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ORIGINAL ARTICLE

High fat diet deteriorates the memory impairment induced by arsenic in mice: a sub chronic in vivo study

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Abstract

Both arsenic (As) and obesity are associated with brain disorders. However, long term studies to evaluate their concomitant adverse effects on the brain functions are lacking. Present study was conducted to evaluate the long term co-exposure of As and high fat diet (HFD) on memory and brain mitochondrial function in mice. Male mice were randomly divided into 7 groups fed with HFD or ordinary diet (OD) and instantaneously exposed to As (25 or 50 ppm) in drinking water for, 4, 8, 12, 16 or 20 weeks. Step-down passive avoidance method was used for memory assessment and post exposure various parameters including mitochondrial damage, level of reactive oxygen species (ROS), malondialdeid (MDA) and glutathione (GSH) were determined. Results indicated that the retention latency decreased in As (25 and 50 ppm) and HFD received mice after 12 and 16 weeks respectively. Same results were observed at significantly shorter duration (8th week) when As was administered along with HFD as compared to control group. In the HFD alone fed mice increased the mitochondrial membrane damage, levels of ROS and MDA were observed while GSH contents decreased significantly. Concomitant administration of HFD and As amplified those mentioned toxic effects ($p < 0.001$). In conclusion, our findings demonstrated that the simultaneous HFD and As impaired memory at least three times more than exposing each one alone. These toxic effects could be due to the mitochondria originated oxidative stress along with the depleted antioxidant capacity of the brain of mice.

Keywords High fat diet · Arsenic · Memory · Oxidative stress · Mitochondria

Introduction

It is estimated that over 200 million people worldwide are chronically exposed to arsenic (AS) at toxic levels just due to consumption of arsenic-contaminated water (Tolins et al. 2014). Toxic effects of arsenic depends on the dose and the duration of exposure (Mukherjee et al. 2006). Chronic arsenic administration can cause skin pigmentation, cardiovascular, endocrine, gastrointestinal and respiratory diseases, anemia, reproductive adverse effects, cancer, immunological effects and neurological disorders (Ng et al. 2003; Tolins et al. 2014). High levels of As in water have been reported in several countries including Argentina, Bangladesh, Chile, China, Hungary, India, Mexico, Taiwan and the United States (Karim 2000).

Inorganic and methylated arsenic can cross the blood brain barrier and store in many brain areas (Tyler and Allan 2014). Numerous studies have revealed toxic effects of arsenic exposure on the nervous system and cognition in children and adults (Jiménez-Capdeville and Giordano 2003; Luo et al. 2009; Tyler and Allan 2014). It was shown that verbal abilities and long-term memory impaired in children following arsenic exposure (Calderon et al. 2001). In animal models, chronic arsenic administration revealed to induce memory and cognitive impairment (Nagaraja and Desiraju 1994; Rodrıguez et al. 2001). Studies have shown that sodium arsenite exposure lead

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to neurobehavioral changes and alterations in learning tasks (Rodrıguez et al. 2002). Also, arsenic exposure exhibited some damage to spatial memory (Luo et al. 2009). Several Studies have reported that the arsenic exposure induced neuronal necrosis and apoptosis (Dewji et al. 1995).

Brain mitochondria play important roles in neurotransmission, neuronal plasticity and behavioral adaptation (Mattson 2008; Mattson et al. 2008). Mitochondria is the main source of ROS generation via electron transport chain (ETC) (Serrano et al. 2003). Over production of ROS results in lipids, proteins or DNA damage and ultimately neuronal cell death (Paradies et al. 2011). There is strong evidence that Alzheimer's disease (AD) and other types of dementia are pathogenetically associated with oxidative stress and mitochondrial dysfunction (Liu et al. 2002). Mitochondrial dysfunction can change neuronal function via the increasing of ROS production, decreasing ATP synthesis and inducing of apoptosis (Markham et al. 2014). Various studies demonstrated that generation of ROS and oxidative stress play important roles in arsenic induced neurotoxicity (Jomova et al. 2011; Samuel et al. 2005). Arsenic increased lipid peroxidation in brain via depletion of GSH and decreased the activity of superoxide dismutase, catalase and glutathione reductase (Chaudhuri et al. 1999). Chronic arsenic exposure decreased mitochondrial complexes activities and increased ROS levels in the brain (Prakash et al. 2015). Further, it is indicated that striatum, cortex and hippocampus may be more susceptible than other regions of the brain to arsenic-induced oxidative stress (Samuel et al. 2005).

