Free Radical Biology and Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

SEXUAL DIMORPHISM IN SELENIUM METABOLISM AND SELENOPROTEINS

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ARTICLE INFO

Keywords:
selenium
selenoproteins
selenocysteine
sex
sexual dimorphism

ABSTRACT

Sexual dimorphism, the condition in which males and females in a species differ beyond the morphology of sex organs, delineates critical aspects of the biology of higher eukaryotes, including selenium metabolism. While sex differences in selenium biology have been described by several laboratories, delineation of the effects of sex in selenium function and regulation of selenoprotein expression is still in its infancy. This review encompasses the available information on sex-dependent parameters of selenium metabolism, as well as the effects of selenium on sex hormones. Gaps in the current knowledge of selenium and sex are identified and discussed.

1. Introduction

It is widely recognized that intrinsic sex differences account for variations observed in eukaryotic biology. Thus, it is not surprising that selenium biology will also display significant sexual dimorphism. The hierarchical nature of selenium physiology [1–6], the unique mechanism for incorporation of this trace element into selenoproteins as the amino acid, selenocysteine, and the different functions attributed to these selenoproteins [7,8] deem sex-specific effects as an additional regulatory role in our understanding of the sophisticated biology of selenium.

The complexities of sexual dimorphism in selenium biology have been discussed in several detailed review articles [3,9–11], but recent discoveries warrant an updated examination of the subject. This review will feature novel recent findings and unveil research areas that are still unknown or poorly understood regarding the interaction between sex and selenium. Moreover, it will highlight the need to consider sex differences in any analysis of selenium biology. We will explore the subject from two approaches: the effects of sex on selenium-dependent parameters and the effects of selenium on sex-dependent parameters. These two considerations may be intertwined and difficult to discern, nonetheless are relevant to construct a comprehensive perspective of selenium biology.

2. Significance

The importance of investigating sex and gender differences in the health sciences has come to the forefront in recent years, after concerns were raised that "a lack of systemic and consistent inclusion of women in NIH-supported clinical research could result in clinical decisions being made about health care for women based solely on findings from studies of men—without any evidence that they were applicable to women." [12] The Office of Research on Women's Health Report expands upon this, stating "Over the past 20 years, research has revealed that from single cells to multiple biological systems and mechanisms, sex differences exist —and these differences are not just hormone based. Sex differences research is needed not only in fields such as endocrinology and immunology, but also in rapidly evolving scientific disciplines such as epigenetics, systems biology, and neuroscience; and new technology-enabled fields such as genomics, proteomics, and metabolomics."

3. Sexual dimorphism in selenocysteine incorporation, selenium metabolism and selenoproteins

3.1. Sex hormones

Androgens, estrogens, and progestogens comprise the three main classes of endogenous sex hormones. Because they are responsible for male sex characteristics, androgens are referred to as the male sex hormones. Perhaps the most well-studied androgen is testosterone. Likewise, estrogens and progestogens are aptly termed the female sex hormones. Sex hormones are primarily synthesized in the gonads. Thus, gonadectomy is a useful tool in determining the influence of endogenous sex steroids by allowing their near-complete removal. GnRH (gonadotropin-releasing hormone) from the hypothalamus stimulates

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https://doi.org/10.1016/j.freeradbiomed.2018.03.036
Received 1 February 2018; Received in revised form 14 March 2018; Accepted 18 March 2018

the anterior pituitary to release LH (luteinizing hormone) and FSH (follicle-stimulating hormone) which act on the testes and ovaries to secrete testosterone and estrogen, respectively. Collectively, this regulatory system is known as the HPG (hypothalamic-pituitary-gonadal) axis [13]. In this review, relevant aspects of selenium metabolism and selenoproteins will be discussed in light of their sexual dimorphism and their regulation by sex hormones.

3.2. Selenocysteine incorporation

In higher eukaryotes, selenocompounds need to be metabolized and ultimately converted to selenide, which is utilized in the production of selenocysteine, the amino acid present in the active site of selenoenzymes. The selenocysteine incorporation mechanism has been extensively studied [8,14–16]. Selenide is phosphorylated by the actions of the selenophosphate synthetase 2 (SEPHS2), a selenoenzyme, in order to be attached to a specific serine-charged tRNA, the $tRNA^{Ser[Sec]}$. The tRNA is first charged with a serine residue and by the actions of the phosphoseryl-$tRNA^{Ser[Sec]}$ kinase (PSTK) and selenocysteine synthase (SepSecS), it results in a tRNA charged with selenocysteine. The $tRNA^{Ser[Sec]}$ is then utilized during selenoprotein translation to insert at in-frame UGA sequences the amino acid selenocysteine. As UGA also specifies termination of translation, other factors are required to ensure the insertion of selenocysteine in the nascent polypeptide chain. These factors include, but are not restricted to, a specific cis structure in the 3'-UTR of the selenoprotein mRNA (SECIS), a selenocysteine-specific elongation factor (EFSec), a SECIS binding protein (SBP2), and a selenocysteine tRNA associated protein (secp43). Once all these factors are properly assembled, selenoproteins can be synthesized.

