Selenomethionine

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Selenium is an essential trace element. Although this chalcogen forms a wide variety of compounds, there are surprisingly few small-molecule organic selenium compounds (OSeCs) in biology. Besides its more prominent relative selenocysteine (SeCys), the amino acid selenomethionine (SeMet) is one example. SeMet is synthesized in plants and some fungi and, via nutrition, finds its way into mammalian cells. In contrast to its sulfur analog methionine (Met), SeMet is extraordinarily redox active under physiological conditions and via its catalytic selenide (RSeR')/selenoxide (RSe(O)R') couple provides protection against reactive oxygen species (ROS) and other possibly harmful oxidants. In contrast to SeCys, which is incorporated via an eloquent ribosomal mechanism, SeMet can enter such biomolecules by simply replacing proteinogenic Met. Interestingly, eukaryotes, such as yeast and mammals, also metabolize SeMet to a small family of reactive selenium species (RSeS). Together, SeMet, proteins containing SeMet and metabolites of SeMet form a powerful triad of redox-active metabolites with a plethora of biological implications. In any case, SeMet and its family of natural RSeS provide plenty of opportunities for studies in the fields of nutrition, aging, health and redox biology.

Keywords: aging ; selenium ; selenomethionine (SeMet) ; reactive selenium species (RSeS)

1. Introduction

Selenium is an essential trace element in humans [1]. Since its discovery by Joens Jacob Berzelius (1779–1848) in 1817, the element has fascinated chemists and biochemists alike. During the last five decades, hundreds of organic selenium compounds (OSeCs) have been produced to mimic the unique biological activity of selenium enzymes, such as the human glutathione peroxideases (GPx), human thioredoxin reductase (TR) and iodothyronine deiodinase (ID) [2][3]. Notably, nature itself produces only a few organic selenium compounds on its own. Besides the rather prominent amino acid SeCys and intermediates involved in its biosynthesis from inorganic selenite SeO_3^{2-} and subsequent metabolic degradation to methylselenide CH_3SeH, dimethylselenide $(CH_3)_2Se$ and dimethylselenonium $(CH_3)_3Se^+$, such natural small-molecule selenides are rare. The few notable exceptions found Nature include compounds such as the histidine derivative and ergothionine analog selenoneine present in tuna fish and inorganic selenocyanate ($SeCN^-$) in the green freshwater algae *Chlorella vulgaris* [4][5].

Indeed, SeCys dominates most discussions of selenium in proteins and enzymes, which is hardly surprising, as most of the roughly 25 selenium proteins identified in humans to date contain one or more SeCys residues [6]. In fact, SeCys is often referred to as the 21st amino acid, and its insertion into human proteins is controlled tightly via specific SeCys insertion sequences (SECISs). In contrast, the other natural selenium amino acid, selenomethionine (SeMet), occupies a more exotic niche in biology, although SeMet combines some truly amazing and exciting features worth discussing. SeMet, for instance, is produced in plants and fungi and in many organisms literally sneaks into proteins and enzymes in place of its sulfur analog methionine (Met), thereby endowing these proteins with extra redox activity [7]. SeMet on its own is also highly redox active, similar to the flagship antioxidant ascorbic acid, and in yeast is a fine source of numerous, equally active metabolites, such as selenohomocysteine, selenoglutathione, *γ*-glutamylselenocysteine and *Se*-adenosylselenohomocysteine. In humans, SeMet is absorbed via intestinal transport channels and subsequently enters the methionine pool, where it is stored and consequently recruited from to become integrated into proteins [8]. Once in the liver, SeMet follows the methionine cycle and *trans*-selenation pathways to produce *S*-adenosyl SeMet, adenosyl selenohomocysteine, homocysteine, selenocystathionine and SeCys, as shown in Figure 1 and Figure 2 [9].