On the other hand, the wrong style of life and diet would influence cognitive health and memory (Solfrizzi et al. 2011). Various studies have revealed that chronic high fat diet results in learning, memory and synaptic plasticity impairments as well as increasing the risk of dementia in elderly (Elias et al. 2005; Kalmijn et al. 1997, Kalmijn et al. 2004; Knopman et al. 2001). Also HFD diminished cognitive performance in school children (Zhang et al. 2005a). Furthermore, HFD is associated with cognitive impairment caused by cerebral ischemia/reperfusion injury, traumatic brain injury and Alzheimer's disease (Alzoubi et al. 2013). Previous studies have proposed that HFD increase dementia through elevated ROS and oxidative stress in brain (Chinen et al. 2007; White et al. 2009; Zhang et al. 2005b)

The effects of arsenic toxicity and high fat diet on the impairments of memory have individually been determined in the previous studies. So, present study was conducted to evaluate the simultaneous effects of As and HFD on the memory in mice. We hypothesized that the combination of HFD and arsenic exposure could impair memory more severely than each condition alone. Also we investigated the role of impairment of mitochondrial functions by arsenic in HFD induced memory decline. To our knowledge, this is the first study to evaluate the concomitant long term exposure to As and HFD on the learning and memory in invivo.

Experimental

Chemicals

Sodium arsenite, 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES), mannitol, ethylene glycol tetra acetic acid (EGTA), bovine serum albumin (BSA), 2,7- di chloro fluorescein diacetate (DCFH-DA), 3,4 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT), Rhodamine 123, thiobarbituric acid, trichloroacetic acid,1,1,3,3-tetramethoxypropane, reduced glutathione, oxidized glutathione, Coomassie Brilliant Blue were purchased from Sigma-Aldrich (St Louis, Missouri, USA). Sucrose 5, 5′-dithiobis-2-nitrobenzoic acid (DTNB), dimethyl sulfoxide (DMSO), NaCl, KCl, $CaCl_2$, $MgCl_2$ and $NaHCO_3$ were obtained from Merck company (Darmstadt, Germany).

Animals and diets

Male Naval Medical Research Institute (NMRI) mice (30–35 g) were obtained and qualified by the local animal care guidelines with an ethics committee No. (IR.AJUMS.REC.1395.405). After 1 week of adaptation, the mice were housed six per cage in polycarbonate cages with corncob bedding in 20 ± 4 °C temperature with a 12 h light/12 h dark cycle and 10% humidity. Mice were received an ordinary diet (OD; 11% of all calorie supply from fat) or a high-fat diet (HFD; 57% of all calorie supply from fat) for 4, 8, 12, 16 or 20 weeks.

According to some studies the grain-based diet contained 19.5–28.6 ppb arsenic (mainly inorganic arsenic: iAs), and it may be compromised the training design. To evade this issue a purified diets without grain components has been used (Paul et al. 2011). The level of As in high fat and ordinary diet was 10 ppb and 15 ppb respectively, that include very lower concentration of arsenic compared to the examined concentration (25 and 50 ppm). Small animals such as mice might be less at risk than human to arsenic toxicity due to a quicker metabolism and clearance of this toxic agent (Paul et al. 2011). Moreover, a recent study has shown that 10 times higher arsenic concentration in drinking water is needed (50 ppm) to attain arsenic concentrations similar to those seen in the west Bengal (Shi et al. 2013). Therefore we used diH_2O or diH_2O plus As in doses of 25 or 50 ppm in the present study (Paul et al. 2011). Water containing arsenic was replaced every 3 days to minimize its oxidation effect. Water and food consumption and body weight monitoring have been done every week in all exposure groups. Group assignment: mice were divided into 7 groups, control group (untreated mice, $n = 8$), OD0 (divided into 5 groups that received ordinary diet for 4, 8, 12, 16 or 20 weeks, $n = 8$), OD25 (divided into 5 groups that received ordinary diet concomitant with 25 ppm As in water for 4, 8, 12, 16 or 20 weeks, $n = 8$), OD50 (divided into 5 groups that

