻ (Fig. 6) (see part A) (90).

Importantly, although animal models are required for ethical reasons, especially when studying mechanisms of disease or assessing new, potentially toxic treatments, all sepsis models have limitations. One general advantage of animal models is that the time at which the inflammation or infection starts is known, which is usually not possible in clinical studies.

Despite the higher resistance to inflammation in rodents than in humans, mice models are commonly used to study sepsis. One of the models widely used is induction of an inflammatory response by injection of lipopolysaccharide (LPS). This LPS mouse model has a major limitation in that, although the LPS model mimics activation of Toll-like receptor 4 (TLR4) by Gram-negative bacterial wall components, it has been criticized for its hyperinflammatory nature, with no actual infection present (61,62,81,160,263,297). However, the LPS models may be more reproducible than bacterial models, which may vary regarding bacterial loading charge, and additional ischemic colitis or formation of an abscess for cecal ligation and puncture models (62,263). In the peritonitis sheep model previously cited, a peritoneal injection of a precise quantity of feces has been used, although initial experiments used cecal ligation and puncture (265,267). In addition, the acute response varies depending on the model used, being generally stronger in LPS models than in cecal ligation and puncture models or models with injection of Gram-positive or Gram-negative bacteria (61). However, in ICU patients with bacterial sepsis, the infection will generally have been treated with antibiotics and source control (e.g., catheter removal, surgical drainage of infected abscess) if required (77,141,282,285). This situation could not have been anticipated by adaptive mechanism and the sepsis reaction continues despite the infectious ‘cause’ having been effectively removed. In ICU patients with bacterial sepsis, the host response is thus more an inflammatory response caused by a treated infection, than a response to an ongoing infection. The LPS model could therefore be considered relevant in this setting, despite its limitations.

A major limitation of all sepsis mice models is that the protein contents and responses of animals, particularly those in rodents and for proteins in serum, may differ from those of patients (61,62,81,160,226,245,263,297,298) (Table 2). Nevertheless, numerous reagents have been developed for mice that make mice models the most common preclinical model for sepsis (263). Selenoprotein expression is also a difficult domain to study. Such research has been conducted in mice when studying diabetic mellitus in relation to hypothalamic oxidative stress (37,310) and more generally in mammalian selenoprotein expression (264).

Another key limitation of all sepsis animal studies is that every model is an approximation that attempts to mimic the situation of a patient with sepsis receiving resuscitation and/or organ support yet such patients are very heterogeneous in term of inflammatory response, unlike the animal models (62,245,284). It is very difficult to summarize in just a few animals the many different characteristics of hundreds of patients included in a phase III clinical study. Because of limited animal numbers, it is necessary to have a homogeneous control group. The supportive care in the large sheep animal sepsis model is close to patient resuscitation with fluid loading guided by pulmonary artery catheter and ventilation through intubation (265,267). However, as an illustration of this limitation on control group, it was not possible in the peritonitis sheep model to add antibiotics after the induction of the peritonitis, because of possible survival of some control animals and the need to obtain a reproducible survival time in the control group (265). Yet in ICU patients, peritonitis would have been treated with source control and antibiotics (77,141,285). It is also not possible to perform direct measurements of plasma selenoprotein-P in sheep.

Despite these limitations of animal models, the similarity of the decrease in plasma selenoprotein-P or selenium concentration seen in the acute phase of sepsis in the various mammalian models –LPS mice, LPS rats and peritonitis sheep– favors the extrapolation of these results for further exploration in the clinical arena (Fig. 3 and 4).

Sodium selenite as an oxidant cytotoxic agent in sepsis

Selenite may have beneficial cytotoxic effects on hyperactivated leukocytes in sepsis

Oxidation by Na₂SeO₃ induces loss of function and cell death in leukemic cells and activated macrophages due to redox cycling, as previously developed in the earlier section on “Selenocompounds, especially sodium selenite, as oxidant cytotoxic chemotherapeutic agents” (63,79,111,224,252,262,292). Hyperactivated leukocytes may have reduced cell adhesion and oxidative functions, and be driven towards apoptosis, necrosis, autophagosis, pyroptosis or necroptosis at a lower concentration threshold of Na₂SeO₃ than quiescent leukocytes, but nevertheless within micromolar ranges (Fig. 2, upper-right corner and center-right box and Fig. 6). During sepsis, the upregulated expression of the cysteine/glutamate exchange system in neutrophils and macrophages might also favor the uptake of Na₂SeO₃, as with cancer cells (65,202) (Fig. 2, upper-right corner). Nevertheless, Na₂SeO₃ is likely to have only a transient cytotoxic action, as it acts equally as a Se donor, inducing the synthesis of antioxidant selenoenzymes (43,126,171,253,262,294) (Fig. 2, lower-right corner).

Cell studies

Kim and Stadtman first introduced the concept of using the oxidant properties of Na₂SeO₃ in sepsis in 1997 (147). They reported that the addition of Na₂SeO₃ to the nuclear extraction buffer at concentrations > 3 to 5 μ M for 20 minutes inhibited NF- κ B binding to DNA. Inducible NO synthase (iNOS) was inhibited by Na₂SeO₃ in LPS-activated Jurkat T cells in a dose-dependent manner from 5 μ M to 100 μ M (147). Similarly, Na₂SeO₃ can inhibit activator protein (AP-1) binding to DNA (114), or reverse the activation of NF- κ B in human airway epithelial cells (139). Finally, the cytotoxic action of Na₂SeO₃ on activated macrophages decreases their ROS production and later cell death (168,250) (Table 1).

Animal studies

In a non-resuscitated Wistar rat model, a 70% lethal IP dose of LPS caused them to become rapidly ill within hours; they were prostrated, asthenic and had diarrhea. By contrast, rats that were given an IP dose \geq 0.6 mg/kg of Se as Na₂SeO₃ 1 hour after the LPS remained apparently healthy for 5 hours, but all succumbed to fatal respiratory failure at 5 hours (88). The minimum lethal IP dose in control (non-septic) rats was 3 mg/kg Se as Na₂SeO₃ (88). From these results, we concluded that: (i) Na₂SeO₃ has a smaller margin of safety in sepsis; and (ii) if the margin of safety could be improved, interest in the cytotoxic effects of Na₂SeO₃ in sepsis may increase. The mechanisms of LPS and Na₂SeO₃ toxicity seem to differ (e.g., NO and lactate did not increase in case of Na₂SeO₃ toxicity). Therefore the toxic effects may not be cumulative, but may act in opposition to one another, at least up to a given Na₂SeO₃ concentration (88).

In a peritonitis sheep model, we assessed whether the mechanism of action of Na₂SeO₃ was as a Se donor or as a cytotoxic drug (9,85,86,296). High dose Na₂SeO₃ (between a quarter and a half of the TBSe of a 25 kg sheep) was injected 9 hours after the onset of peritonitis, by rapid IV injection of 2 mg Se (0.08 mg/kg) as Na₂SeO₃ followed by 0.06 μ g/kg/h Se (bolus group) or as a continuous infusion (4 μ g/kg/h Se as Na₂SeO₃), which should have delivered a similar Se dose to the bolus group if the survival time was increased (296). Our hypotheses were: (i) that a concentration of 2 to 4 μ M of Se as Na₂SeO₃ would be required to induce an oxidant cytotoxic effect on blood leukocytes; and (ii) that the beneficial effects would be related to the oxidant cytotoxic action of Na₂SeO₃ rather than to the Se intake. The rapid IV (bolus) injection led to a peak in plasma Se concentration between 4 to 15 μ M followed by a decrease in plasma Se concentration over 5 mins (296). Improvements in microcirculatory parameters, hemodynamic variables (macro-circulation), and survival time were noted in this group, and the increase in lactate concentrations was delayed by 5 hours. Despite the large Se intake, the continuous infusion group had a similar evolution to that of the control group: the Se concentration was 0.4 μ M until 12 hours and increased to 0.6 μ M at 18 hours, for an initial value of 0.8 μ M. We concluded that these results therefore support a beneficial effect of Na₂SeO₃ acting as a cytotoxic drug rather than as a Se provider, with benefit only seen with the peak in blood Na₂SeO₃ concentration obtained by rapid IV injection (296).