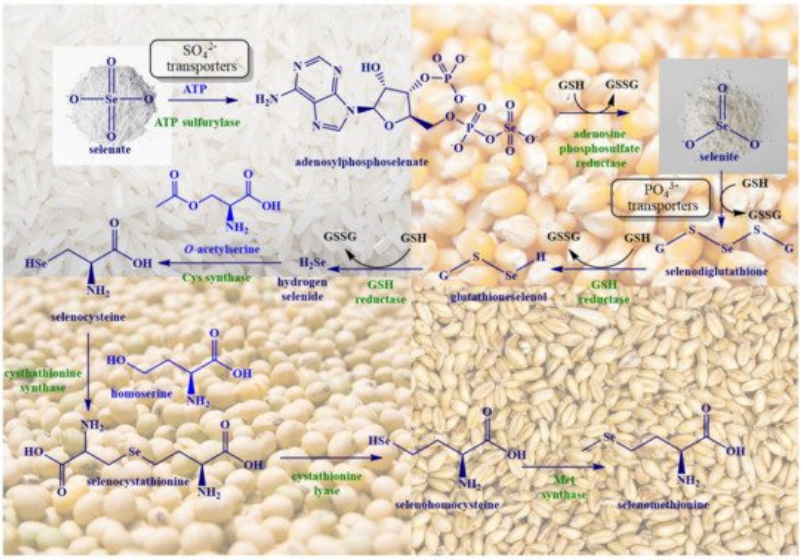

Figure 1. Biosynthesis of SeMet in plants involves the uptake of SeO_4^{2-} via SO_4^{2-} transporters and its interaction with ATP to produce adenosylphosphoselenate, which is reduced to SeO_3^{2-} by adenosylphosphosulfate reductase. SeO_3^{2-}, either absorbed via PO_4^{3-} transporters or reduced from SeO_4^{2-}, is further reduced to selenide by GSH via intermediates such as selenodiglutathione and glutathioneselenol. The interaction of selenide with *O*-acetylserine results ultimately in the formation of SeCys. Interaction of SeCys with homoserine in the presence of cystathionine synthase generates selenocystathionine which is cleaved enzymatically by cystathionine lyase to selenohomocysteine, pyruvate and ammonia. This is followed by the formation of SeMet from selenohomocysteine via methionine synthase.

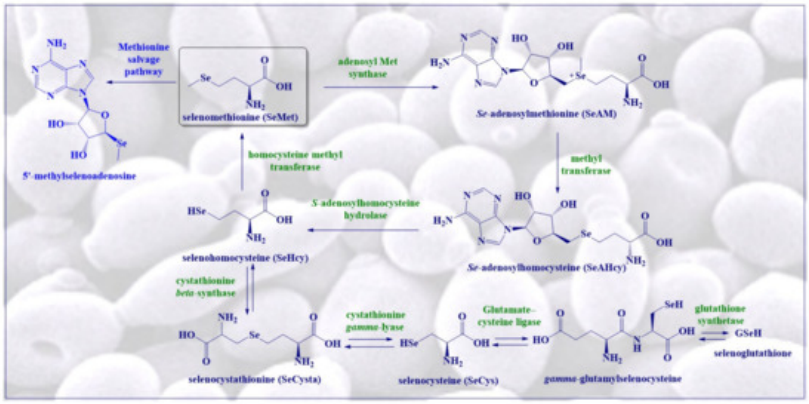

Figure 2. Structures of some of the metabolites of SeMet found in selenium-enriched yeast.

As part of this minireview, we shall therefore provide some essential information about this fascinating and in many aspects unique proteinogenic amino acid, from its biosynthesis in plants and metabolism in yeast to its ability to replace Met in proteins and its role as a food supplement. From the onset, we would like to emphasize that we have focused on some of the more recent and exciting discoveries in this field and therefore shall refer to the existing literature for more basic information [10][11][12][13].

2. Biosynthesis of SeMet in Plants

Higher organisms, such as mammals and humans, are unable to synthesize SeMet. This task is left to plants and fungi, including yeast (*Saccharomyces cerevisiae*) and a few edible mushrooms, such as the Shiitake (*Lentinula edodes*) and King Bolete (*Boletus edulis*) mushrooms [14][15]. Plants absorb SeO_3^{2-} and SeO_4^{2-} from the soil and convert these inorganic salts to different organic forms of selenium following a sequence of biochemical events, as shown in Figure 1. The absorption of SeO_4^{2-} and SeO_3^{2-} in plants is controlled tightly and involves certain transporters, such as sulfate (SO_4^{2-}) and phosphate (PO_4^{3-}) transporters in rice and wheat, respectively [16][17][18]. SeO_4^{2-} interacts with ATP in the presence of ATP sulfurylase (ATPS) to produce adenosylphosphoselenate, which is subsequently reduced by adenosine phosphosulfate reductase to SeO_3^{2-} consuming the reduced form of glutathione (GSH) as the electron donor [19]. SeO_3^{2-}, either absorbed via PO_4^{3-} transporters or reduced from SeO_4^{2-}, interacts spontaneously with GSH to produce selenodiglutathione (GSSeSG), which is subsequently reduced by GSH reductase (GSR) to generate glutathioneselenol (GSeH), which is again reduced by GSR in the presence of GSH to form hydrogen selenide (H_2Se) [20]. The interaction of H_2Se with *O*-acetyl serine in the presence of cysteine synthase results in the formation of SeCys [21].

