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Selenium neurotoxicity in humans: Bridging laboratory and epidemiologic studies☆

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HIGHLIGHTS

- Acute overexposure to the metalloid selenium (Se) is neurotoxic in the human.
- Neurotoxicity of chronic Se overexposure needs to be better characterized.
- Chronic Se overexposure might induce lethargy and amyotrophic lateral sclerosis.
- The different Se chemical species strongly vary in their neurotoxic effects.
- Peripheral biomarkers of Se exposure may not reflect Se central nervous system levels.

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ABSTRACT

Selenium is a metalloid of considerable interest in the human from both a toxicological and a nutritional perspective, with a very narrow safe range of intake. Acute selenium intoxication is followed by adverse effects on the nervous system with special clinical relevance, while the neurotoxicity of long-term overexposure is less characterized and recognized. We aimed to address this issue from a public health perspective, focusing on both laboratory studies and the few epidemiologic human studies available, with emphasis on their methodological strengths and limitations. The frequently overlooked differences in toxicity and biological activity of selenium compounds are also outlined. In addition to lethargy, dizziness, motor weakness and paresthesias, an excess risk of amyotrophic lateral sclerosis is the effect on the nervous system which has been more consistently associated with chronic low-level selenium overexposure, particularly to its inorganic compounds. Additional research efforts are needed to better elucidate the neurotoxic effects exerted by selenium overexposure.

1. Introduction

The intense debate on the role of the metalloid selenium (Se) in human health encompasses cancer etiology (Dennert et al., 2011; Vinceti et al., 2013b), diabetes mellitus (Stranges et al., 2010; Koyama et al., 2013), amyotrophic lateral sclerosis (ALS) (Vinceti et al., 2012), and 'Keshan' cardiomyopathy (Lei et al., 2011; Li et al., 2012), alongside other infectious and non-communicable diseases. Se effects on human health may be both beneficial (Rayman, 2000) and detrimental (Vinceti et al., 2001), and the safe range of dietary Se intake is still uncertain and controversial, as shown by the most recent epidemiologic evidence and by the various standards issued

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by different agencies (Vinceti et al., 2009; Fairweather-Tait et al., 2011; Hurst et al., 2013; Vinceti et al., 2013a). Recent field and laboratory studies have added to this ambiguity, thus further hampering the risk assessment of this metalloid and the definition of permitted limits of environmental exposure, and preventing consensus on public health policy (Vinceti et al., 2013a, 2013b).

Among the intriguing aspects are the role of Se in the etiology of neurological disease (Vinceti et al., 2001, 2009), also taking into account the complex peculiarities of Se physiopathology and metabolism in the brain (Buckman et al., 1993; Pullen et al., 1995; Whanger, 2001; Bou-Resli et al., 2002; Schweizer et al., 2004; Scharpf et al., 2007; Benner et al., 2013). Unfortunately, the relation between Se exposure and neurological diseases has been addressed in few human studies, in some cases affected by relevant methodological limitations, and therefore it necessitates further validation and extension. A number of studies also suggested or evidenced the key importance of additional factors of interest when assessing Se biological activity and toxicity, such as the chemical form of Se, and the concurrent exposure to other toxic chemicals (i.e. mixed exposures) (Gammelgaard et al., 2011; Michalke and Berthele, 2011; Zwolak and Zaporowska, 2012; Solovyev et al., 2013; Vinceti et al., 2013c; Weekley and Harris, 2013).

In this review, we have briefly analyzed Se neurotoxicity on the basis of the scarce epidemiologic evidence available, also considering the biological plausibility of findings from laboratory and veterinary medicine studies and the recent interest in Se neurotoxicity in risk assessments of metals and metalloids (Fresquez et al., 2013). For the selection of the literature eligible for this review, we examined in detail PubMed-indexed papers using as MeSH search terms “Nervous System Diseases” associated with “selenium/toxicity”. Moreover, we systematically scanned PubMed to retrieve the human and laboratory studies on Se investigating its neurotoxicity. Some caveats need however to be outlined. First of all, a relation between Se and neurological disease calls into question not only its toxicity but also its nutritional role. In fact, both an *increase* and a *decrease* in the amount of bioavailable Se might theoretically enhance the risk of neurological disease and its progression. The hypothesis that an increased Se intake may reduce the risk of diseases such as Alzheimer’s disease or amyotrophic lateral sclerosis (ALS), or counteract their clinical progression has been evaluated in laboratory studies (Scharpf et al., 2007; Bellinger et al., 2012; Raman et al., 2012), some of which indicated beneficial effects of organic and inorganic Se compounds in experimental models of neurodegenerative diseases (Schweizer et al., 2004; van Eersel et al., 2010; Wirth et al., 2010; Zhang et al., 2010; Caito et al., 2011; Dasuri et al., 2013). However, no such effects have been confirmed by human investigations. Moreover, our review did not analyze the possible inverse relation between Se status and psychiatric disorders, a currently controversial issue (Berr et al., 2012; Gao et al., 2012; Hurst et al., 2013; Miller et al., 2013).

