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Role of Copper and Selenium in Reproductive Biology: A Brief Update

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Abstract

Among the indispensable trace elements required for normal physiological growth and development of the body; Copper (Cu) and Selenium (Se) have a paramount significance in human reproduction. Male testosterone levels have been suggested to play a role in the severity of Cu deficiency. In females, estrogen causes increase in plasma Cu levels by inducing ceruloplasmin and alteration of hepatic subcellular distribution of Cu. Thus, changes in Cu levels due to estrogen are thought to protect Cu-deficient females against mortality.

During pubertal maturation, the Se content of male gonads increases and it is localized in the mitochondrial capsule protein of the mid-piece. In females, infertility and abortion aberrations are caused due to Se deficiency.

Keywords: Copper; Selenium; Human reproduction

Introduction

Trace elements [Copper (Cu), Selenium (Se), Zinc (Zn), Iron (Fe), Molybdenum (Mo), Manganese (Mn), Cobalt (Co), Chromium (Cr), and Iodine (I)], inorganic substances that are vital for sustaining life, are required in minute amounts every day (generally less than 100 mg/day [1,2]. Trace element homeostasis is important for optimal health, enzymatic reactions, immune function, respiration, gene transcription, and cell proliferation, nervous and reproductive system. Various diseases that include genetic disorders [3,4], cancer [5], diabetes [6], neurodegenerative diseases [7,8] and reproductive abnormalities [2] are associated with aberrant trace element homeostasis. Accumulating evidences intensely indicate that loss of trace element homeostasis have a profound effect on reproductive system of animals, including humans. Among the outlined trace elements, Zn, Cu, and Se have an imposing role in human reproduction. Contrary to Zn and Cu which are metals, Se is non-metal with diverse biological effects which are mediated through Se containing proteins (seleno-proteins) that are present in all three domains of life. All seleno-proteins contain at least one selenocysteine, a Se containing amino acid. Most of the seleno-proteins serve as oxidoreductases [9-13]. Cu and Se are redox active elements due to presence of unpaired electrons which allow their participation in redox reactions involving mostly one electron loss (oxidation) or gain (reduction). On the other hand, Zn has no unpaired electrons when in the Zn^{2+} state, preventing its participation in redox reactions. However, this redox activity of Cu and Se results in formation of highly damaging free hydroxyl radicals, which subsequently causes oxidative stress, unless homeostasis is tightly regulated. In biological systems Zn, Cu and Se are mostly bound to proteins, forming metalloproteins. In biological system Zn, Cu and Se accomplish pivotal roles to maintain optimum health. Apart from Cu and Se, other trace elements are the focus of several recent comprehensive reviews/books and will not be considered further [1,2,14-17]. The remainder of this chapter will instead focus on essentiality, and clinical and biochemical spectrum conditions pertaining to Cu and Se (Table 1) in human reproductive system.

Copper

Cu is the third-most abundant transition metal in the body [22] and a vital trace metal that plays a fundamental role in the biochemistry of all living organisms; affecting enzyme activity, both as a cofactor and as an integral component of many metalloenzymes [23].The average intake of Cu by human adults varies from 0.6 to 1.6 mg/d. In human body Cu is found in relatively high amounts: a healthy 70 kg adult contains about 110 mg of Cu, approximately 10 mg in liver, 8.8 mg in brain and 6 mg in blood [24,25]. Duodenum is the primary site of Cu absorption. The biological functions of redox active Cu includes electron-transfer catalysis by means of its two accessible oxidation states: Cu^{+} (cuprous) and Cu^{2+} (cupric) [26]. Cu is involved in many aspects of metabolism, including mitochondrial oxidative phosphorylation, neurotransmitter synthesis and function, pigment formation, connective tissue biosynthesis, and Fe metabolism [27] (Table 1). Biliary excretion is the main route of Cu excretion from the body. Due to immaturity of biliary excretion system and high proficiency of Cu absorption, neonates are more susceptible to Cu poisoning [28]. Cu homeostasis in the body is securely synchronized as it is an important component of numerous metalloenzymes and metalloproteins, and perturbations in Cu levels are known to underlie the pathoetiology of wide spectrum of diseases including reproductive, hemopoietic, nervous, skeletal, cardiovascular integumentary, and immune systems [1].