In a Lewis rat model, Gründling et al., using a closer analysis of the microcirculation, studied the effects of IP LPS injection on leukocyte to endothelium adhesion in the intestinal microcirculation with or without Na₂SeO₃ administered IV immediately after the LPS injection. They observed decreased leukocyte

to endothelium adhesion in the Na₂SeO₃ group and improved intestinal microcirculation 2 hours after LPS injection (106).

The peritonitis sheep model is a model that replicates as close as possible the resuscitation management routinely provided in patients with septic shock. The intravenous dose of Se (2 mg in a 25 kg animal, 0.08 mg/kg) was close to the highest Na₂SeO₃ dose administered intravenously in clinical sepsis studies (2 to 4 mg Se as Na₂SeO₃ the first day) (9,182,296,314). A dose of 4 mg is the highest dose considered as safe - by multiple oral ingestions - based on numerous animal toxicity studies (154,203). The rapid IV injection of 2 mg Se as Na₂SeO₃ enabled blood concentrations from 4 to 14 μM Se, likely as Na₂SeO₃, to be achieved which are in the range of cellular cytotoxic concentrations (Table 1, Fig. 2) (296). However, this peritonitis sheep study (253) was not designed to determine the margin of safety, the optimal regimen of Na₂SeO₃ administration in sepsis treatment, or the effect of combined selenoprotein-P and Na₂SeO₃ administration. Doses administered by IP injection to obtain beneficial effects in rats were much greater (≥ 0.25 mg/Kg Se as Na₂SeO₃, corresponding to 20 - 25 mg in humans). The minimum lethal dose was 3 mg/Kg in healthy rats, but decreased to values ≥ 0.6 mg/Kg in this LPS rat model (88).

Potential benefit of combining the endothelial protective effects of selenoprotein-P with the cytotoxic effects of Na₂SeO₃ in sepsis

A major intervention seems necessary to disrupt the dysregulated cascades or complex maladaptive state of the innate response seen in the early phase of sepsis and, especially, septic shock (5) (Fig. 8) (see Part A, Fig. 1) (90). Use of the cytotoxic effects of Na₂SeO₃ against activated leukocytes should reduce their associated oxidative stress and limit the inflammatory cascades in which they are involved (Part A, Fig 2, 3 and 4). However, Na₂SeO₃ may also be toxic against activated endothelium. In addition, cytotoxicity against leukocytes may increase release of danger-associated molecular patterns (DAMPs) if leukocyte necrosis occurs, which, in turn, could further activate the endothelium (part A) (91,142,143). An infusion of selenoprotein-P prior to the Na₂SeO₃ injections may transiently protect the endothelium and reduce endothelial activation, thus restoring the margin of safety of the oxidant cytotoxic effect of Na₂SeO₃, which targets the hyperactivated leukocytes, and may limit any activation of DAMPs (Fig.7). It is likely that this combined treatment would need to be repeated because the cytotoxic effects of Na₂SeO₃ should only have an impact on circulating leukocytes and not on the bone marrow, as shown in leukemia treatment (301). Moreover, the cytotoxic action of Na₂SeO₃ against circulating immune cells is transitory due to the oxidative action of Na₂SeO₃ especially on thiol groups and disulfur bridges (Fig. 2). In the peritonitis sheep model (296), the degree of increase in lactate concentration and its slope were similar in the bolus and control groups, although the increase occurred about 5 hours later in the bolus group suggesting that Na₂SeO₃ has a transient effect; a similar pattern was seen for hypotension.

Importantly, mitigation of oxidative stress may interfere with the bactericidal activities of immune cells. However, as previously indicated, in patients with sepsis, infection is generally treated effectively with antibiotics and source control (77,141,282,285); therefore, reducing the bactericidal activities of circulating immune cells in these patients may be less important than during the natural - without antibiotic and source control - evolution of infection. In addition, high concentrations of Na₂SeO₃ are likely to have bactericidal, antiviral and antifungal activities, at least in the blood (155,172,235,252), which may replace, to some extent, the decrease in bactericidal activities of immune cells.

As high Na₂SeO₃ blood concentrations may be a double-edged sword, this hypothesis needs to be tested in carefully conducted preclinical studies to (i) confirm and clarify whether high blood concentrations of Na₂SeO₃ - through rapid injection - could reduce leukocyte to endothelium adhesion; and (ii) whether the combination of perfusion of selenoprotein-P followed by rapid injection of Na₂SeO₃ could have a synergistic action and decrease the toxicity of Na₂SeO₃ in sepsis. Only then could clinical trials be performed using Na₂SeO₃ as a cytotoxic drug through rapid IV injection of therapeutic doses to achieve cytotoxic concentrations in the blood in combination with previously infused selenoprotein-P (166,305).

Conclusion

In our earlier manuscript (Part A) (90), we described the key role played by oxidative stress and increased redox potential in leukocytes and the endothelium, in the very early phase of sepsis and preceding endothelial damage (SHINE). Activated leukocytes present in this context may be considered as an acute, benign

hematological tumor. In the initial phase of sepsis, because of supportive care, patients can survive in an unnatural human-made state of dysregulated host immune response that could be considered as a complex maladaptive state. An intervention to interrupt the multiple interacting cascades at this phase could provide beneficial effects on outcomes.

In this manuscript, we highlight the dual function of selenoprotein-P, providing physiological Se transport from the liver to the tissue and having antioxidant effects, especially against ONOO⁻. GPX3 seems to have a secondary and above all a delayed function against endothelial oxidative damage. Experimental data support the concept that the decrease in plasma Se and selenoprotein-P concentrations in the very early phase of sepsis is related to downregulation of liver selenoprotein-P excretion, rather than to Se deficiency. Yet, Se supplementation for presumed Se deficiency has been the basis for many of the related ICU trials. This decrease in plasma selenoprotein-P seems to precede the increase in lactate concentrations by several hours. In addition, the downregulation of selenoprotein-P liver excretion makes it unlikely that Na₂SeO₃ could be an effective Se donor in the early phase of sepsis.

Multiple *in vitro*, *in vivo*, and human cancer studies have demonstrated the oxidant cytotoxic properties of high Na₂SeO₃ concentrations. Using the oxidant properties of Na₂SeO₃ to control sepsis was proposed long ago by Stadtman and colleagues (147). In addition to the reduction in NF-κB-related activation, hyperactivated leukocytes may be particularly sensitive to Na₂SeO₃ oxidant cytotoxicity. Experimental data from rats and sheep are in favor of such an action. However, the general cytotoxicity of Na₂SeO₃ is likely to be markedly increased in sepsis. Combining the benefits of the cytotoxic effects of peaks in Na₂SeO₃ concentrations to reduce leukocyte activity with the endothelial-protective effects of a selenoprotein-P infusion may prove to be a potentially valuable treatment in early sepsis to decrease the inflammatory reaction and oxidative stress - below a level that induces organ failure. Because of the double-edged nature of the suggested pharmaceutical approach, further evaluation in animal models is needed to assess effectiveness and safety before it can be considered for testing in clinical sepsis trials.

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Author Contributions

Xavier Forceville (X.F.) Pierre Van Antwerpen (P.V.A.), Djillali Annane (D.A.), and Jean-Louis Vincent (J.-L.V.) took part in the manuscript writing.

X.F.: conceived the review and wrote the first draft; P.V.A. critically revised the article, especially the biochemical aspects; D.A. and J.-L.V. critically revised the article, especially the clinical implications; all authors read and approved the final version.