received ordinary diet concomitant with 50 ppm As in water for 4, 8, 12, 16 or 20 weeks, $n = 8$), HF0 (divided into 5 groups that received high fat diet for 4, 8, 12, 16 or 20 weeks, $n = 8$), HF25 (divided into 5 groups that received high fat diet concomitant with 25 ppm As in water for 4, 8, 12, 16 or 20 weeks, $n = 8$) and, HF50 (divided into 5 groups that received high fat diet concomitant with 50 ppm As in water for 4, 8, 12, 16 or 20 weeks, $n = 8$). Upon the 20 weeks administration of OD or HFD and arsenic the animals were scarified to evaluate the mitochondrial functions (Cordner and Tamashiro 2015).

Behavioral training

The step-down passive avoidance task is used to evaluate state-dependent learning and memory. All groups underwent a behavioral process examination in 0, 4, 8, 12, 16 and 20 weeks. The apparatus consisted of a box made of Plexiglas with dimensions of $40 \times 30 \times 30$ cm^3 and a floor of steel bars. Each of the steel bars was 0.3 in. in diameter with a spacing of 1 cm. A wooden platform with dimensions of $4 \times 4 \times 4$ cm^3 was provided in the center of floor. Electric shocks (1 Hz, 15 V, 15 s) using a stimulator connected to the floor bars transmitted to the animals' hands and feet. When the animal was placed on the podium, the natural tendency of the animal was to get down on the floor bars. While upon the receiving of the shock the animal learns to not go down. The step-down latency was considered as memory retrieval during training and testing stages (Nootarki et al. 2015). In the training phase, animals were slowly placed on the wooden platform in the middle of the device and the delay of coming down from the platform was recorded by a chronometer. When the mouse stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s. Before ending of the shock, the animal was removed (Guan et al. 2016; Jafari-Sabet 2011). This training procedure was carried out between 9:00 a.m. and 15:00 p.m. and animals with latencies longer than 30 s were excluded from the study. The test phase was conducted 24 h after the training phase same as the training phase with the difference that the shock did not apply. Thus, each animal was slowly placed on the wooden platform again and step-down latency was considered as memory retrieval. In the present study, maximum time to stop the mouse on the podium was a 300 s (Nootarki et al. 2015). The retention test was also carried out between 9:00 a.m. and 3:00 p.m. At the end of each test, the surface of the apparatus was thoroughly cleaned to remove of olfactory cues (Guan et al. 2016).

Brain analysis for arsenic absorption

As was measured by atomic absorption spectrophotometer in the brain samples. For determination of As, an extract of these samples were prepared by wet ingestion in a mixture of nitric acid, sulfuric acid, and perchloric acid. For reducing As (V) to As (III), potassium iodide and hydrochloric acid were added to the extracts and incubated for 1 h (Bustamante et al. 2005). As in the mineral extracts was determined by a hydride generation-atomic absorption spectrophotometer (Perkin-Elmer4100 Perkin Elmer Norwalk, Connecticut) (Tadanobu et al. 1990).

Mitochondrial isolation

Brain mitochondria isolation was accomplished via different centrifugation method (Bradford 1976). The animals were sacrificed by decapitation and their brain were quickly removed, washed with cold buffer and cut into small pieces. Brain pieces were homogenized in an ice-cold isolation buffer having sucrose 70 mM, mannitol 200 mM, HEPES 10 mM, EGTA 1 mM, and BSA 0.1% (pH 7.4) (Rezaei et al. 2014). Then nuclei, unbroken cells and other non-subcellular tissues were sedimented by centrifuging at 1500×g for 10 min at 4 °C and the pellet was discarded. Then, the supernatant centrifuged at 10,000×g for 10 min and the superior layer was carefully discarded. The packed lower layer (heavy mitochondrial fraction) was washed by suspending in the isolation buffer and centrifuged again at 10,000×g for 10 min. Finally, the mitochondria pellet were suspended in Tris buffer (Tris-HCl 0.05 M, sucrose 0.25 M, KCl 20 mM, $MgCl_2$ 2.0 mM, and Na_2HPO_4 1.0 mM, pH 7.4) at 4 °C. Protein concentrations were determined by the Bradford method (Coomassie blue protein binding method) and BSA used as a standard (Sadegh 2003). Mitochondria were used within the first 4 h after isolation. All steps were done on ice to have a high quality mitochondrial preparation.