Wilson's disease, an autosomal recessive disorder, is caused by mutations in ATP7B gene in which Cu accumulates in liver and secondarily in other organs. Grossly elevated hepatic Cu content, augmented urinary Cu excretion and decreased serum ceruloplasmin levels are good indicators of the Wilson's disease [29-32]. Cu poisoning manifestations include nausea, epigastric pain, vomiting, diarrhea, intravascular hemolysis, and severe Cu toxicity may also cause death. Indian childhood cirrhosis and idiopathic Cu toxicity are the other examples of Cu toxicity associated diseases in humans [33]. Strikingly, accumulating evidences suggest that increased Cu levels in brain due to chronic Cu toxicity can result in cognition waning in rats [34,35].

On the other hand, Menkes disease, X-chromosome linked human disorder characterized by progressive neurological impairment, peculiar hair and death in infancy, is associated with abnormal Cu metabolism. Cu deficiency results from alteration in Cu transport, the entrapment of Cu in intestinal and kidney cells or vascular endothelial cells in the blood-brain barrier (BBB). The Menkes disease patients

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Cu dependent enzymes/proteins	Selenoproteins
Monoamine oxidase	Glutathione peroxidases (GPx 1-6)
Ceruloplasmin	Thioredoxin reductase (TR 1-3)
Cytochrome c oxidase	Cytochrome c oxidase
Lysyl oxidase	Selenoprotein P
Diamine oxidase	Selenoprotein W
Dopamine β-hydroxylase	Selenophosphate synthetase
Hephaestin	15 kDa selenoprotein
Glycosylphosphatidylinositol- anchored ceruloplasmin	Selenoprotein H, I, K, M, N, O, R, S, T, V
β-amyloid precursor protein	
Glucose regulated protein 78	
peptidylglycine α-amidating- mono-oxygenase	
Prion protein	
Cu-Zn superoxide dismutase	
Tyrosinase	
Metallothionein	
Blood-clotting factors V and VIII	
Transcuprein	
Albumin	
Angiogenin	

Source: [17-21]

Table 1: Copper and selenium dependent enzymes/proteins.

have low hepatic Cu and plasma ceruloplasmin levels. The disorder is a result of a mutation on the X-chromosome close to band q-13 and Menkes disease gene (ATP7A) has been shown to be expressed in intestinal epithelial cells [36,37]. Generally, anemia and leukopenia are related to Cu deficiency. In addition to Wilson's and Menkes disease, other diseased conditions like albinism, Down's syndrome [38], cytochrome-coxidase deficiency [39] and Cutis-laxa [40] also lead to fluctuations in Cu metabolism.

Role of copper in reproductive system:

Effect of copper on male reproduction: Male rats fed with low Cu diets exhibited decreased Cu levels in testis [41]. Anemia, heart hypertrophy and death in male rat (castrated or not) are also caused by Cu deficiency. Testosterone level in the male has been suggested to play a role in the severity of Cu deficiency. The presence of testosterone could influence male rats to the toxic effects of Cu deficiency. There is an observed 50% reduction in testosterone levels in castrated male, and this testosterone reduction significantly improved the anemia induced by Cu deficiency and increased the survival of rats by two weeks compared to non-castrated males, thus it improved the severity of the Cu deficiency. However, the protection was only temporary [42].

Copper deficiency in female reproduction and pregnancy: As opposed to Cu-deficient male rats, Cu-deficient female rats are protected against mortality due to Cu deficiency [43]. Endogenous estrogens are suggested to play a role in the protection against Cu-deficient state, as evidences indicate that estrogens alter the hepatic subcellular distribution of Cu, and induce the synthesis of ceruloplasmin thereby increasing the plasma Cu levels [44-46]. Notwithstanding, even ovariectomized females, where plasma estrogen is reduced by 48%, are protected against the severity of Cu deficiency. Thus, ovariectomized or intact female rats are not susceptible to severe Cu deficiency [47-52].

Cu, required for various enzymes/proteins involved in normal central nervous system (CNS) functioning, also affect norepinephrine and dopamine levels in the CNS by synthesis and/or release of neurotransmitters [8,53-56]. Thus, females taking oral contraceptives are at higher risk of acquiring physiological and behavioral changes due to altered amine metabolism in brain [57]. There is an increased pressure on indispensable metal homeostasis of the pregnant female towards the completion of fetus development at the end of gestation [58]. Despite the fact that liver has the highest Cu concentration compared to other organs of the body; Cu is not significantly withdrawn from maternal storage tissues such as liver during pregnancy. Increased intestinal absorption of Cu and food consumption is responsible for transient augmentation in plasma Cu level observed during mid-pregnancy [59,60]. Infants completely dependent upon parenteral nutrition, without supplementation of Cu, develop hypochromic normocytic anemia, neutropenia and skeletal abnormalities in association with profound hypocupremia 14~ and these abnormalities responded well to oral Cu supplementation [2]. Hypomyelination is also reported in pups of Cu-deficient rat dams [53].

