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Review

Mechanistic aspects of the interaction between selenium and arsenic ☆

Huawei Zeng *, Eric O. Uthus, Gerald F. Combs Jr.

Agricultural Research Service, Grand Forks Human Nutrition Research Center, United States Department of Agriculture, 2420, 2nd Avenue, Grand Forks, ND 58202-9034, USA

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Abstract

Selenium is an essential trace element for humans and other animals, and there is mounting evidence for the efficacy of certain forms of selenium as cancer-chemopreventive compounds. However, over the years, numerous elements such as As, Cu, Zn, Cd, Hg, Sn, Pb, Ni, Co, Sb, Bi, Ag, Au, and Mo have been found to inhibit anti-carcinogenic effects of selenium, which may affect the anti-carcinogenic activity of selenium. The interaction between selenium and arsenic has been one of the most extensively studied. The proposed mechanisms of this interaction include the increase of biliary excretion and direct interaction/precipitation of selenium and arsenic, and their effects on zinc finger protein function, cellular signaling and methylation pathways. This article focuses on these proposed mechanisms and how anti-carcinogenic effects of selenium may be affected by arsenic.
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1. Introduction

Selenium (Se) is an essential trace element for humans and animals, and is required for the growth of mammalian cells in culture [1,2]. The current recommended dietary daily allowance for Se is 55 μg for healthy adults [3]. At such intakes, Se supports the expression of a variety of selenoproteins through the tRNA-mediated incorporation of selenocysteine. These selenoproteins include glutathione peroxidases and thioredoxin reductases, which have important antioxidant and detoxification functions. In addition, a cancer-chemoprotective effect of Se has been observed [4–7].

Interest in the study of Se status and cancer risk has been stimulated by the landmark finding that supplementation of a moderate daily dose of Se could substantially reduce cancer risk in humans [8]. Some epidemiological studies [9,10] have found that Se status can be negatively associated with cancer risk, and intervention studies [4,8] have found that supplements/high Se intakes are effective in reducing mammary, prostate, lung, colon, and liver cancer risk [4,8]. In experimental animals, anti-carcinogenic effects have been consistently associated with Se at supranutritional intakes (>1 mg/kg diet) that are at least 10 times those required to prevent clinical signs of Se deficiency and to support near-maximal tissue activities of selenoenzymes [7,11].

A number of mechanisms have been proposed that may account for the chemoprotective effects of Se including antioxidant protection, altered carcinogen metabolism, enhanced immune surveillance, cell cycle effects, enhanced apoptosis and inhibition of angiogenesis

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* Corresponding author. Tel.: +1 701 795 8465; fax: +1 701 795 8220.
E-mail address: hzeng@gfhnrc.ars.usda.gov (H. Zeng).

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[5,11]. However, the protective functions of Se may be subject to inhibition by numerous elements that may exist in foods or be encountered in the environment, including arsenic (As) [12,13].

There is some evidence suggesting that As can be beneficial for animal growth [14], and pharmacological amounts of As have been shown to be effective treating certain forms of leukemia [15]. However, As is better known for its negative impact on human health. Through epidemiological studies, As exposure has been associated with increased risks to cancers of the lung, skin, bladder, and liver. The US Environmental Protection Agency has classified As as a known human carcinogen (category A) [16,17]. Arsenic exposure is mainly through diet and drinking water. Arsenic is present in the environment in various chemical forms but inorganic As as trivalent arsenite (As^{3+}) and pentavalent arsenate (As^{5+}) are the major forms of As in surface and underground water [17,18].

Although As and Se are metalloids with similar chemical properties, they have dramatically different biological effects. Therefore, biological interactions between As and Se depend upon their respective chemical forms. Antagonistic effects or mutual detoxification between As and Se have been confirmed in many animal species including humans [12,19,20], since 1938 when Moxon discovered that As treatment could protect against Se toxicity in cattle [21]. It is generally accepted that uptake of one of these elements causes release, redistribution, or elimination of the other element by urinary, biliary, and/or expiratory routes [13]. However, the precise mechanism at the cellular level is still unknown. There are several proposed mechanisms to explain the interaction between Se and As, and these mechanistic aspects may shed light on how As may affect the anti-carcinogenicity of Se.

2. Metabolic interaction between arsenic and selenium

Studies of the interaction between As and Se began with the finding that chronic and acute Se toxicities could be minimized by the administration of arsenite and certain other arsenicals [20–23]. Earlier work demonstrated that As markedly increased the excretion of Se into the gastrointestinal tract when both arsenite and selenite were injected at subacute doses [20,24]. In addition, there were roughly corresponding decreases in the amounts of Se retained in the liver. The ability of As to promote the elimination of Se into the gut was observed in many experiments that used different doses, forms of As and Se, and time intervals between the As and Se injections [24]. Also, As decreased the amount of Se in the carcass, blood, and expired air, but the administration of large doses of an organic arsenical, sodium arsanilate, decreased the elimination of Se into the gastrointestinal contents and increased the amounts in the expired air, and the net effect being a slight decrease in Se retained in the carcass [24]. Conversely, it was found that selenite stimulated the gastrointestinal excretion of As in experiments similar to those in which As stimulated the gastrointestinal excretion of Se [24]. Further study demonstrated that As greatly increased the amount of Se excreted in rat bile [24,25]. This key observation was seen with several forms of Se and As over a wide dose range, and the large amounts of Se excreted in the bile of rats treated with As were approximately equivalent to the decreases in the retention of Se in the liver [25]. Therefore, it was proposed that Se and As reacted in the liver to form a conjugate that was excreted into bile; such an explanation is consistent with the fact that As and Se each increase the biliary excretion of the other [20,25].

More recently, it has been demonstrated that the in vivo antagonism between arsenite and selenite has its molecular basis in the formation of a novel As–Se compound: seleno-bis (*S*-glutathionyl) arsinium ion, $[(GS)_2AsSe]^-$, which is subsequently excreted in bile [26]. The detection of $[(GS)_2AsSe]^-$ in bile after intravenous injection of rabbits with selenate and arsenite suggests that both metalloids are first translocated to the liver [26]. The current hypothesis is that selenate is first reduced to selenite and, then, to selenide by a putative selenate reductase and/or reduced glutathione (GSH) [26]. Because of high intracellular concentrations of GSH in hepatocytes, the OH groups of arsenite are thought to be substituted by glutathionyl moieties forming the known compound $(GS)_2As–OH$ [26]. Selenide may then react with $(GS)_2As–OH$ to form $[(GS)_2AsSe]^-$. The latter could then be exported from the hepatocytes to bile by ATP-driven glutathione *S*-conjugate export pumps [27]. This observation provides the chemical basis that As and Se each increase the biliary excretion of the other at high/toxic dose ranges [20,25]. However, the existence of an interaction between As and Se through the biliary excretion at normal Se and As daily intakes (low dose ranges) still remains to be determined.

3. Direct arsenic and selenium interaction/precipitation

Although increased biliary excretion of Se may be the principal mechanism by which As interacts with Se, other mechanisms may also be important. The direct interaction of minerals in aqueous solutions may also play a major role in dissolution, precipitation, and absorption processes [28,29]. Many chemical forms of As and Se have been observed in nature but the relative quantitative importance of the forms vary very much. In the environment and diets, Se occurs in the +6 oxidation state as selenate (contain SeO_4^{2-}), +4 oxidation state as selenite (contain SeO_4^{2-}), 0 oxidation state as elemental