SeMet is synthesized from SeCys in several steps. The α-amino acid homoserine interacts with SeCys to produce a selenocystathionine adduct, which is subsequently hydrolyzed to selenohomocysteine, pyruvate and ammonia, as illustrated in Figure 1. Selenohomocysteine is then converted to SeMet by methionine synthase [22]. There are two types of methionine synthase, i.e., cobalamine-dependent methionine synthase (E.C. 2.1.1.13) and cobalamine-independent methionine synthase (E.C. 2.1.1.14). The main function of both methionine synthases involves the catalysis of the transfer of functional methyl groups from 5-methyltetrahydrofolate to the thiol moiety of (seleno)homocysteine to produce tetrahydrofolate and (Se)Met [23]. Among the various plant species, cereals and forage crops primarily convert Se to SeMet, which they subsequently store. These plants also incorporate SeMet into proteins in lieu of Met, as the $tRNA^{Met}$ responsible for the incorporation of Met does not distinguish between Met and SeMet, an issue of the blatant hijacking of a sulfur pathway by selenium we shall discuss on several occasions during this review. Indeed, the production of SeMet in plants is not linked to any specific stimuli or requirements and is mainly running side by side to the synthesis of Met [24]. Whether Met or SeMet are synthesized then depends mostly on the amount of selenium available in the soil and not on any sophisticated design or game plan(t).

Yeast as a eukaryote can reduce SeO_3^{2-} and synthesize SeMet following the footsteps of plants, although it also produces other selenium species, including elemental red selenium $Se^{\pm 0}$, often in form of nanoparticles, a metabolic detoxification pathway actually also common in many bacteria and fungi, including *Lactobacillus plantarum, Escherichia coli* and *S. cerevisiae* [25]. Compared to plants and yeasts, mammals are unable to synthesize SeMet, as they turn SeO_3^{2-} into GSSeSG, H_2Se and SeCys, yet do not process SeCys to SeMet [9].

3. SeMet in Yeast

The nonspecific and accidental biosynthesis of SeMet in yeast from SeO_4^{2-} or SeO_3^{2-} follows the one in plants [26]. Interestingly, yeast is also able to take up SeMet quite readily from external sources. Once inside the yeast cell, SeMet plays several rather special roles. As some metabolic enzymes are unable to distinguish between Met and SeMet, just as in plants, this enables SeMet to take on the false identity of its sulfur analog and literally to sneak into proteins in place of Met [27][28]. It is important to mention that the amount of total Met in yeast (*S. cerevisiae)* is very low, i.e., around 0.75%, based on dry weight [29]. The extent to which Met is replaced by SeMet depends upon the conditions in which yeast is cultivated. Under standard industrial conditions, 30–45% of Met can be substituted by SeMet, while controlled laboratory-based experimental conditions may yield an amazing >98% substitution of SeMet for Met in the entire protein pool, as found, for example, in a wild-type yeast [30][31].

Furthermore, in such fungi, SeMet can requisite the machinery responsible for changing Met into many other natural sulfur compounds, and this results in the production of a plethora of interesting selenium compounds, some of which are shown in Figure 2.

Liquid chromatography coupled with orbitrap mass spectrometry, for example, has been utilized to hunt for such OSeCs in *S. cerevisiae* treated with SeO_3^{2-}, SeO_4^{2-} and SeMet [32]. The highest amount of Se inside cells has been observed in yeast cells treated with SeMet as compared to SeO_3^{2-} or SeO_4^{2-}. Treatment of yeast with SeMet significantly enhances the intracellular level of SeMet in yeast in less than 15 min, confirming a surprisingly fast and comprehensive uptake of SeMet by these cells. SeO_3^{2-} and SeO_4^{2-} are also taken up and processed in yeast to organic selenides, such as selenohomocysteine (SeHcy), *gamma*-glutamylselenocysteine, selenoglutathione (GSeH), 5′-methylselenoadenosine, *Se*-adenosylhomocysteine (SeAHcy) and *Se*-adenosylmethionine (SeAM), in addition to elemental selenium as mentioned before.

