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Early life arsenic exposure and brain dopaminergic alterations in rats

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ABSTRACT

Recently, we found that early life exposure to arsenic at low doses resulted to cause brain cholinergic deficits and exhibited a trend of recovery on withdrawal of arsenic exposure. In continuation to this, the present study has been carried out to assess the impact of low level arsenic exposure on brain dopaminergic system and associated behavior in developing rats and investigate if neurobehavioral changes are recovered or persistent. Early life exposure (PD22–PD59) to arsenic (2 or 4 mg/kg body weight, p.o.) in rats resulted to increase the motor activity on PD60, compared to controls. The hyperactivity in arsenic exposed rats was found to be linked with increase in the binding of DA-D2 receptors (38%, 56%), mRNA expression of DAR-D2 receptor gene (68%, 97%) and expression of tyrosine hydroxylase protein (1.93, 2.73-fold) in the corpus striatum as compared to controls on PD60. Exposure to arsenic enhanced generation of ROS (47%, 84%) and was associated with decrease in the mitochondrial membrane potential (13.3%, 15.33%), activity of mitochondrial complexes and increased oxidative stress. Disruption in the expression of pro-apoptotic, anti-apoptotic and stress marker proteins was also distinct in the corpus striatum of arsenic exposed rats. The severity of changes in the behavioral and neurochemical endpoints were found to persist in rats exposed to arsenic at high dose and exhibited a trend of recovery at low dose on withdrawal of arsenic exposure on PD90. Early life arsenic exposure appears to be critical and vulnerable as development of dopamine receptors continues during this period.

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1. Introduction

Presence of arsenic as a contaminant in the ground water in several regions of the globe is one of the major problems due to associated health effects (Kapaj et al., 2006; Chen et al., 2011; Hughes et al., 2011). Identification of new arsenic contaminated sites in the Asian region has therefore aroused a great concern due to the risk of exposure of a large population (Rahman et al., 2009; Saha and Shukla, 2013; Van Geen et al., 2014). It has been estimated that around 140 million people are exposed to arsenic, a metalloid world over by contaminated water (Kris, 2009). Besides, arsenic has anthropogenic uses as an alloying agent in the manufacture of electronic transistors and semiconductors, wood preservatives, metal adhesives and pigments (Fowler and Sexton, 2007; Wlodarczyk et al., 2011). Mining, smelting of ores, burning of fossil fuels, weathering and volcanic eruptions also significantly contribute to introduce arsenic in the environment (Vall et al., 2012). Presence of high levels of arsenic in the air and soil in certain regions therefore enhances the risk of exposure (Tsai and Lee, 2013). Rodriguez et al. (1998) reported that the population residing near mining sites in Mexico was at a greater risk of exposure to arsenic and other metals by mineral debris that contaminated soil, dust and surface water. Moreover, use of mining waste as a plastering material for homes and buildings may also expose the population to arsenic and other metals (Rodriguez et al., 1998). In the living systems both in plants and animals, arsenic is present in organic form while in the natural state, it exists in the inorganic form which is more toxic (ATSDR, 2007). Human exposure to arsenic could also occur through the food chain by consuming contaminated vegetarian and sea food (Rosso et al., 2013). Dietary exposure to arsenic by consuming rice and rice products that may contain high levels of inorganic arsenic is a potential threat to the health of the general population at large (Davis et al., 2012; Jackson et al., 2012).

Due to increasing incidences of human exposure to arsenic, there is lot of concern to find out a link with environmental arsenic exposure, tissue arsenic levels and potential clinical effects. Chronic exposure to arsenic has been associated with hyperpigmentation,

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keratosis and skin lesions (Haque et al., 2003; WHO, 2005; Ling et al., 2013) and found to affect the functioning of different body organs including liver, lung, kidney, bladder and skin (Hughes et al., 2011). Risk to develop cancers of skin and internal body organs is enhanced following arsenic exposure (Yorifuji et al., 2011; Du et al., 2012; Smith et al., 2012). Arsenic exposed population has been found to suffer from vascular and nonvascular complications (Bailey and Fry, 2014; Stea et al., 2014). Diabetes, hypertension and atherosclerosis have been frequently reported in recent years due to arsenic exposure (Abhyankar et al., 2012; Jovanović et al., 2012; Mahram et al., 2013). Increase in arsenic induced cardiovascular problems are imminent and a cause of concern (States et al., 2009; Abhyankar et al., 2012). Consumption of drinking water with arsenic above 50 μg/l during pregnancy was associated with increased risk of fetal loss and infant death (Rahman et al., 2007, 2010; Ahmed et al., 2011). Besides affecting the growth of infants, a number of studies have found that exposure to arsenic may enhance immunosuppression and increase the incidences of infectious diseases both in mothers and growing children (Raqib et al., 2009; Ahmed et al., 2011). Peripheral neuropathies in arsenic exposed individuals are quite common in clinical practice (Barton and McLean, 2013). Neurological deficits both in children and adults have been reported following environmental and occupational exposure to arsenic (Rosado et al., 2007; Dong and Su, 2009). Experimental and clinical studies have revealed that prenatal exposure to arsenic may affect the normal development of the progeny and brain functions during early life (Vahter, 2009; Roy et al., 2011; Goggin et al., 2012). A number of investigators have found impairment in comprehension, intelligence and higher cognitive functions including memory in arsenic exposed children (Rocha-Amador et al., 2007; Von Ehrenstein et al., 2007; Brinkel et al., 2009; Vahter, 2009; Parvez et al., 2011). In a study on the pre-school aged children in Bangladesh, Hamadani et al. (2011) found that early life arsenic exposure affected both the verbal and full scaled IQ with striking changes in the girls. A negative correlation between the IQ and urinary arsenic levels was observed in this study (Hamadani et al., 2011). Poor scores in intellectual functions were also found to be associated with higher arsenic levels in urine and hair in studies carried out in other parts (Wright et al., 2006; Hinhumpatch et al., 2013; Parajuli et al., 2013; Wasserman et al., 2014). In a recent study, arsenic levels in the brain of children and young individuals residing in the polluted mega-city of Mexico City were found to be 78 μg/g (Calderón-Garcidueñas et al., 2013). However, in another study on human exposure to metals, arsenic levels in autopsied brain samples of individuals living near hazardous waste incinerator in Tarragona (Catalonia, Spain) were found below 0.05 μg/g (Mari et al., 2014). Arsenic levels in the brain of normal Japanese were found to be 0.22 μg/g (Katoh et al., 2002). Interestingly, Studies on autopsied brain samples of arsenic exposed individuals are limited and moreover, levels of arsenic in the brain vary which could possibly be due to difference in the exposure regimen and other obvious reasons.