Selenium

Se is of fundamental prominence to human health. Owing to comprehensive study by Schwarz and Foltz, Se was proved as an indispensable nutrient necessary for both normal growth and reproduction in animals [61]. Se is a crucial component of several major metabolic pathways, including antioxidant defense function, thyroid hormone metabolism, and immune system. Se, an important trace element, deficiency is involved in heart disease and increased cancer risk. Keshan disease in humans is caused due to Se deficiency. Se toxicity, characterized by loss of hair and changes in ectodermal appendages, has also been reported in humans [62]. Se is as a cofactor of glutathione peroxidase which confers protection to cell from free radicals [18,63-68]. Se is a component of the unusual amino acids selenomethionine and selenocysteine. Se plays a key role in the physiological functioning of the thyroid gland which produces thyroid hormone (TH) and in every cell that uses TH, by participating as a cofactor for three iodothyronine deiodinases (Table 1). The iodothyronine deiodinases are the subfamily of deiodinase enzymes that use Se [21,69-71,18]. There are widespread variances in Se dietary intake across different populations, depending on the soil Se content and thus the Se content in foodstuffs and inter-individual dietary habits. So, Se enters the food chain through plants. Dietary Se is absorbed in the small intestine and incorporated into proteins by yet unknown complex mechanisms. According to WHO, 40 μg and 30 μg Se/day is sufficient to meet normal requirements of adult male and female, respectively [72].

Effect of Selenium on male reproduction: Low fertility and poor growth are associated with consumption of Se-deficient in farm animals [73]. During pubertal maturation in males, there is a significant increase in Se content of male gonads [74,75]. In addition to this, oligospermia, increase in abnormal spermatozoa, and a decline in the ratio of motile to immotile spermatozoa also been reported in Se-deficient rats. Increased fragility and decreased stability of the mitochondrial sheath causes disorganization of the mitochondrial sheath of the mid-piece. Se is localized in the mitochondrial capsule protein [(MCP), cysteine- and proline-rich selenoprotein)] of the mid-piece [76-80].

Testosterone secretion is affected by Se deficiency as its deficiency causes changes in the LH receptors of Leydig cells [74,75]. Pituitary gland, the bulbourethral and prostate glands, and the caput and corpus epididymis have shown the highest Se retentions [75,81]. Numerous studies have demonstrated the protecting effect of Se against Cd-induced toxicity [82]. Se also inhibits DNA, RNA and protein synthesis. Prostate cancer is caused due to high level of Cd in the prostate [83,84] and Se at non-toxic levels could help in the inhibition of the growth of cancerous cells (Table 2) [85]. A recent study has shown that dietary

Sex	Manifestations	References
Male	Testosterone biosynthesis	[87]
	Formation and normal development of spermatozoa	[88]
	Gluthathione peroxidase-4 shields developing- sperm cells from oxidative DNA damage	[89,90]
	Increased dietary Se intake increases male fertility, improved sperm quality, sperm motility, sperm count	[90-94]
Female	Low serum Se associated with miscarriage in pregnancy	[95,96]
	Probably linked with preeclampsia	[97]
	Lower Se concentration linked with preterm labor	[98]
	Decreased serum Se and glutathione peroxidase associated with obstetric cholestasis	
	Decrease in maternal plasma Se concentration connected to gestational diabetes mellitus	

Source: [18,21,66]

Table 2: Effects of selenium dyshomeostasis on human reproductive system.

Se of roosters can affect apoptosis of germ cells and cell cycle-related genes in the testis during spermatogenesis [86].

Selenium deficiency, female reproduction, pregnancy and lactation: Among the major outcomes resulting from Se deficiency in females are infertility, abortion and retained placenta. In addition to this, the offspring born from Se-deficient mother suffer from muscular weakness [61,99,100]. Se requirement of lactating and pregnant mothers is increased which can be explained on the basis of Se transport to the fetus via the placenta as well as to the infant via the breast milk [101,102]. It's worth noting here that Se level in human milk is robustly affected by maternal Se intake and status [103]. Molecular sieve chromatography have revealed that majority of the Se in human milk is protein-bound [104]. Infants and young children Se requirements are high because of their rapid growth (Table 2). Se deficiency may lead to miscarriages, gestational complications as well as damage to the nervous and immune systems of the fetus. During the early stage of pregnancy, low concentration of Se in serum, has been associated with low birth weight of child at birth [105].

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