Notably, while yeast can synthesize SeMet following the sulfur pathway, it is not the preferred selenium compound produced in *S. cerevisiae*. Popular notions that selenium-enriched yeast contains mostly SeMet therefore are not entirely correct. Among the various selenium compounds found in this fungus, the rather exotic SeAHcy shown in Figure 2 dominates the field, as it amounts to around 70% of total selenium content [32]. In contrast, the individual shares of other selenium compounds are below 10%. Interestingly, SeAM is also formed in yeast and can take on some of the roles of its more popular sulfur analog, *S*-adenosylmethionine (SAM), which acts as a methyl donor in various eukaryotic cells. SeAM serves, for example, as a precursor in the synthesis of SeAHcy and is also involved in the methylation of lipids, proteins, nucleic acids and various secondary metabolites. Furthermore, methyltransferases are able to transfer methyl groups from SeAM to different nucleic acids, i.e., ribosomal and transfer RNAs and even DNA [33].

SeAHcy is hydrolyzed by *S*-adenosylhomocysteine hydrolase to adenosine and SeHcy, as shown in Figure 2. Unlike methionyl-tRNA synthetase, which does not discriminate between Met and SeMet, *S*-adenosylhomocysteine hydrolase actually demonstrates a slight discrimination, as its hydrolase activity against SeAHcy is relatively low as compared to its

activity against *S*-adenosylhomocysteine. This also explains why SeHcy is found in yeast in relatively small amounts of around 8.5% of selenium compounds, despite the presence of excessive amounts of SeAHcy, for instance in yeast cells treated with SeMet. The presence of 5′-methylselenoadenosine, a rather exceptional selenide shown in Figure 2, in such cells treated with SeMet has been reported [34] Considering the overall situation in yeast, SeMet follows the same metabolic pathways as Met, although the distribution of selenium species differs significantly from that of sulfur analogs. In any case, neither SeMet nor SeHcy is the main selenium compound in *S. cerevisiae*, with more exotic substances such as SeAM and chiefly SeAHcy dominating the field.

4. Redox Activity and Catalysis of SeMet

As mentioned already, many organisms are unable to distinguish between SeMet and Met and therefore tend to accept SeMet in many physiological processes in place of Met. This has notable consequences, as SeMet tends to be more reactive than Met and often acts as a redox cycler and catalyst. This strong antioxidant potential associated with selenium is found for SeMet as a free amino acid, for SeMet in proteins and enzymes and, notably, also for a range of other SeMet precursors and follow-on products containing the same selenide RSeR' motif [35]. Then again, one may mention that the selenide RSeR' generally is less reactive compared to the selenol(ate) RSeH or RSe^-. Nonetheless, the literature is rich in examples underlining the biological redox activity of SeMet.

In simple assays, SeMet protects dihydrorhodamine 123 and supercoiled plasmid DNA from oxidation mediated by peroxynitrous acid (ONOOH) [36][37]. This protective effect is attributed to radical-mediated oxidation of SeMet to its oxidized selenoxide form SeMetO [38]. The reaction of SeMet with ONOOH follows a second-order rate constant of k ~2.4 × 10^3 $M^{-1}s^{-1}$, which is almost tenfold higher than the one for Met at just 3.64 × 10^2 $M^{-1}s^{-1}$. Not surprisingly, SeMet therefore competes significantly with cellular targets at similar concentrations [38][39]. The oxidation of SeMet to SeMetO is not limited to ONOOH, and an analogous reactivity has also been observed for other oxidants, such as H_2O_2, the enzymatic monooxygenase system, amino acid-, peptide- and protein-bound hydroperoxides, hypothiocyanous acid HOSCN and hypochlorite HOCl-derived chloramines [40][41][42]. Moreover, a preference of hydroperoxides (ROOH) for SeMet over Met and GSH has also been noticed, and these hydroperoxides produced in amino acids, peptides and proteins tend to oxidize SeMet quite rapidly, as compared to the standard oxidant H_2O_2 [43]. SeMet is therefore a good, albeit not outstanding, antioxidant and may protect proteins against oxidative stress (OS) caused by a range of reactive oxygen species (ROS).

5. Implications of SeMet in Aging and Diseases Related to OS

The high redox activity of SeMet has major physiological consequences, which can be classified as the result of (a) SeMet as an antioxidant, (b) SeMet as a GPx-like redox catalyst, (c) SeMet as a provider of selenium, (d) SeMet as an intermediate for a family of RSeS and (e) SeMet as a substitute for Met in proteins and enzymes. In most instances, a medley of these different aspects unique to this selenium amino acid is responsible for the physiological activities recorded in practice. Here, the scope of biological activities of SeMet is extremely broad, including simple selenium supplementation as a nutraceutical, antioxidant, anti-inflammatory and preventive activities. As there are numerous reports on such possible activities in the literature a few selected and rather interesting highlights of such activities need to suffice as a part of this review, with relevant literature provided for further information.

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