Mitochondrial viability assessment

Mitochondrial total dehydrogenase (complex II) activity was analyzed by determining reduction of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide) to formazan. The mitochondria tubes that contain 100 μL of mitochondrial suspensions (0.5 mg protein / mL) were incubated at 37 °C. Then, 50 μL MTT 0.4% was added to it and incubated at 37 °C for 30 min. The product of purple formazan crystals were dissolved in 100 μL dimethyl sulfoxide (DMSO), and the absorbance was measured by spectrophotometer reader at 570 nm (UV-1650PCShimadzu). Finally, Succinate dehydrogenase (SDH) activity was evaluated as a percentage of control (Naserzadeh et al. 2015).

Mitochondrial membrane potential assessment

The mitochondrial membrane potential ($\Delta\Psi m$; MMP) was measured by using rhodamine 123 as a cationic fluorescent probe. Rhodamine 123 would store more in healthier

mitochondria matrices and the red-to-green fluorescence ratio is less in healthy mitochondria compared to impaired mitochondria. Then 10 μM of rhodamine 123 was added to mitochondrial solution (0.5 mg protein/mL). The ability of mitochondria for uptake the Rh123 was determined as differences between control and treated mitochondria by measurement Fluorescence intensity (LS50B PerkinElmer, Waltham, Massachusetts, USA; the excitation and emission wavelength of 490 nm and 535 nm) (Hassani et al. 2015).

Lipid peroxidation measurement

The level of Malondialdehyde (MDA) was determined in terms of thiobarbituric acid reactive substances (TBARS) production. 1 mL of mitochondrial fractions (0.5 mg protein/mL) was added to 250 μL trichloroacetic acid (70%) and centrifuged at 3000×g for 15 min. The supernatant was mixed with 1 mL TBA (0.8%) and were located in a boiling water bath for 30 min. The absorbance was measured at 412 nm by a spectrophotometer. Values were expressed as μg/mg protein. TBARS concentrations of the samples were calculated from a standard curve using 1, 1, 3,3-tetramethoxypropane (Baracca et al. 2003).

Mitochondrial GSH measurement

Reduced glutathione (GSH) was measured by using Ellman's reagent or DTNB (30 mM). 1 mL of mitochondrial suspension (0.5 mg protein/mL) homogenized and treated with 1 mL of trichloroacetic acid (10%) to remove the proteins (that may contain -SH group other than GSH) from the sample. The supernatant was taken following the centrifugation at 5000 rpm and treated with DTNB. Following exposing to trichloroacetic acid and centrifugation of samples, supernatants neutralize using triethanolamine. GSH reacts with DTNB to produce TNB and the total TNB formed (yellow product) was measured by reading the absorption at 412 nm using a spectrophotometer (UV-1601PC, Shimadzu, Japan). Glutathione levels were determined using a standard curve of the known concentrations of GSH (Siegers et al. 1988).

Measurement of the mitochondrial ROS

The mitochondrial ROS was measured using the fluorescent probe DCFH-DA. Briefly, isolated mitochondria (0.5 mg protein/mL) were washed with phosphate-buffered saline (PBS) and then incubated with 1.6 mM DCFH-DA at 37 °C for 10 min. The fluorescence intensity was measured using fluorescence spectrophotometer at Ex = 500 nm and Em = 520 nm. The ROS level was presented as the fluorescence intensity percentage relative to the control group (UV-1650PC Shimadzu, Kyoto, Japan) (Keshtzar et al. 2016; LeBel et al. 1992).

