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Review

Toxicity mechanisms of arsenic that are shared with neurodegenerative diseases and cognitive impairment: Role of oxidative stress and inflammatory responses

Claudia Escudero-Lourdes*

Laboratorio de Inmunotoxicologia, Facultad de Ciencias Quimicas, Centro de Investigación y Estudios de Posgrado (CIEP), Universidad Autónoma de San Luis Potosí (UASLP), Av. Dr. Manuel Nava #6. Col. Univeristaria, San Luis Potosí, S.L.P., Mexico

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ABSTRACT

Arsenic (As) is a worldwide naturally occurring metalloid. Human chronic exposure to inorganic As compounds (iAs), which are at the top of hazardous substances (ATSDR, 2013), is associated with different diseases including cancer and non- cancerous diseases. The neurotoxic effects of iAs and its methylated metabolites have been demonstrated in exposed populations and experimental models. Impaired cognitive abilities have been described in children and adults chronically exposed to iAs through drinking water. Even though different association studies failed to demonstrate that As causes neurodegenerative diseases, several toxicity mechanisms of iAs parallel those mechanisms associated with neurodegeneration, including oxidative stress and inflammation, impaired protein degradation, autophagy, and intracellular accumulation, endoplasmic reticulum stress, and mitochondrial dysfunction. Additionally, different reports have shown that specifically in brain tissue, iAs and its metabolites induce hyper-phosphorylation of the tau protein and over-regulation of the amyloid precursor protein, impaired neurotransmitters synthesis and synaptic transmission, increased glutamate receptors activation, and decreased glutamate transporters expression. Interestingly, increased and sustained pro-inflammatory responses mediated by cytokines and related factors, seems to be the triggering factor for all of such cellular pathological effects. Therefore, this review proposes that iAs-associated cognitive impairment could be the result of the activation of pro-inflammatory responses in the brain tissue, which also may favor neurodegeneration or increase the risk for neurodegenerative diseases in exposed human populations.

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* Fax: +52 444 8262372.
E-mail addresses: cescuder@uaslp.mx, clauescu@yahoo.com (C. Escudero-Lourdes).

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1. Introduction

Neurodegeneration and progressive loss of neuronal structure in specific brain areas are the basis of the main neurodegenerative disorders, such as Alzheimer disease (AD) and Parkinson disease (PD), which in turn are the main causes of dementia. The main manifestations of dementia include an important cognitive deficit, behavior and thinking impairment, which, in later stages, results in a disability of performing daily tasks and is, ultimately, fatal. Both dementia and non-dementia cognitive impairment occur more frequently in elderly patients. Mild cognitive impairment is considered a transitional state between normal aging and dementia and represents an opportunity for interventions to prevent or slow the progression of dementias (Manly et al., 2008).

Important research has demonstrated an interesting association between the main neurodegenerative disorders, AD and PD, and chronic diseases such as cancer, diabetes, cardiovascular disease, chronic infections and stress, seizures, etc. These conditions have been demonstrated to trigger or worsen the neuropathological complications and significantly enhance mortality (Jabir et al., 2015). Interestingly, several shared molecular mechanisms between these chronic diseases and neurodegenerative diseases include oxidative stress and the associated pro-inflammatory responses (mediated by NF-KB, MAPKs, and AP-1 activation) (Glass et al., 2010; Friedlander, 2003; Uttara et al., 2009). Other common mechanisms include misfolded proteins, apoptosis dysregulation, mitochondrial dysfunction, and mitochondrial DNA aberrations (Filosto et al., 2011; Jabir et al., 2015).

Currently, in the clinical literature, it is well recognized that healthy individuals very often develop an important cognitive decline after suffering an inflammatory challenge such as an infection, surgery or head injury (Rogers and Lahiri, 2004; Craft et al., 2012; Tokutomi et al., 2008; Ramaiah and Lam, 2009). These observations suggest that any persistent pro-inflammatory stimulus could induce the same negative effect on human cognitive functions; it is now clear that different environmental factors, such as nutrition (van de Rest et al., 2015), stress levels (McEwen et al., 2015; McEwen et al., 2016), and continuous exposure to toxicants (Genuis and Kelln, 2015) appear to play an important role in the increased risk for cognitive impairment and dementia and that some of them act through the induction of oxidative stress and sustained inflammatory responses.

Historically, chronic human intoxication with iAs has been correlated with different chronical diseases including different types of cancer (skin, bladder, renal, liver and lung cancer) and non-cancerous diseases, such as diabetes and cardiovascular and neurological diseases (Zierold et al., 2004; Bardach et al., 2015), which are the same diseases that are described to increase the risk for AD and PD. Interestingly, all these clinical entities share an inflammatory component as a common pathogenic factor (Verdile et al., 2015; Conti and Shaik-Dasthagirisaeb, 2015; Crusz and Balkwill, 2015). In fact, several studies have demonstrated that As induces a strong inflammatory response that could be dependent on or independent from oxidative stress generation even at concentrations that are considered low by the official norms that dictate the arsenic content in drinking water (Escudero-Lourdes et al., 2010; Valavanidis et al., 2009; Wu et al., 2008; Fry et al., 2007).

Importantly, epidemiological studies have also suggested a correlation between human exposure to iAs and neurodegenerative diseases such as AD and PD (Dani, 2010; Gharibzadeh and Hoseini, 2008), but this association has not been proven yet. However, chronic exposure to high and moderate As concentrations (based on United States and world regulations for As content in drinking water) is clearly associated with impaired intellectual functioning in children and adults (Hamadani et al., 2011; Wasserman et al., 2014; Dong and Su, 2009; Naujokas et al., 2013).

In 2010, Gong and O'Bryant (2010b) highlighted some of the biochemical, pathological, developmental and clinical features that are common between arsenic exposure and AD and proposed an hypothesis for As-induced AD neurodegeneration, which involves the induction of oxidative stress; however, the mechanisms linking oxidative stress with neurodegeneration were not approached. On the other hand, Gong-O'Bryant's hypothesis could explain not only AD development after chronic exposure to As, but also other neurodegenerative diseases that are influenced by environmental factors like Parkinson and ALS, which also share several pathogenic factors including the chronic inflammatory state and increased ROS production in brain tissues.

In this review, we present evidence that has not been reviewed before, showing that exposure to arsenic leads to the same cellular pathogenic characteristics that are shared among the principal neurodegenerative diseases: induction of sustained inflammatory and oxidative mechanisms, intracellular proteins accumulation, defects in protein degradation systems, activation of the unfolded protein response and impaired mitochondrial function. We also describe the currently known iAs-associated neurotoxic mechanisms and their association with pro-inflammatory responses. Based on these observations, we propose that, through the activation of inflammatory responses, arsenic may induce cognitive dysfunction and neurodegeneration in exposed populations.

To introduce the readers to the context of what leads researchers to propose that human chronic exposure to arsenic is associated with cognitive impairment or neurodegeneration in exposed populations, the following section describes the global problem of arsenic-contaminated water, followed by the description of its metabolism and accumulation in the brain and in other tissues.

2. Arsenic

Arsenic is a worldwide-occurring metalloid that can be found in the environment from natural and anthropogenic sources (Brinkel et al., 2009) at an average concentration of 1.8 ppm (parts per million, μg/mL) (Dani, 2010). The inorganic form of arsenic (iAs) is at the top of the list of toxic substances threatening human health (ATSDR, 2013). Mining and use of pesticides and herbicides are the