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Dr Xavier Forceville created a very small start-up in 2005 (Sérénité-Forceville). In 2015, Pharm. V Cotereau volunteer manager of Sérénité-Forceville, former vice president of the French pharmacist association, filed a new patent for the treatment of sepsis entitled: “Kit for treating sepsis and/or any systemic (SIRS) or damaging cellular hyper-inflammation”. Its reference numbers are: PCT number PCT/FR2016/051569, European demand 16742342.5, US demand Attorney Docket Number: 0727-1267.

I am the main shareholder of this company. One of my brothers is also a shareholder.

Pr Pierre Van Antwerpen, Pr Djillali Annane and Pr Jean Louis Vincent declare no competing financial interests.

List of Abbreviations

AP-1 = activator protein-1
APR = acute phase response
COVID-19 = Coronavirus disease 2019
ECM = extracellular matrix
ESL = endothelium surface layer
ETE = essential trace element
Fe = iron
GPX = glutathione peroxidase
GPX1 = intracellular cytosolic GPX
GPX3 = plasma GPX
GPX4 = phospholipid hydroperoxide GPX
GSH = glutathione
HSe⁻ = hydrogen selenide
ICU = intensive care unit
IFN- γ = interferon gamma
IL = interleukin
IP = intra-peritoneal
IV = intravenous
LPS = lipopolysaccharide
MOF = multiple organ failure
MPT = mitochondrial permeability transition pore complex
M1 = type 1 cytokine-associated myeloid response
M2 = type 2 cytokine-associated myeloid response
Na₂SeO₃ = sodium selenite
NADPH = nicotinamide adenine dinucleotide phosphate
NF- κ B = nuclear factor kappa-light-chain-enhancer of activated B cells
NO• = nitric oxide
O = oxygen
O₂^{-•} = superoxide anion
ONOO⁻ = peroxynitrite
PLP = pyridoxal 5'-phosphate
PSTK = phosphoserine tRNA kinase
ROHNS = reactive oxygen, halogen and nitrogen species
ROS = reactive oxygen species
S = sulfur
SBP2 = SECIS-binding protein 2
SCLY = selenocysteine β -lyase
Se = selenium
Sec = selenocysteine
SECIS element = ARN selenocysteine insertion sequence
SeCys₂ = selenocystine
SELENOP = Selenoprotein-P
SeMet = selenomethionine
SEPSECS = Sec synthase

SHINE = shock induced endotheliopathy

SOFA = sequential (sepsis-related) organ Failure assessment score

SPS2 = selenophosphate synthetase 2

TBSe = total body selenium

TBW = total body weight

TGF- β_1 = transforming growth factor- β_1

TNF- α = tumor necrosis factor- α

TRX = thioredoxin

TXRND = thioredoxin reductase

TXNRD1 = cytosolic TXNRD

TXNRD2 = mitochondrial TXNRD

UGA codon = normally read as a stop signal but called the Sec insertion in the presence of a SECIS element

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Table 1 Acute cytotoxic effects of sodium selenite

Studies	Hypothesis	Main results centered on Na ₂ SeO ₃	Duration*	Cytotoxic effect (Na ₂ SeO ₃)	Cytotoxic concentrations
Detached/attached cells					
Skin BLB/c MK-2 keratinocyte cancer cells ¹ (1999)	Oxidative stress and apoptosis depend on selenocompounds.	Selenite, and for higher conc. selenocystamine, generated oxidative 8-OHdG DNA adducts and apoptosis but not selenomethionine. All induced selenoenzymes.	24 h	8-OHdG-DNA 64 μ M** (higher conc. induced cell detachment). Most probably by oxidative effect.	Apoptosis In detached cells 64 μ M 127 μ M 17% 99% In attached cells: No
Prostate cancer and normal cells					
Prostate LNCaP cancer cells (2001) ²	Acute and long term effect of Na ₂ SeO ₃ on redox state.	Na ₂ SeO ₃ acute exposure induced mitochondrial injury and cell death, mainly apoptosis. Induction of GPXs and TXRNDs is max for 0.5 μ M	72 h 24 h	Oxidative effect - Oxidative effect (protection by SOD mimic, or NAC) - Decreased GSH/GSSG for conc. > 0.5 μ M	Cell death (apoptosis?) 1 μ M 2.5 μ M 19% 92%
Prostate LNCaP cancer cells (2009) ³	Role of O ₂ ^{-•} and mitochondrial dysfunction in Na ₂ SeO ₃ cytotoxicity.	- Na ₂ SeO ₃ induced: (i) cell death and apoptosis by O ₂ ^{-•} (inhibited by MnSOD); (ii) decrease of MMP; (iii) release of cytochrome c and activation of caspases 9 & 3. - Effects are dose and time dependent.	6 min 18h 5d	O ₂ ^{-•} & mitochondria 2.5 μ M: O ₂ ^{-•} increased MMP divided by 6 No decrease in cell viability for conc. lower than 1 μ M	Cell death 1.5 μ M 2 μ M 45% 50%
Normal and malignant prostate cells ⁴	Mechanism of the greater sensitivity of cancer cells than normal cells (already reported) to Na ₂ SeO ₃ .	- Cancer prostate cells were more sensitive to NaSe than matched pairs of normal prostate cells, in which MnSOD was greater. - Higher GSH content may explain the higher NaSe conc. required than for LNCaP	48h	Bcl-2/bax Na ₂ SeO ₃ (25 to 100 μ M) decreased Bcl-2 expression and increased bax only in cancer cells. This results in decreased Bcl-2/bax ratio in cancer cells.	Apoptosis Cancer cells 25 μ M 50 μ M 100 μ M 4-12% 7-30% 12-35% Normal cells 25 μ M 50 μ M 100 μ M 1-5% 2-10% 5-10%
Immune cells					
Jurkat T (JT) cells and J774.2 Macrophages (MP) ⁵	Mechanism of Na ₂ SeO ₃ -induced cell death on immune cells.	Na ₂ SeO ₃ concentration > 5 μ M induced cell death by necrosis instead of apoptosis in JT and MP. Cytotoxic effect may be related to MnSOD blockage leading to increased conc. of O ₂ ^{-•} within the mitochondria.	6 h 72 h 72h	ROS production 10 μ M for MP or 100 μ M for JT lead to 75 %** and 50%+ loss of ROS prod. Na ₂ SeO ₃ at 1 μ M did not affect JT and MP viability	Cell death (necrosis?) For both JT and MP 5 μ M 10 μ M 30 μ M ≠50% ≠80% 80+-95%+ Oxidative mitochondrial damage is suspected.
Leukemia NB4 and Jurkat cell line and normal monocyte cells ⁶	Mechanism of Na ₂ SeO ₃ -induced cell death in leukemic cells	Inhibition of RhoA/ROCK1 activation by Na ₂ SeO ₃ in leukemic cells – but not in normal monocytes – inducing Erk1/2 mediated apoptosis.	6h 18h	RhoA/ROCK1 axis Reduced activation	Apoptosis 20 μ M ≠ 40% in leukemic cells vs no in non-activated monocytes

Results are given only for selenite; Na₂Se: sodium selenite (Na₂SeO₃); Concentrations are expressed in μmol/L (μM) Se as Na₂SeO₃; 1 μg Se /L corresponds to 0.0127 μmol/L (molecular weights of Se and Na₂SeO₃ are 78.96 and 172.9 g/mol, respectively); * Duration: duration of exposure in minutes (min), hours (h), or days (d); con.: concentration; 8-OHdG DNA adducts: 8-hydroxydeoxyguanosine deoxyribonucleic acid ; ** 64 μmol/L was the lowest concentration studied ; GPXs: Glutathione peroxidases; TXNRDs: Thioredoxin reductases ; SOD : superoxide dismutase; NAC: N-acetylcysteine ;GSH: Glutathione (reduced form) GSSG: Glutathione disulfide (oxidized form) ; O₂^{•-}: Superoxide anion; MMP: mitochondrial membrane potential; Bcl-2/bax: Anti-apoptotic Bcl-2 protein family associates with the outer mitochondrial membrane and counteracts effects of pro-apoptotic bax (Bcl-2 like protein 4); ROS: Reactive oxygen species; JT: Jurkat T cells; MP: Macrophages; prod: production. RhoA: prototype protein of Rho GTPases superfamily/ ROCK1: Rho-associated coiled-coil-forming kinase 1 (Upregulation of RhoA and ROCK1 is related to cancer progression); Erk1/2: Extracellular signal-regulated kinase 1 and 2.