Statistical analysis

Data were presented as means ± SE for the different tests. All results were analyzed using Graph Pad Prism (version 5.04, Graph Pad Software Inc., San Diego, CA, USA). Statistical significance was determined using the one-way or two-way analysis of variance with the Tukey post hoc test. Statistical significance was set at $p < 0.05$.

Results

Effect of diet and as exposure on the body weight

Control mice that were fed with HFD for 20 weeks weighted more than OD control group ($p < 0.01$). Further, co-exposure to As and HFD revealed a significant weight loss in comparison to HFD control group ($p < 0.01$). However, weight loss was not significant in OD fed mice following the mentioned period (Table 1).

Effect of diet and as exposure on the average of daily water and as intakes

HFD control mice drank less water than OD control group ($p < 0.01$). Moreover, consumption of both doses of As (25 and 50) in OD and HFD groups decreased animals' water intake compared to their control ($p < 0.01$). Daily water intake increased in OD + As 50 ppm versus OD + As 25 ppm groups. Significantly the same results were observed in HFD + As 50 ppm when compared to HFD + As 25 ppm ($p < 0.05$) (Table 1).

Effect of diet and as exposure on brain to body weight ratio

The average total brain to body weight ratio after 20 weeks training was significantly lower in control HFD mice compared to OD controls ($p < 0.05$, 13%). As exposure increased the brain to body weight ratio in both OD and HFD mice at 25 (20% and 31% respectively) and 50 ppm (21% and 59% respectively) compared to their control ($p < 0.01$) (Fig. 1).

Brain distribution of as

Exposure to As at 25 and 50 ppm concentration for 20 weeks resulted in accumulation of it in the brain of OD and HFD treated mice ($p < 0.001$). Also, there was a significant increase of brain As accumulation in OD or HFD + As 50 ppm compared to OD or HFD + As 25 ppm ($p < 0.05$, 119% and 50% respectively). Also, brain As accumulation in HFD groups was higher than OD groups significantly ($p < 0.05$, 120% and 51% respectively) (Fig. 2).

Table 1 Effect of diet and As exposure on the average of daily water drink, As intake and body weight

Groups Variables	Ordinary diet			High fat diet		
	Control	As 25 ppm	As 50 ppm	Control	As 25 ppm	As 50 ppm
body weight(g)	39 ± 3	37 ± 5	36 ± 3	46 ± 9^{a*}	35 ± 4^{b*}	29 ± 2^{b*}
water drink(mL/day)	11 ± 1	8 ± 1^{a*}	5 ± 1^{a**}	9 ± 1^{a*}	6 ± 1^{b}	4 ± 1^{b*}
As intake(μg/day)	0	188 ± 17	228 ± 25^{c}	0	155 ± 32	215 ± 38^{e}

Each value was presented as means ± SEM ($n = 8$). Letter a: Significantly different from control OD group ($p < 0.05$), Letter b: Significantly different from control HFD group($p < 0.05$), Letter c: Significantly different from OD + As 25 ppm group, Letter d: Significantly different from OD + As50 ppm group ($p < 0.05$), Letter e: Significantly different from HFD + As 25 ppm group ($p < 0.05$). a* and b*: $p < 0.01$, a**: $p < 0.001$. p values were from one-way ANOVA, followed by Tukey's test for multiple comparisons

Effects of as and diet on state-dependent memory

The mean initial latency did not differ significantly amongst the different groups whereas the retention latency was significantly different among the groups. Figures 3a-e show comparisons of step-down latency in OD and HFD mice, received diH_2O or diH_2O plus arsenic in doses of 25 or 50 ppm for 4, 8, 12, 16 and 20 weeks. The results revealed that the HFD alone did not cause any significant change in the retention latency in the passive avoidance test before 12 weeks, but retention latency decreased in the control HFD mice compare to control group ($p < 0.05$) after 16 weeks. As 25 and 50 ppm significantly ($P < 0.05$ and $P < 0.01$) decreased step-down latency on test day in OD groups after 12 weeks, but when As 25 and 50 ppm was administered along with HFD, it produced significant dose-dependent decrease in retention latency as compared to control group after 8 weeks ($P < 0.01$ and $P < 0.001$).

