Chapter 21. Selenium, selenoproteins and brain function

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Summary: After the discovery of selenium (Se) as an essential trace element, direct evidence that Se plays a role in brain function remained relatively scarce for many years. This was probably due to the remarkable stability of brain Se levels during times of dietary Se restriction in experimental animals. In these experiments, activities of the first known Se-dependent enzymes, e.g. glutathione peroxidase (GPX), thioredoxin reductase (TrxR), and deiodinase (Dio), were also little changed in the brains of rodents fed Se-deficient diets for extended periods of time. Thus, the lack of spontaneous neurological deficits seemed to exclude an important role for Se in brain function. This notion remained largely unchanged despite the purification of selenoprotein P (SePP) from serum as a neurotrophic factor for cultured neurons and the finding that selenite is an essential component of media for in vitro culture of central neurons. Only later experiments revealed that Se-deficiency exacerbated the outcome of neurological disease in certain animal models. Oxidative stress is considered to play a role in neurodegenerative processes, and GPX1-transgenic mice provided the first molecular proof for an involvement of selenoproteins in such conditions. Then, gene targeting of SePP led to clear-cut spontaneous neurological deficits in Se-deficient animals and placed SePP at center stage for the privileged Se supply to the brain. Whether impaired expression of selenoproteins in human brain contributes to the incidence or severity of neurodegenerative disease remains to be established. Still, available evidence already suggests that selenoproteins are playing important roles for brain development, function, and disease in mice - and also most likely in humans.
Introduction

In 1957, Schwarz and Foltz identified Se as an essential trace element for rats. When maintained on a Se-deficient diet, animals developed liver necrosis, but could be rescued with a preparation called "factor 3" which was shown to contain Se [1]. Although subsequent studies revealed that the initial Se-deficient diet was also vitamin E-deficient, Se was now recognized as an essential trace element and no longer simply regarded as a potential environmental toxin. Unlike in most other organs, brain Se levels remained quite stable during dietary Se restriction [2-4]. Only one report demonstrated spontaneous neurological symptoms in Se-deficient mammals, i.e. "leg crossing", in Balb/c mice maintained on a Se-deficient diet [5], a finding which may be strain-specific since similar observations were not reported in other strains of mice or rats.

Oxidative stress, i.e. a disproportionate increase of reactive oxygen species leading to the oxidation of cellular constituents like proteins, DNA, and lipids, is thought to contribute to the cellular damage during excitotoxicity and pathogenesis of neurodegenerative disorders [6-8]. Given the reactions catalyzed by known selenoenzymes, it is conceivable that selenoproteins modulate the outcome of neurological disease in animal models. GPx1 degrades hydrogen peroxide, the product of superoxide dismutase (SOD). GPx4 degrades phospholipid hydroperoxides thereby potentially protecting cellular membranes from oxidative damage. Methionine sulfoxides are formed from protein-bound methionine during oxidative stress and can be reduced by methionine sulfoxide reductase (Msr) A and MsrB; the latter being also known as selenoprotein R. Mammalian TrxR accepts a wide range of substrates including hydrogen peroxide modulated redox-sensitive transcription factors. In fact, in animal models of neurodegenerative disease Se-deficiency generally exacerbated the neurological and histological damage and a simple Se-supplementation most often proved beneficial.

Stroke

During stroke or hypoxia/ischemia-reperfusion (HI), a dramatic increase in reactive oxygen species occurs that is believed to trigger molecular events culminating in increased apoptosis, necrosis, and neuroinflammation that may further increase neuronal cell loss and subsequently lead to memory impairment and motor incoordination [8-11]. Since stroke is among the leading causes of disabilities in aging Western societies, efficient treatments are urgently needed. Superoxide radicals (O$_2^-$) liberated during HI are degraded by SOD. The role of SOD in tissue protection is clearly illustrated after HI by increased cell death in mice with reduced SOD1 activity [12,13] and in mice protected from HI by over-expression of SOD1 [14]. During catalysis, SOD consumes O$_2^-$ and produces the less reactive hydrogen peroxide (H$_2$O$_2$). However, in the presence of Fe$^{2+}$, H$_2$O$_2$ may decompose...