¹ (262); ² (315); ; ³ (308); ⁴ (133); ⁵ (250); ⁶ (168).

Table 2. Reference values for plasma selenium (Se) and selenoprotein concentrations

<p>Total plasma Se (France, Belgium)¹: $1 \pm 0.15 \mu\text{mol/L}$ (incorporated into proteins) Total plasma Se (US)²: 1.57 ± 0.01; median 1.4 (1.1 – 1.9) $\mu\text{mol/L}$ About 60% of plasma Se is contained in selenoprotein-P, 30% in GPX3 and 10% in albumin. Selenoprotein-P: 40-80 nmol/L corresponding to about 5-6 mg/L GPX3: 260-340 nmol/L corresponding to about 26 mg/L Unregulated pool of Se (Se-methionine mainly included in albumin) increase for plasma $> 1.1 \mu\text{mol/L}$ ³ Small Se metabolite molecules account for less than 1-3% of total plasma Se ⁴. Whole body Se in a Se-replete person is about 18 $\mu\text{g}/100\text{g}$ ⁵. With 39 ml/kg of plasma volume, plasma Se contains an average of 0.3 mg about 2% of total body Se (10-15 mg Se)⁵ and plasma selenoprotein-P about 1.3% of total body Se. It is less with a European Se intake, about 0.2 mg Se.</p> <p>In rats (control rats)⁶ Total plasma Se: 6.9 to 5.6 $\mu\text{mol/L}$ About 60% of plasma Se is contained in selenoprotein-P Selenoprotein-P: about 26 mg/L ⁶ (plasma volume of 4% body weight) Whole body Se is about 15 $\mu\text{g}/100 \text{ g}$. Plasma Se contains about 13% of total body Se, and plasma selenoprotein-P about 8% of total body Se. In tissue, GPXs contains between 33 to 40% of total body Se.</p>
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Se: Selenium; GPX3: plasma glutathione peroxidase (231); Selenoprotein-P contains up to 10 selenocysteine residues; Equivalence for selenium: $1 \mu\text{mol/l} = 78.9 \mu\text{g/l}$; $1 \mu\text{g/l} = 0.013 \mu\text{mol/l}$ (46,195). ¹ (93,200) ² (84), see Rayman for other values in Europe (217). ³ For a plasma concentration of 1.6 $\mu\text{mol/L}$ in US, with 67% of Se in selenoproteins, 75% of Se in selenoproteins is under the form of selenoprotein-P, and 25% under the form of GPX3. The additional 33% Se is, in proteins, mainly albumin under the form of Se-methionine (48,299). Plasma Se concentration $> 1.1 \mu\text{mol/L}$ leads to a plateau for GPX3 and selenoprotein-P (48). ⁴ (51,116) ⁵ Body Se content varies from less than 5 mg to over 20 mg depending on Se intake. It seems likely to be between 10-15 mg in a Se-replete person weighing 70 kg (48). ⁶ (54,219).

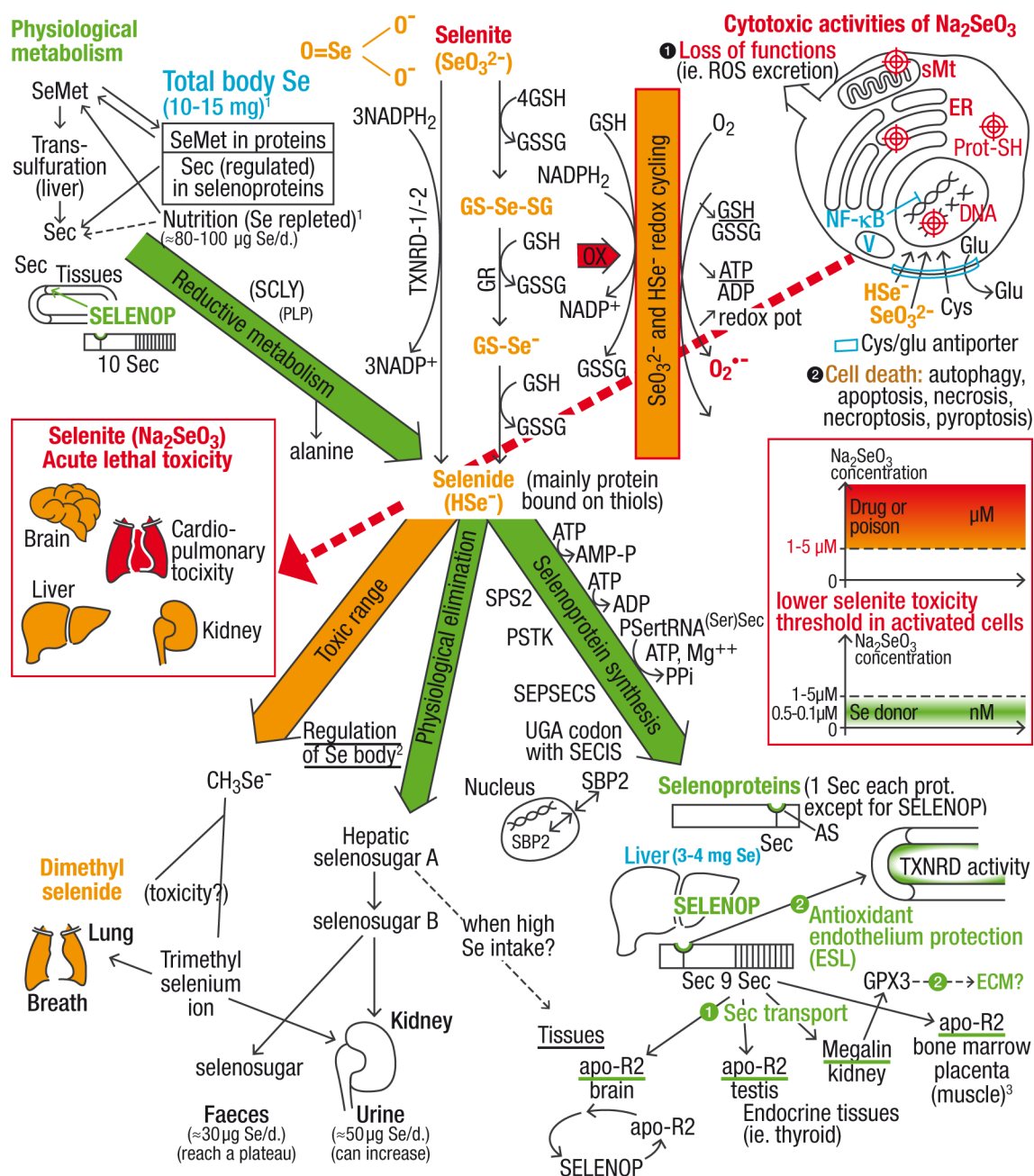
Figure 1 Comparison between serine, cysteine and selenocysteine

		pKa	Atomic number	Electronegativity	Polarizability
Serine (Ser)	$\begin{array}{c} \text{H} \\ \\ \text{NH}_3^+ - \text{C} - \text{COO}^- \\ \\ \text{CH}_2 - \text{OH} \end{array}$		8	3.44	O
Cysteine (Cys)	$\begin{array}{c} \text{H} \\ \\ \text{NH}_3^+ - \text{C} - \text{COO}^- \\ \\ \text{CH}_2 - \text{SH} \end{array}$	8.22	16	2.58	S 2.9 Å³
Selenocysteine (Sec)	$\begin{array}{c} \text{H} \\ \\ \text{NH}_3^+ - \text{C} - \text{COO}^- \\ \\ \text{CH}_2 - \text{Se}^- \end{array}$	5.43	32	2.55	Se 3.89 Å³

The respective pKa values of cysteine (Cys) and selenocysteine (Sec) are indicated. At physiological pH, Sec is dissociated whereas Cys is not. Sec is present at the active site of selenoenzymes, required for their activity and specifically inserted (see Fig. 2, *lower-right corner*). For the chalcogen atoms O, oxygen; S, sulfur; and Se, selenium are indicated: in the *upper left quadrant* their atomic number; in the *bottom left* their electronegativity and in the *bottom right* their polarizability (measure of how easily an electron cloud is distorted by an electric field). Selenomethionine is not indicated on this figure. The Se inserted in place of S in methionine is not considered biologically active, is non-specifically inserted, and constitutes a Se pool (see Fig. 2, *upper-left corner*).