Effects of diet and as exposure on brain mitochondrial dehydrogenase activity and membrane potential collapse

The results showed a significant decrease in the mitochondrial reduction of MTT to formazan in HFD versus OD fed groups ($p < 0.01$). As 50 ppm exposure decreased mitochondrial dehydrogenase activity in OD ($p < 0.001$) and HFD ($p < 0.01$) fed groups in comparison to their controls (Fig. 4a). As shown in Fig. 4b, HFD had no statistically significant effects on MMP collapse in HFD control compared to OD control group, but As exposure significantly induced this variable in OD ($p < 0.01$, 56%) and HFD ($p < 0.05$, 59%) fed mice compared to their controls.

Effects of diet and as exposure on brain mitochondrial oxidative stress

Increased ROS formation is expressed as DCF fluorescence intensity unit. As shown in Fig. 4c, HFD induced a significant rise at ROS formation in brain's mitochondria ($p < 0.001$, 58%). Exposure to As 50 ppm increased this variable in OD fed mice ($p < 0.05$, 32%) comparing to its control.

The results of lipid peroxidation revealed that mitochondrial MDA level was significantly higher in control HFD mice compared to OD group ($p < 0.05$). Also, As exposure significantly increased mitochondrial MDA level in OD ($p < 0.05$) and HFD ($p < 0.01$) fed mice compared to OD control (Fig. 4d).

Glutathione decreased significantly in the control HFD group compared to the control OD fed mice ($p < 0.01$, 47%). Further,

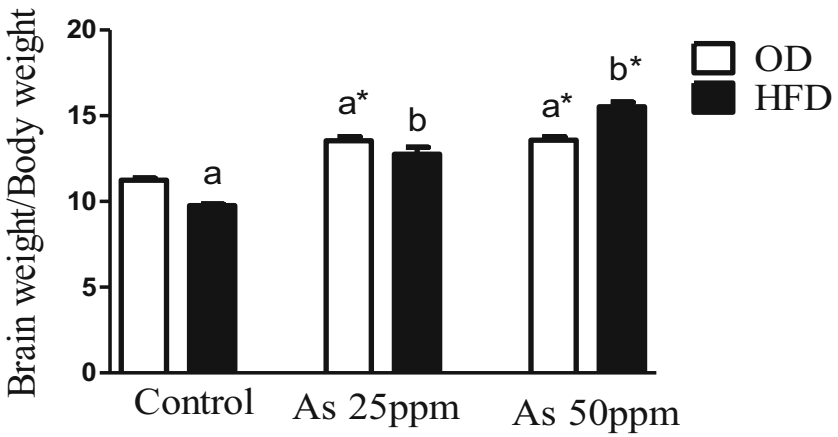

Fig. 1 Effects of arsenic and diet on the brain to body weight ratio in control OD or HFD fed and As 25 or 50 ppm treated OD or HFD mice (Mean ± SE; $n = 8$). a: significant difference compared to the control OD ($p < 0.05$), b: significant difference compared to the control HFD ($p < 0.05$), a* and b* $p < 0.01$. p values were from one-way ANOVA, followed by Tukey's test for multiple comparisons