Arsenic easily crosses the blood brain barrier and is accumulated in the brain (Jin et al., 2006; Brinkel et al., 2009). Recently, Andrade et al. (2014) found that arsenic and manganese may influence the deposition of lead in the brain and other body tissues of rats and thus arsenic is an important contributor in enhancing the toxicity in situations where exposure to metal mixture is imminent. Nutritional deficiencies and poor detoxification by affecting the process of methylation are other important factors which may increase the toxicity of arsenic and lead to central nervous system abnormalities (Liu et al., 2014). Disruption of REDOX signaling is one of the potential mechanisms widely accepted in arsenic induced neurotoxicity (Jomova et al., 2011). A number of experimental studies have revealed that arsenic affects the levels of brain neurotransmitters and their receptors which are important regulators of behavior (Liu et al., 2013; Zhang et al., 2013). The development of the brain starts prenatally and continues over a large period of time during the early postnatal period through a complex process in a well orchestrated manner. As the basic brain structures are formed and proliferation and migration of neurons take place during this time, the developing brain is vulnerable to adverse effects of environmental chemicals (Rice and Barone, 2000; Weiss, 2000; Costa, 2004; Bellinger, 2013a). A number of experimental studies have been carried out to assess the effect of arsenic, considered to be a developmental neurotoxicant during prenatal and/or lactational periods (Bellinger, 2013b). In view of incidences of direct exposure to arsenic, there is a lot of concern to assess the effect during the pre-adolescent stage as the formation of synapse and receptors take place during this time. However, not much data is available. Recently, we found that exposure to arsenic during early life resulted to cause cholinergic alterations in the brain with impairment in the memory and learning of developing rats (Chandravanshi et al., 2014). A trend of recovery in neurobehavioral changes was observed on withdrawal of exposure suggesting that arsenic induced cholinergic alterations are transient (Chandravanshi et al., 2014). While impaired cognitive deficits in arsenic exposed population are attributed to cholinergic dysfunctions, a number of experimental studies have found that arsenic may affect the motor functions (Ram Kumar et al., 2013; Rodriguez et al., 2010). In spite of the intense involvement of the dopaminergic system in modulating the motor behavior, not much is known about the mechanism of arsenic induced brain dopaminergic alterations. Impact of arsenic on key dopaminergic endpoints in the developing brain is also not understood. The present study has therefore been aimed to investigate effect of arsenic exposure during early life from PD22 to PD59 on selected behavioral and neurochemical endpoints associated with the dopaminergic system immediately after exposure on PD60. To further understand if arsenic induced changes persist or recover, effect on the neurobehavioral endpoints was further studied 30 days after withdrawal of arsenic exposure on PD90. As stated, the study is in continuation to our earlier study using the same doses (2 or 4 mg/kg body weight) of arsenic (Chandravanshi et al., 2014) as arsenic exposure at doses 3–4 mg/kg body weight/day has been found to cause structural alterations in myelinated tracts in brain regions (Rios et al., 2009; Zarazua et al., 2010; Martínez et al., 2011).

2. Materials and methods

2.1. Animals and treatment

Experimental rats (male, postnatal 21 day old) of Wistar strain obtained from the central animal breeding colony of CSIR-Indian Institute of Toxicology Research (CSIR-IITR), Lucknow, India were used in the present study. Rats were housed in polypropylene cages in a controlled environment at 22 ± 2 °C under standard animal house conditions in a 12-h light–dark cycle and fed pellet diet and water *ad libitum*. On PD22, rats were randomly divided in to three groups and treated with sodium arsenite as follows,

Group I – Rats were treated with sodium arsenite (2 mg/kg body weight, p.o.) dissolved in distilled water once daily from PD22 to PD59.
Group II – Rats were treated with sodium arsenite (4 mg/kg body weight, p.o.) dissolved in distilled water once daily from PD22 to PD59.
Group III – Rats were treated with normal saline (p.o.) identically as in Groups I and II and served as controls.

Effect on the spontaneous motor activity was studied 24 h after the last dose of arsenic treatment on PD60. For neurochemical studies, separate set of rats in each group was used. Rats were sacrificed on PD60 and brain was taken out quickly and washed in ice cold saline. The corpus striatum from the brain was dissected out following the method as described by Glowinski and Iversen (1966). Separate set of rats in each treatment group was used for the assay of different neurochemical endpoints. Assay of ROS generation, mitochondrial complexes, mitochondrial membrane potential and parameters associated with oxidative stress was done the same day rats were sacrificed. Corpus striatum was stored frozen at −80 °C for receptor binding assay, mRNA expression of DAR-D2 receptor gene, immunoblotting and

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