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Figure 2 General metabolism of selenium, and the oxidant or antioxidant effects of selenite according to its cellular concentration



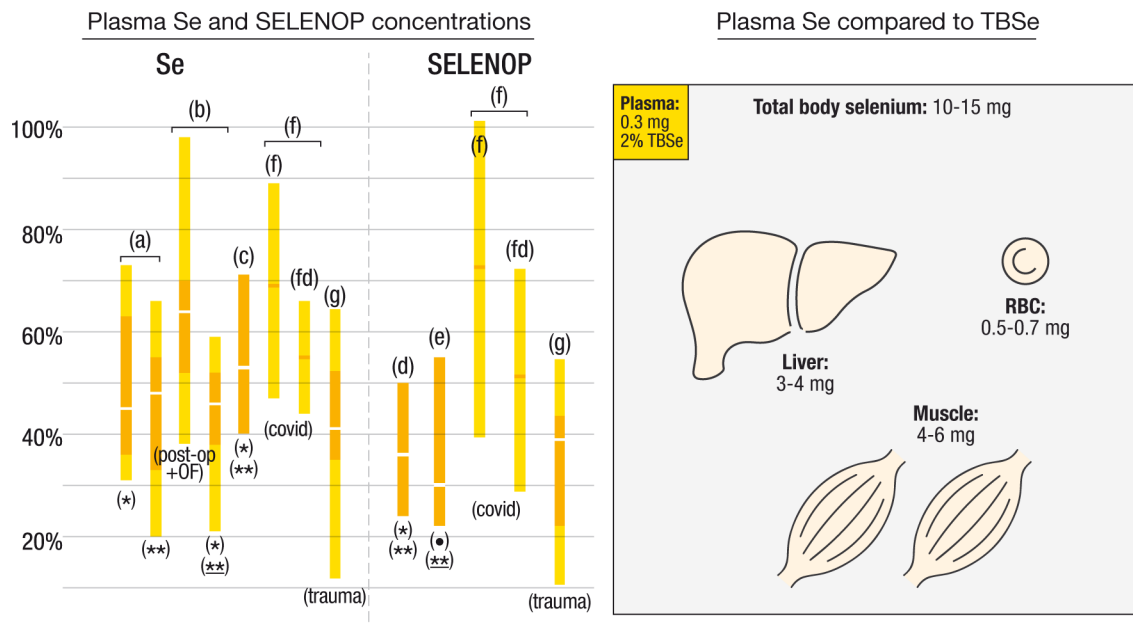
Physiological metabolism: (from upper-left to lower-right corner) The average total body Se content indicated corresponds to that of a 70 kg person replete in Se. It is in the form of selenomethionine (SeMet) and selenocysteine (Sec) provided by ingestion and protein catabolism. In the liver, SeMet could be transulfurated to Sec, which is reduced by selenocysteine β-lyase (SCLY) in the presence of pyridoxal 5'-phosphate (PLP) into alanine and the checkpoint selenocompound, selenide (HSe⁻) – mainly bound to proteins – before the Se is inserted into Sec only present at the active site (AS) of antioxidant selenoenzymes (green line in the cavity of the rectangle). A complex energy-requiring process involving the selenoenzyme selenophosphate synthetase 2 (SPS2), phosphoseryl tRNA kinase (PSTK) and Sec synthase (SEPSECS) allows Sec cotranslational insertion through a phosphoseryl-tRNA^{(ser)sec} (PSerRNA^{(ser)sec}) into the active site of selenoproteins, in the presence of cytoplasmic Sec insertion

sequence (SECIS)-binding protein 2 (SBP2) factor (*green line*). Its insertion used a UGA codon that called for Sec insertion in presence of the SECIS element. The liver delivers Sec to the tissues within the selenoprotein-P (SELENOP), which contains 10 Sec, as an exception (*green lines*). Sec is transported from the liver to the tissues by selenoprotein-P, which binds receptors such as apo-R2, and megalin. Selenoprotein-P also has an antioxidant thioredoxin reductase activity (TXNRD) and non-specific binding favored by acidosis. Physiologically, Se is eliminated in urine and – in cases of intoxication – by the breath. Cytotoxicity (*from upper-right to lower left*): SeO_3^{2-} is one of most toxic selenocompounds. However, nanomolar SeO_3^{2-} concentrations induce selenoprotein synthesis, without toxicity. Its cytotoxicity is concentration-dependent above about a 1-5 μM threshold, which is lower in activated than in quiescent cells (*right-hand box*). SeO_3^{2-} and HSe^- cellular intake involves the cystine/glutamate exchange system (Cys/glu antiporter), which is overexpressed in neutrophils and macrophages during sepsis. The toxicities of SeO_3^{2-} and its subsequent compounds up to HSe^- are due to their ability to generate superoxide anion ($\text{O}_2^{\bullet-}$) in the presence of oxygen and reduced glutathione (GSH) in various redox cycling processes (*medium-right part*). They react with thiol group (RSH) by a one-electron transfer, produce reactive oxygen species, consume intra cellular glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH) and increase the intracellular redox potential.

Cellular toxicity: (*upper-right corner*) the main targets are protein oxidation (Prot-SH), lipid peroxidation in mitochondria illustrated as a swollen form (sMt); endoplasmic reticulum (ER); and DNA inducing double strand breaks. In addition, SeO_3^{2-} could inhibit transcription factor to DNA binding, or cell adhesion. Cell death related to SeO_3^{2-} occurs by all known mechanisms. Acute general toxic symptoms of SeO_3^{2-} (*middle left-hand box*) are similar to sepsis with multiple organ failure and especially cardiopulmonary failure - *illustrated in red*. However, SeO_3^{2-} toxicity is transient as the produced HSe^- can be further metabolized into Sec.