2. Laboratory studies on Se neurotoxicity

The neurotoxic effects of Se have long been investigated in laboratory studies (Kasuya, 1976; Ammar and Couri, 1981; Rasekh et al., 1997, 1998) and several recent studies on this issue have been published (Xiao et al., 2006; Ayaz et al., 2008; Morgan et al., 2010; Souza et al., 2010; Maraldi et al., 2011; Estevez et al., 2012). One of the pioneering studies on Se neurotoxicity showed the ability of both inorganic and organic Se compounds to induce behavioral and neurological manifestations in mice, with selenite being much more toxic than selenomethionine (Ammar and Couri, 1981). In this investigation, Se species induced a decrease in locomotion followed by ataxia and hind limbs paralysis and dysfunction, generalized muscular flaccidity and catalepsy-like state; respiratory and heart rates also markedly decreased, and were followed by death due to respiratory and cardiac arrest.

The neurotoxic effects inducible by Se compounds include among others an increase of central nervous system (CNS) dopamine levels (Rasekh et al., 1997) and metabolites (Tsunoda et al., 2000), alteration of cholinergic signaling and degeneration of cholinergic neurons (Estevez et al., 2012), inhibition of glutamate uptake (Nogueira et al., 2003; Ardais et al., 2010; Souza et al., 2010) and prostaglandin D synthase (Islam et al., 1991; Matsumura et al., 1991; Akarsu et al., 1998; Ardais et al., 2010), decrease of total antioxidant status, gangliosides and sulphydryl groups (Islam et al., 2004; Medeiros et al., 2012), of activity of adenosine deaminase (Bitencourt et al., 2013), succinic dehydrogenase and acetylcholine esterase (Nehru and Iyer, 1994), and finally increase of thiobarbituric acid reactive substances and lipid peroxidation (El-Demerdash, 2001; Islam et al., 2004; Glaser et al., 2010; Medeiros et al., 2012). Additional Se-induced CNS alterations are hypothermic and nociceptive responses as well as CNS arousal (Mallory Boylan et al., 1990; Rasekh et al., 1998), and reduction of locomotor activity (Rasekh et al., 1997, 1998; Morgan et al., 2010). Finally, inorganic Se has also been shown to induce apoptosis in cultured mouse cortical neurons even at very low concentrations (Xiao et al., 2006). Some of these effects are differentially exerted in various CNS regions, even with opposite mechanisms (Zia and Islam, 2000; Islam et al., 2004; Glaser et al., 2010; Medeiros et al., 2012). Se-induced neuromuscular blockade, tetanic spasm, alteration of nerve-fiber action potentials and nerve membrane depolarization (Liu et al., 1989; Lin-Shiau et al., 1990; Ayaz et al., 2008), and inhibition of human squalene monooxygenase, which may in turn lead to peripheral demyelinating neuropathy (Gupta and Porter, 2002), are all additional findings from experimental studies with potential clinical implications.

The neurotoxicity of Se compounds is also manifested by its ability to induce degeneration of motor neurons. In the study by Maraldi et al. (2011), human neuroblastoma SKNBE cells were shown to be more prone than other human cell lines to the neurotoxicity of inorganic and organic Se compounds: the lowest effects on viability were observed at levels as low as 8 μg/l. Moreover, Se induced a broad range of intracellular effects including increased intracellular levels of reactive oxygen species, inducible nitric oxide synthase and 3-nitrotyrosine, and superoxide dismutase-1 translocation from the cytosol to the mitochondria, the latter phenomenon characterizing the neurodegerative process in the ALS form associated with superoxide dismutase-1 mutation. In another study, inorganic tetravalent Se, selenite, induced degeneration of cholinergic neurons and depletion of glutathione, impairing locomotor activity in *Caenorhabditis elegans* model (Morgan et al., 2010; Estevez et al., 2012). The cholinergic motor neurons in the ventral cords exhibited several neurodegenerative signs following Se exposure: axonal beading, cellular swelling and nuclear cytoplasmatic boundary loss and fragmentation. Se disrupted the orderly array of presynaptic densities in this region, as previously observed at the neuromuscular junction in a superoxide dismutase-1 mouse model (Fischer et al., 2004). Moreover, veterinary research on inorganic and organic Se poisoning in swine showed acute neuromuscular signs with progressive posterior paralysis and in some cases forelimb involvement, progressing to lateral recumbence and death (Harrison et al., 1983; Wilson et al., 1983; Anonymous, 2010; Nathues et al., 2010; Raber et al., 2010). These findings were obtained both in observational studies following accidental acute and chronic Se intoxication, and experimentally by administering Se-accumulator plants and various Se forms (Hartley et al., 1984; Panter et al., 1996). Pathological findings were selective degeneration of the ventral horns in the spinal cord, bilateral poliomyelomalacia in the cervical and lumbar/sacral spinal cord