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EDITORIAL

Selenium in biology and medicine—further progress and increasing interest

The last issue of the *Journal of Trace Elements in Medicine and Biology* contained a series of interesting publications covering basic and clinically oriented research on the essential trace element selenium and its function in the broad field of life sciences including medicine. The recent progress in the molecular and functional analysis of the mammalian selenoproteome and the molecular and functional characterisation of selenocysteine-containing proteins was the subject of the last editorial. Table 1 presents a current overview on those selenoproteins which have been partially or fully characterized and which now have become exciting targets for innovative and selective drugs based on the peculiar highly reactive active site of selenoenzymes such as the thioredoxin reductase or the deiodinase family (S. Gromer, S. Urig, and K. Becker (2004) The thioredoxin system—from science to clinic. Med Res Rev 24(1): 40–89; G. Mugesh, and W.W. du Mont (2001) Structure-activity correlation between natural glutathione peroxidase (GPx) and mimics: a biomimetic concept for the design and synthesis of more efficient GPx mimics. Chemistry 7(7): 1365–1370).

This issue of the journal now presents a second set of selenium-oriented scientific reports which continue and expand the success story of the exponential career of this trace element. Se is an indispensable ingredient for most pro- and eukaryotic life forms with exception of the plant kingdom, though some seleniferous plants accumulate selenium from the soil either to make it available for mammalian consumption or help to remediate industrially contaminated soil and environment by extracting and accumulating Se.

One paper addresses the pertinent question of toxicity of Se administered in high doses to humans. This issue has led to serious controversies in the past and present due to repeated reports on fatalities and severe intoxications in relation to inappropriately high or accidentally excess Se intake. Reid et al. report on the outcome of a randomized controlled clinical trial testing effects of 1600 (8 patients) versus 3200 (16 patients) μg/day (microgram per day!) of selenized yeast administered for an average of almost 12 months (sic!) to patients with biopsy-proven prostate cancer. Blood chemistry was reported as ranging in normal limits, and plasma Se increased to 492 and 640 ng/ml respectively in the two groups. Side effects (exhalation of dimethylselenide, hair and nail changes) were more pronounced in the very high dose group. Though authors state that they "observed no obvious Se-related serious toxicities" they concede that more information and studies on Se toxicity are needed. This report should not provide the observational basis for unrestricted high-dose application of Se-containing agents as data provided here refer to a very special preparation of "selenized yeast" also used in the recent "Clark study" reporting on marked tumor preventive effects with respect to prostate (and colorectal) cancer in those participants belonging to the lower plasma Se percentiles (L.C. Clark, G.F. Combs, B.W. Turnbull, E.H. Slate, D.K. Chalker, J. Chow, L.S. Davis, R.A. Glover, G.F. Graham, E.G. Gross, A. Krongrad, J.L. Lesher, H.K. Park, B.B. Sanders, C.L. Smith, and J.R. Taylor (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. JAMA 276: 1957-1963; A.J. Duffield-Lillico, B.L. Dalkin, M.E. Reid, B.W. Turnbull, E.H. Slate, E.T. Jacobs, J.R. Marshall, and L.C. Clark (2003) Se supplementation, baseline plasma Se status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU International 91(7): 608–612). Currently, the no adverse effect level (NOAEL) for Se is set at an intake of 400 μg/day. As major differences still exist for Se intake and endpoints of supply between Se-rich regions such as many parts of North America or Japan versus low intake in Europe utmost care has to be taken not to linearly transfer data, results and interpretations between these regions as effective mechanisms have evolved and are in action which balance Se intake and excretion. This is also indicated by the study of van Cauwenbergh et al. in this issue documenting a Se status in the Antwerp region resembling that of an

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Table 1. Mammalian selenoproteins whose functions or biochemical characteristics have already been assigned