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Figure 3 Low plasma Se and selenoprotein-P concentrations at admission to ICU in sepsis and septic shock, trauma and COVID patients. Plasma Se compared to Total Body Se (TBSe)

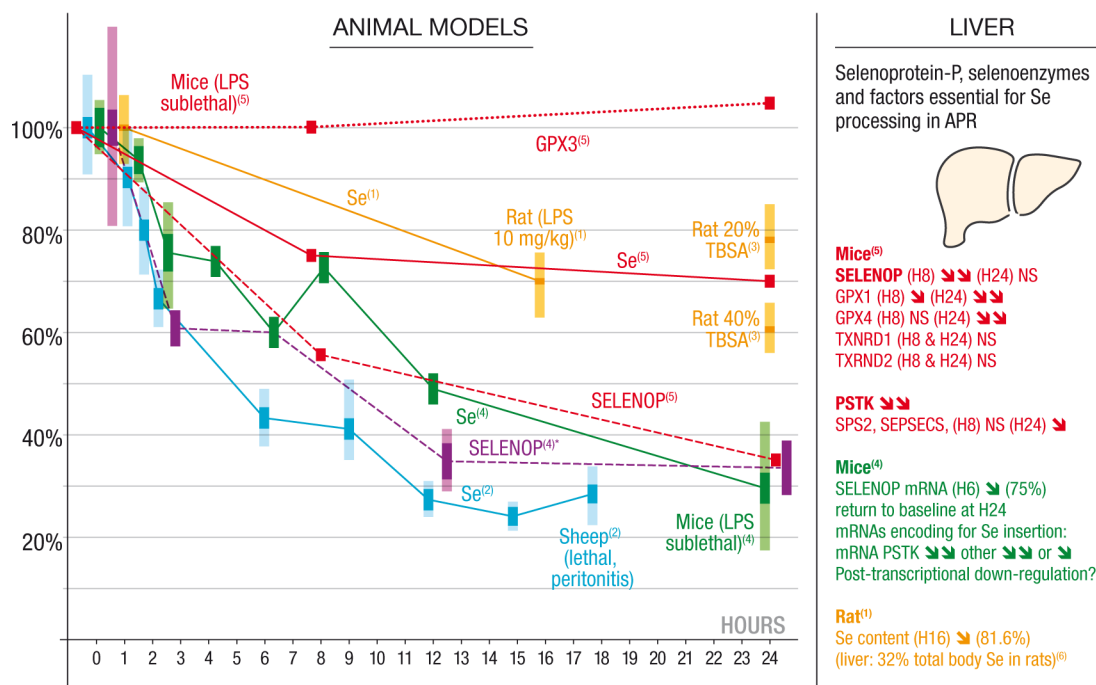


(Left part) On admission to the ICU, low plasma Se and selenoprotein-P (SELENOP) concentrations are observed in non-COVID sepsis (*) and septic shock (**) patients but also in patients with COVID-19, or an acute phase response (APR) (•), such as trauma patients (expressed as a percentage of reference values). Results are given in medians with the top and bottom of the box encompassing the 25th and 75th percentile and capped lines indicating the 10 to the 90th percentile, or mean and standard deviation. The corresponding studies for plasma Se concentration are classified by their publication date: (a) sepsis patients n = 13, septic shock patients n = 12 (93); (b) 15 post-operative patients with organ failure (OF), and 15 sepsis patients of which 12 had septic shock (underlined) (233); (c) sepsis and septic shock patients n = 1089 (27); (f) COVID-19 patients at admission to hospital and during hospitalization (n= 33 patients, samples = 166), (fd) decrease is significantly lower in deceased patients than in surviving patients (193). Results are given as mean \pm SD (193); (g) severe trauma patients at admission to hospital (n = 24) (33). When not cited, the reference plasma Se value of the German study by Sakr et al. and of the EPIC study were chosen (132,233). Similarly, for the SELENOP, the reference value of the EPIC study was chosen (132). For plasma selenoprotein-P, the corresponding studies are: (d) severe sepsis and septic shock ICU patients (n = 60) (127); (e) APR with OF and mainly septic shock patients (underlined) (n = 10) (87). Post-op, post-operative patients.

(Right part) The plasma Se contains only 2% of the total body Se (TBSe), ie, 10-15 mg in a 70 kg Se-replete person (48,92). The selenoprotein-P contains about 60% of plasma Se. Selenoprotein-P has a short half-life (4 to 6 hours in healthy rats). Therefore, the plasma represents a daily Se pool that might be about 6% of TBSe. The liver plays a central role in Se metabolism especially for the specific Se pool (selenocysteine, Sec). It contains large amounts of GPX1, which can be mobilized. It is the prime origin of selenoprotein-P, which delivers the Sec from the liver to the tissues (Fig. 2). The reserve pool of Se under the form of selenomethionine (SeMet) is especially present in the muscle mass and liberated by protein catabolism. The erythrocyte Se concentration content is independent of the APR.

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Figure 4 Decrease in plasma selenium and selenoprotein-P concentrations in sepsis and burn animal models and overall picture of downregulation of liver selenoprotein-P synthesis



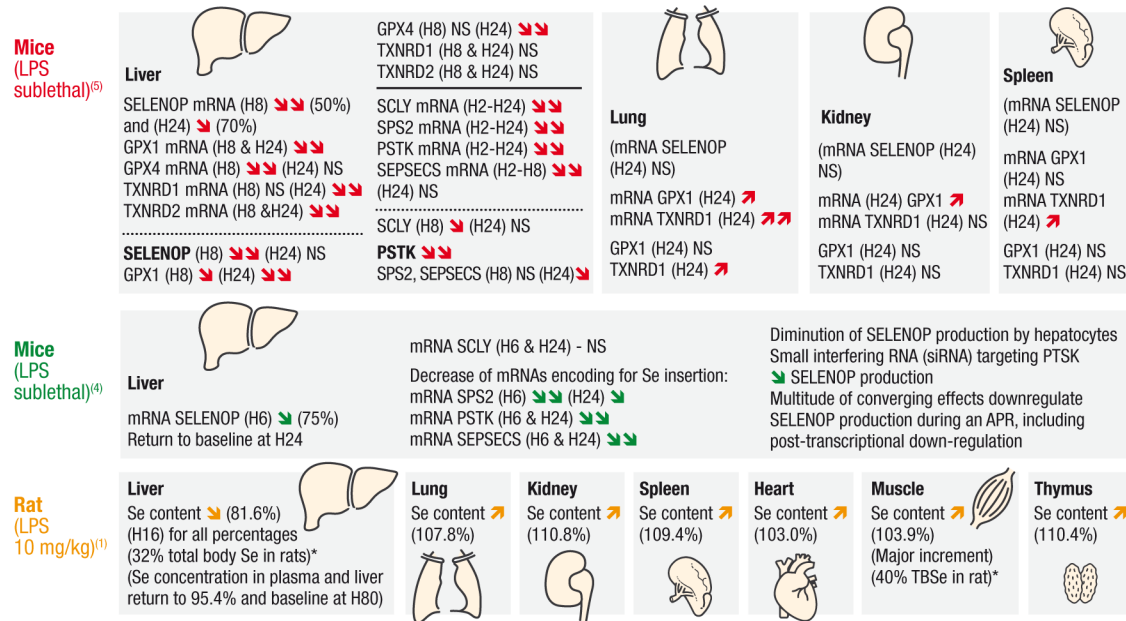
(Left part) A marked decrease in plasma selenium (Se) concentration is observed within a few hours after the onset of sepsis in rats (study 1), sheep (study 2) and mice (studies 4 and 5). In the sheep study (see below), the plasma Se concentration (i) significantly decreased from baseline at H3, (ii) and preceded the onset of septic shock (H10) and (iii) the significant increase in blood lactate (H12). In study 3, such a decrease is also observed at H24 in a non-exudative, non-lethal burn rat model, linked to the importance of the total body surface area (TBSA) burned. A similar decrease in plasma selenoprotein-P (SELENOP) concentration is observed in the two more recent mice studies (studies 4 and 5). However, in the most recent mice study (study 5) there was no decrease in plasma glutathione peroxidase (GPX3) concentration or activity. The concentrations are expressed as a percentage of the initial concentration. Although rats and humans share similar Se body contents (see table 2), the reference plasma Se and selenoprotein-P concentrations are about 6 times higher in rats and mice than in humans and about 7 times higher than in sheep. The results are given as mean ± SD. The studies are classified according to their publication date: (1) non-lethal lipopolysaccharide (LPS) rat model (LPS 10 mg/kg intraperitoneal In injection) (n=5 at each time point) (176); (2) lethal at H18 sheep model of peritonitis induced by autologous feces IP injection (296). This is an intubated, ventilated model with a similar fluid resuscitation algorithm as that for intensive care patients (n=21) (266,296); (3) non-exudative burn rat model “Rat 20% TBSA” and “Rat 40% TBSA” (234); (4) “Mice (LPS sub-lethal)” (LPS 100 µg/mouse IP, about 4 mg/kg; n=8 at each time points). A similar selenoprotein-P decrease was observed both in wild-type and in transgenic mice expressing human selenoprotein-P (SELENOP)^{(4)*} (221); (5) the same sublethal mice model (LPS 5 mg/kg) has been extensively studied for transcriptional and protein expression of the selenoenzymes and the Se insertion process in 2020 (n=4-6 for each time point) (248). * data from reference (20)