Among factors involved in selenocysteine incorporation, current evidence does not indicate their expression or activity being affected by sex. For example, expression of the genes for *Efsec* and *Sbp2* were not regulated by ovariectomization in mice, indicating that if sex influences translational efficiency, it probably does so either through post-translational effects or other members of the selenocysteine incorporation complex [17]. Another example is the deletion of the *Trsp* gene in murine liver, which leads to total ablation of hepatic selenoproteins and equal early mortality rates between females and males [18], confirming the ability to produce selenoproteins during development to be essential for both sexes. It is reasonable to expect that a sex-independent requirement for selenoprotein production, even partially, remains through adulthood. However, this neutral possibility is still untested.

3.3. Intracellular selenium metabolism

Selenide can be produced by different pathways. Dietary selenium is consumed mostly as the organic forms selenomethionine, selenocysteine, and selenocystathionine, or the inorganic forms selenite and selenate. Inorganic selenite is metabolized either by the selenoprotein thioredoxin reductase 1 (TXNDR1) into selenide or by reaction with glutathione. Interestingly, in zebrafish TXNDR1 was shown to have a sex-specific pattern of expression, with females having diminished expression after selenite supplementation while males increased their expression of TXNDR1 regardless of the selenium chemical form [19].

Organic form selenomethionine has been suggested to enter the methionine cycle, be converted into selenohomocysteine, then metabolized by the same enzymes that lead to cysteine formation via the transsulfuration pathway [20,21]. "Trans-selenation" reactions occur sequentially and involve the enzymes cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CGL), and the end product is selenocysteine. Selenocystathionine can also serve as a substrate for CGL, whose actions lead to the formation of selenocysteine. Evidence in yeast demonstrates that selenomethionine toxicity is mediated by the transsulfuration pathway [22] and that trans-selenation-derived selenocysteine can be misincorporated in place of cysteine [23]. This possibility, if present in mammals, would point towards mechanisms for dealing with selenomethionine cytotoxicity.

Interestingly, both CBS and CGL are regulated by sex hormones. Renal CBS activity is higher in male rodents than in female rodents, but lower in men than in women. Castration of mice led to decreases in CBS expression to similar levels as female mice [24]. Paradoxically, treatment of an androgen-responsive human prostate cell line with testosterone downregulated CBS and negatively impacted the transsulfuration pathway flux [25]. These findings combined indicate that CBS is possibly regulated by testosterone acting through transcriptional and post-transcriptional mechanisms. CGL, on the other hand, is regulated by both androgens and estrogens. Ovariectomized rats treated with 17β-estradiol showed an increase in CGL expression in the myocardium [26]. Conversely, treatment of ovariectomized ewes with 17β-estradiol did not elicit any changes in expression of CGL in arteries [27]. These findings suggest that estrogen regulation of CGL seems to be tissue-specific in females. Interestingly, mice lacking CGL display profound sexual dimorphism, with females, but not males, exhibiting drastically reduced plasma levels of methionine and cysteine [28]. Perplexingly, the androgen receptor physically interacts with CGL [29], also allowing for regulation of this enzyme by testosterone through a post-translational mechanism [30].

The regulation of the trans-selenation pathway by sex hormones strongly implies that selenomethionine metabolism and its consequent selenocysteine formation and availability for selenoprotein synthesis are not the same in both sexes. Consequently, it also raises the interesting possibility that intracellular mechanisms offsetting toxic levels of selenomethionine and affecting the differential selenium distribution that we observe in circulation are sexually dimorphic, and could explain some of the sexual dimorphism found in clinical trials using selenomethionine (see section *Sex differences after selenium supplementation*).

In addition to the effects discussed above, selenomethionine can also be misincorporated in place of methionine. The methionyl-tRNA synthetase has long been known to not differentiate between methionine and selenomethionine [31]. Hence, when selenomethionine is in excess, it is assumed that a percentage of $tRNA^{Met}$ is charged with selenomethionine. Misincorporation of selenomethionine may alter physiological characteristics of enzymes, affecting either chemical structure or enzymatic activity, and there is not yet evidence of sexual dimorphism in misincorporation.

3.4. Selenium recycling

The unique pathway selenocysteine takes to be incorporated must be acknowledged. It is speculated that selenocysteine coming either from dietary intake, selenoprotein degradation or trans-selenation pathways should be first decomposed to selenide. Selenide can then be utilized to synthesize selenocysteine-bound tRNA, the form that can be incorporated into selenoproteins. The decomposition of selenocysteine is catalyzed by the action of selenocysteine lyase (Scly), a pyridoxal-phosphate-dependent enzyme that converts it into selenide and alanine, and this enzyme has been demonstrated to affect the synthesis of selenoproteins in mammals [32]. Although not essential to life, as mice lacking Scly are viable [33], this enzyme sits at an interesting metabolic intersection, between trans-selenation, protein degradation, and selenoprotein synthesis.

Mammalian Scly was first isolated from pig liver and first cloned from the liver of male mice [34,35]. It is currently unknown if the expression of Scly varies according to sex. Nevertheless, Scly disruption in mice leads to sexually dimorphic phenotypes. While male $Scly^{-/-}$ mice develop obesity, glucose intolerance and hyperinsulinemia [36], females present a milder phenotype, with weight gain but not changes in glucose sensitivity nor hyperinsulinemia [37].