Selenoproteins	Tissue distribution	Functions
Glutathione peroxidase family (GPx1, GPx2, GPx3, GPx4, GPx6; snGPx-4)	Ubiquitous (GPx1, GPx4), gastrointestinal (GPx2), kidney & plasma (GPx3), olfactory epithelium, Bowmans gland (GPx6), testis, spermatozoa (snGPx4)	Antioxidant device, modulation of lipoxygenases, redox signal transduction
Thioredoxin reductase family (TRx1,2,3; TGR)		Multiple roles in redox regulation, drug metabolism, signal transduction
Thyroid hormone deiodinase family (Dio1,2,3)	Tissue specific expression and regulation mainly in the thyroid, liver kidney and pituitary	Catalyse conversion of T4 toT3 and degradation of rT3 (Dio1 and Dio2) and degradation of T4 and T3 (Dio1 and Dio3)
Selenophosphatase synthetase 2 (SPS2)	Various tissues	Catalyses the production of selenophosphate
15 and 18 kDa selenoproteins (Sel15, Sel18)	Various tissues, brain	Unknown
Selenoprotein M (SelM)	Various tissues including the brain	Unknown
Selenoprotein N (SelN)	Skeletal muscle, liver, brain, heart, stomach	Cell proliferation and regeneration? Mutations lead to rigid spine muscular dystrophy
Selenoprotein P (SelP)	Liver is main source of plasma SelP; ubiquitous	Se transport, antioxidant?
Selenoprotein R (SelR, MsrB)	Various tissues including the brain	R-methionine-sulfoxide-reductase
Selenoprotein T (SelT)	Various tissues	Unknown
Selenoprotein W (SelW)	Mainly in the skeletal muscle, heart muscle, brain, testis and spleen	Antioxidant?
Selenoprotein H, K, M, O, S, V, Y, Z	Various tissues	Unknown
Selenoprotein I	Various tissues	Hypothetical CDP-alcohol phosphatidyltransferase

earlier study in this area and comparable to that of other European countries. However, some years ago a major decrease in Se intake has been reported for the UK in connection to decreased import and consumption of wheat, corn and other cereals originating from Se-rich soils of Commonwealth countries after UK increased their economic relationships with and nutrient import from the European Union—an argument for the need to carefully monitor Se supply and endpoints of Se action and to further support and advance basic and applied research on essential trace elements such as Se.

The group around van Dael et al. reports on a fast and accurate method for the preparation of stable tracers from elemental Se. These reagents and the combined appropriate methods for identification and quantification of their metabolites will be urgently needed in further future studies analyzing their metabolic fate, absorption, retention and elimination kinetics, as well as potential benefits or risks of Se-fortified nutrients, Se-supplements or Se-based drugs and pharmaceuticals.

Venardos and coworkers confirm previous reports and present evidence that severe Se-deficiency increases susceptibility of isolated rodent hearts to damage by ischaemic reperfusion and link this to impaired expression of selenoproteins in the heart.

Se-deficiency also affects hepatic lipid concentration and fatty acid composition in rats even with adequate vitamin E and enhanced fish oil intake as reported by Schaefer and coworkers in this issue. The observed changes may be again be related to the decreased hepatic and tissue levels of selenoenzymes with antioxidative functions. However, possible effects of Se on absorption, storage and desaturation of fatty acids have also to be considered.

Dietary supplementation of laying hens with inorganic and organic selenium (selenized malt) increased selenium content in several hen tissues and their eggs, especially the yolk, but had no obvious effect of egg-laying productivity as reported by Jiakui and Xialong in this issue. The control group received adequate selenium supply, however.

The publication by El-Demerdash analyzed the ''Antioxidant effect of vitamin E and selenium on lipid peroxidation, enzyme activities and biochemical parameters in rats exposed to aluminium''. This element is widely distributed in our enviroment, food chain and in the medical field but is of potential concern as neurotoxic agent. The authors show that vitamin E or selenium in combination with aluminium partially alleviated its toxic effects and might be beneficial in antagonizing aluminium toxicity.

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