(Right part) The liver is the prime origin of plasma selenoprotein-P. The main results of Se and selenoenzyme expression in the liver of mice and rats are indicated. The symbol □ indicates a significant decrease, and □□ a decrease below 60% of the baseline value. In accordance with the decrease to 81.6% of liver Se content in LPS rats (32% of total body Se) (20), a marked decrease in liver GPX1 is observed in mice (248). There is also a marked decrease in liver and plasma selenoprotein-P in

accordance with the decrease in mRNA for selenoprotein-P. In addition, all the liver enzymes (Fig. 2) involved in Sec reduction to selenide and in Se insertion in selenoproteins decreased in the liver: selenocysteine β -lyase (SCLY); and for Se insertion: selenophosphate synthetase 2 (SPS2), phosphoseryl tRNA kinase (PSTK), and the Sec synthase (SEPSECS) (see Fig. 5 for more details).

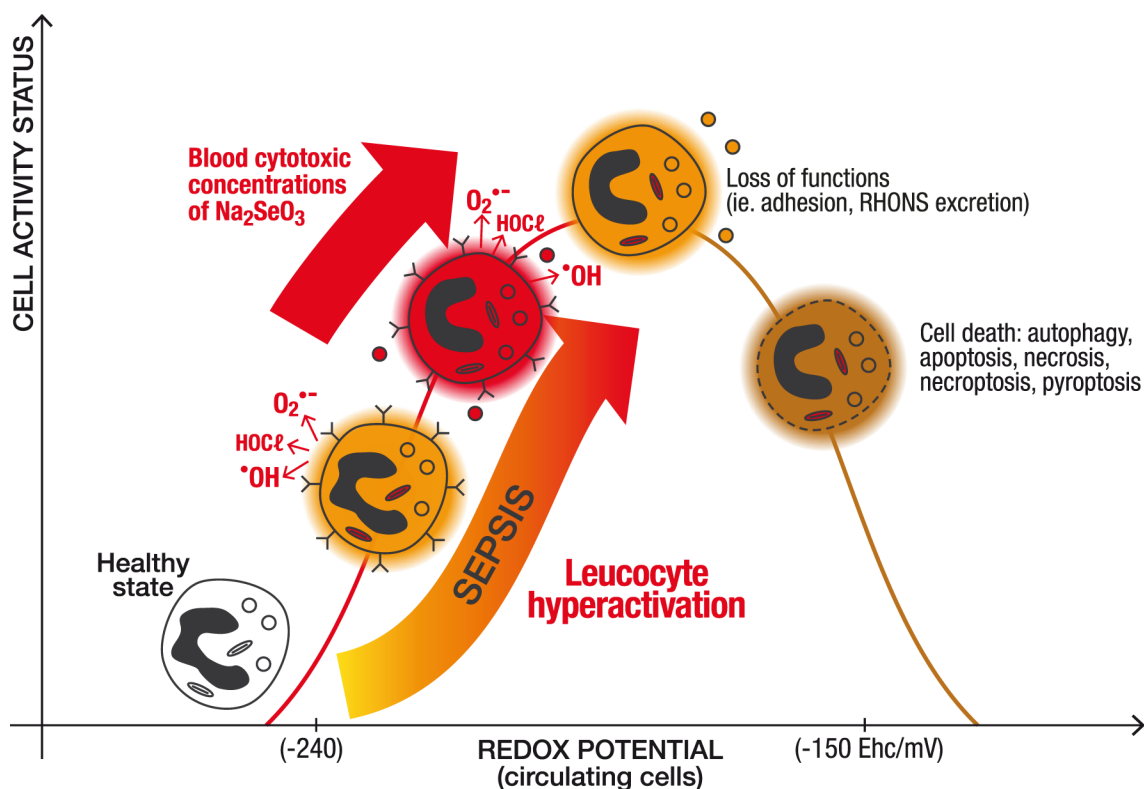
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Figure 5 Se concentration and selenoprotein expressions during the early phase of sepsis



In parallel to the measurements of plasma Se, selenoprotein-P and GPX3 in the early phase of sepsis (acute phase response – APR) (Fig. 4), three studies have consecutively studied: (i) the Se content; (ii) selenoprotein synthesis factor expression and concentration; (iii) and selenoprotein-P (SELENOP) and other selenoprotein expression and concentration in the liver and other organs. Study 1, by Maehira et al. in 2002 (see Fig. 4), concerned a non-lethal lipopolysaccharide (LPS) rat model (LPS 10 mg/kg intraperitoneal [IP] injection) (n=5 at each time point) (176). Study 4, by Renko et al. in 2009 (see Fig. 4), focused on liver selenoprotein-P expression in a sub-lethal LPS mouse model (LPS 100 µg/mouse IP, about 4 mg/kg; n=8 at each time point) (221). This study was performed in wild-type and in transgenic mice expressing human selenoprotein-P. The same sublethal mouse model (LPS 5 mg/kg; study 5) was used to study transcriptional and protein expressions of the selenoenzymes and the Se insertion process by Sherlock et al. in 2020 (n=4-6 for each time point) (248). The symbol □ indicates an increase, □ a decrease, and □□ a decrease to less than 60% of the baseline value. These studies provide concordant and complementary results in favor of a strong downregulation of liver selenoproteins and selenoprotein-P synthesis in the early phase of sepsis (APR) leading to a decrease in liver Se content. Simultaneously, an increase in tissue Se content is observed in multiple organs with no downregulation or upregulation of intracellular selenoenzymes. In the non-lethal rat model, liver Se content return to the baseline value at H80. In the two mice studies, a decrease in selenoprotein-P mRNA was observed in the liver. This was also the case for the mRNA of the enzymes involved in biologically active Se availability and insertion in selenoproteins: selenocysteine β-lyase (SCLY) for Sec reduction to selenide; and for Se insertion: selenophosphate synthetase 2 (SPS2), phosphoseryl tRNA kinase (PSTK), and the Sec synthase (SEPSECS) (see Fig. 2). The strongest downregulation was of the key Se insertion enzyme PSTK, the concentration of which decreased markedly. The result was decreased liver concentrations of selenoprotein-P, glutathione peroxidase GPX1 (half of the liver selenoprotein in mice) (48), and even GPX4, in accordance with the decrease of liver Se content observed in rats at H16. Thioredoxin reductase (TXNRD1 and 2) did not decrease in the liver. Selenoprotein-P mRNAs did not significantly decrease in other organs than the liver. GPX1 and TXNRD1 did not decrease in other organs than the liver or increased in accordance with increased Se content. * data from reference (20). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars.

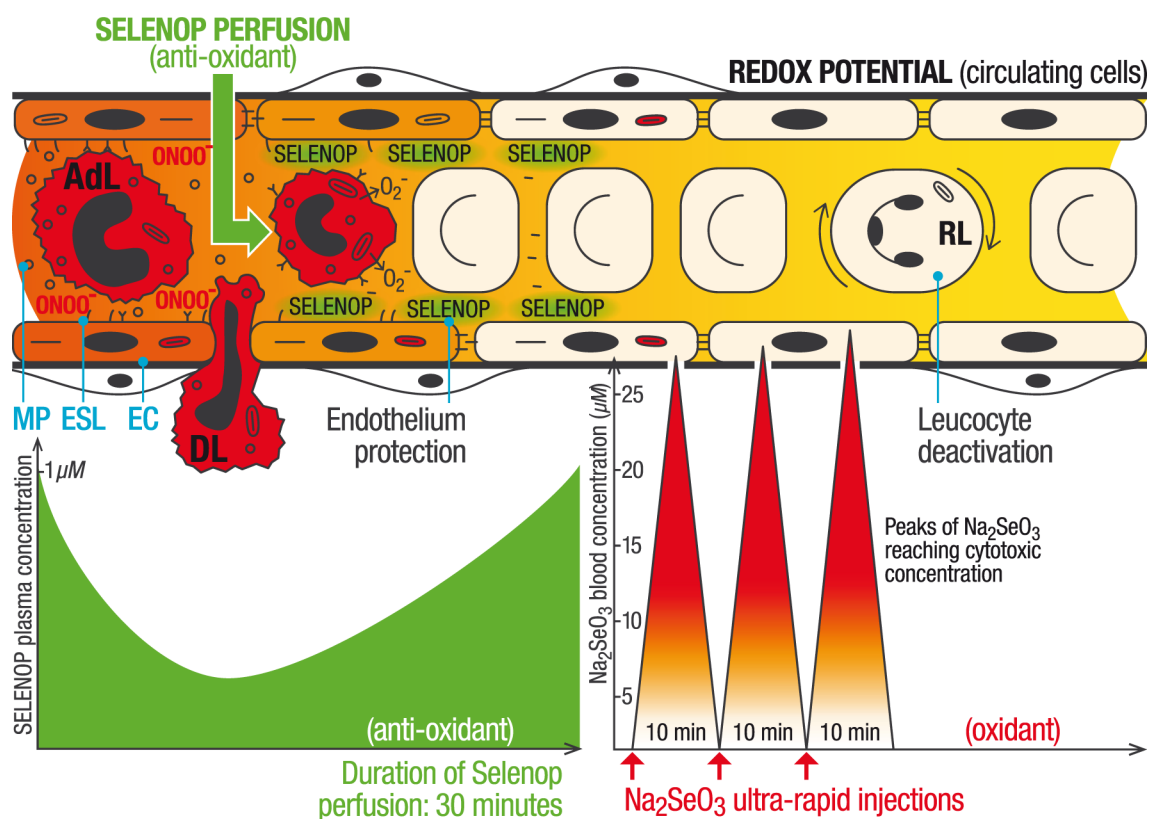
Figure 6 Cytotoxic effects of sodium selenite on hyperactivated leukocytes



The cytotoxicity of sodium selenite (Na_2SeO_3) increases with cell activation, which lowers the cytotoxic concentration threshold (Fig. 2, *center-right box*). Na_2SeO_3 cytotoxicity increases on detached cells. In sepsis, upregulation of the oxidative stress-inducible cystine/glutamate antiporter system is likely to induce increased intracellular Na_2SeO_3 uptake in activated leukocytes, such as neutrophils and macrophages. During early sepsis, leukocytes are activated leading to an increase in their intracellular redox potential (see part A, Fig. 3) (90). The Na_2SeO_3 likely further increase the intracellular redox potential, leading to cytotoxicity by multiple mechanisms (Fig. 2, *upper-right corner*). In the early phase of sepsis, micromolar ($1\text{--}5\ \mu\text{M}$) concentrations of Na_2SeO_3 are more likely to lead to loss of function of leukocytes, especially adhesion, decreased excretion of reactive oxygen halogen and nitrogen species (RHONS), such as superoxide anion ($\text{O}_2^{\bullet-}$), hydroxyl radical ($\bullet\text{OH}$) and hypochlorous acid (HOCl), and to cytotoxic effects, especially on the more active immature leukocytes (such as band neutrophils).

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Figure 7 Schematic view of the potential effect of combined antioxidant and oxidant redox action in the early phase of sepsis by selenocompounds (bypass solution).

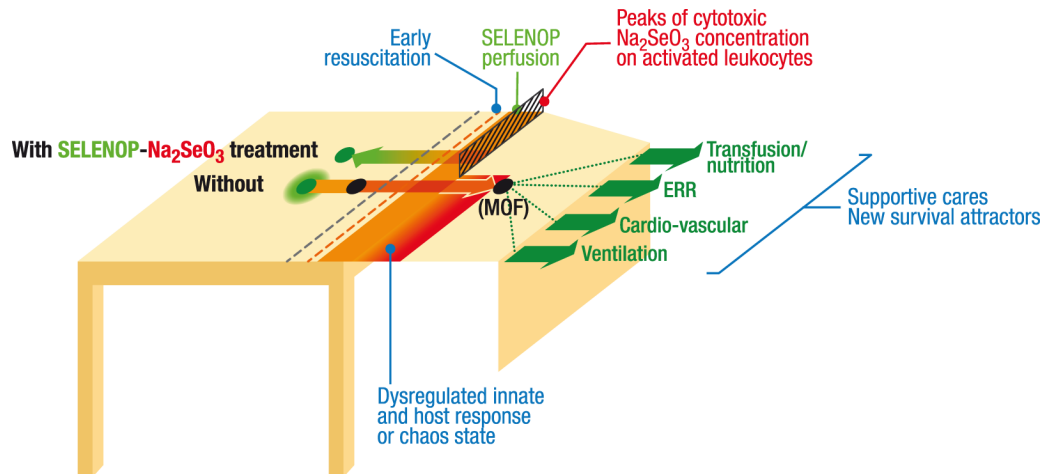


A capillary in early stage sepsis is illustrated (*upper-left of the figure*) with reactive oxygen halogen and nitrogen species (ROHNS) – such as peroxynitrite (ONOO^-) formed by the simultaneous production of superoxide anion ($\text{O}_2^{\bullet-}$) and nitric oxide ($\text{NO}\bullet$) – released by activated adherent leukocytes (AdL) and endothelial cells (EC). Immature forms of leukocytes (band neutrophil cells) are depicted with diapedesis leukocytes (DL). The endothelial surface layer (ESL) is altered, and membrane fragmentation leads to the formation of microparticles (MP) (See part A, Fig. 2 and Fig. 4 for more details) (90). Selenoprotein-P (SELENOP) has an antioxidant thioredoxin reductase activity (TXRND) and non-specific binding favored by acidosis (see Fig. 2). The selenoprotein-P plasma concentration decreases in the acute phase of sepsis (*lower-left box of the figure*) (see Fig. 3, and Fig. 4).

Proposed pharmaceutical intervention: infusion of selenoprotein-P (*upper-left and lower-left box*) could protect the endothelium. Subsequent successive ultra-rapid injections of Na_2SeO_3 (e.g., every 10 minutes) – *lower-right box* – enable peaks of cytotoxic concentration to be reached in the blood and maintain a high concentration for a period of time that may be sufficient to reduce leukocyte activity and adhesion (see Fig. 2 and 6 for cytotoxic action of Na_2SeO_3 at concentration $> 1\text{-}5\ \mu\text{M}$ especially on more active leukocytes such as band neutrophils). The microcirculation might thus be restored (*upper-right*), as illustrated by rolling leukocytes (RL) before irreversible damage of the endothelium occurs. In addition, prior endothelial protection by selenoprotein-P could reduce adverse effects of Na_2SeO_3 on the lung and heart (See Fig. 2, *medium-left box*).

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Figure 8 Major intervention required to interrupt dysregulated sepsis response - or complex maladaptive state - state early



Adapting Thom's Catastrophe Theory, as was already done by Viret, supportive care interventions in the emergency room (ER) and later in the intensive care unit (ICU), such as RRT (renal replacement therapy), are new survival attractors that prevail over homeostasis life attractors. These attractors enable patients to survive outside a natural living state -as illustrated by the table- during their ICU stay (see part A, Fig. 1) (90). In the early stage of sepsis, patients therefore survive in an unnatural human-made condition. At that point of the sepsis course, the innate response is a complex dysregulated immune response, or even a maladaptive state. As a consequence, a major intervention seems necessary to stop this complex condition.

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