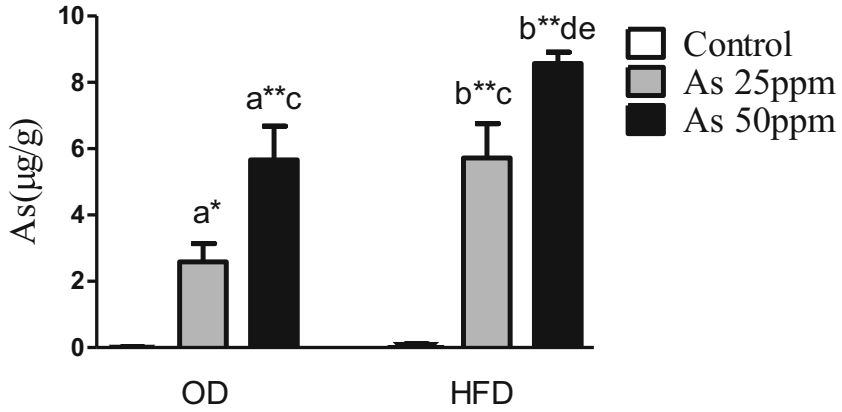

Fig. 2 Effects of arsenic and diet on the brain distribution of As in control OD or HFD fed and As 25 or 50 ppm treated OD or HFD mice (Mean ± SE; $n = 8$). a: significant difference from control OD ($p < 0.05$), b: significant difference from control HFD ($p < 0.05$), c: significant difference from OD + As 25 ppm ($p < 0.05$), d: significant difference from HFD + As 25 ppm ($p < 0.05$), e: significant difference from OD + As 50 ppm ($p < 0.05$). A* $p < 0.01$, a** and b** $p < 0.001$. p values were from one-way ANOVA, followed by Tukey's test for multiple comparisons

both doses of As administration further decreased this antioxidant parameter in OD ($p < 0.01$, 47%) and HFD ($p < 0.001$, 60%) received animals compared to OD control group (Fig. 4e).

Discussion

Inappropriate life style including unhealthy eating habits along with environmental pollutions play an important role in many human diseases (Paul et al. 2011). The effects of As administration on learning and memory impairments have been determined in the previous studies. Hence, present study examined the effects of simultaneous As and HFD exposure on this pattern. To our knowledge, this is the first study indicates that chronic exposure to As acts additively with HFD to impair the learning and memory in mice. The results showed that HFD reduced water intake. Although water intake was less in animals exposed to As 50 ppm, they showed a significant higher As intake compare to control groups or mice that exposed to As 25 ppm. Also, co-exposure to As and HFD accompanied with weight loss and increasing brain to body weight ratio especially in mice exposed to 50 ppm of As. These findings were in agreement with the results of a study by Paul et al showed that chronic exposure to As and HFD lead to reduction of water drinking and weight (Paul et al. 2011). Weight loss could be due to enhanced repair and metabolic actions of cells (Bechara et al. 2014; Petres et al. 1977). It has been shown that As is stored in several tissues and organs and could cross through the blood-brain barrier and invade the brain parenchyma (Jiang et al. 2014; Jing et al. 2012). In our study, the concentrations of As in the brain of mice were higher for As exposed mice than those in controls and this concentration increased in a dose-dependent manner. Interestingly, HFD group showed a higher As content in the brain as compared to OD received mice, although As concentrations were equal in their drinking water. These findings indicated that by chronically increasing the amount of arsenic in drinking water or giving a high fat diet, the level of As in the brain of mice rises which confirms the increasing neurobehavioral toxicity upon the exposure to both As and HFD (Luo et al. 2009; Wasserman et al. 2004). Some studies have reported that consumption of HFD may result in blood–brain barrier (BBB) dysfunction via the increasing of its permeability (Davidson et al. 2013; Davidson et al. 2012). It was suggested that BBB impairment may serves as a critical connection between HFD consumption and Alzheimer's disease pathogenesis (Hsu and Kanoski 2014). According to the investigations, HFD ingestion is associated with increased inflammation and subsequently increased BBB permeability (Abbott et al. 2006; Ek et al. 2001). Therefore HFD can increase permeability and dysfunction of BBB and result in extra As accumulation in the brain.

Mechanism of the toxic effects of As on the nervous system remains to be elucidated. Alteration in basal ganglia has been suggested by some investigators (Morris et al. 1982), but behavioral changes related to As were not well characterized (Morris 1984). It is ascertained that exposure to arsenic could induce changes in memory and attention (Rosado et al. 2007; Sun et al. 2015; Yang et al.). Chronic exposure to arsenic considerably affected memory pattern and attention in students (Tsai et al. 2003). The arsenic concentration in urine displayed an inverse relationship with cognitive performance in children, demonstrating that arsenic adversely affects learning and memory functions (Xi et al. 2009). In animal, exposure to As led to delay in the learning attainment (Yadav et al. 2011), changes in locomotors behavior and deficits in spatial learning patterns (Gora et al. 2014; Huo et al. 2015). In the present study, mice exposed to As showed shorter latency than the control in the step-down passive (Morris 1984) avoidance

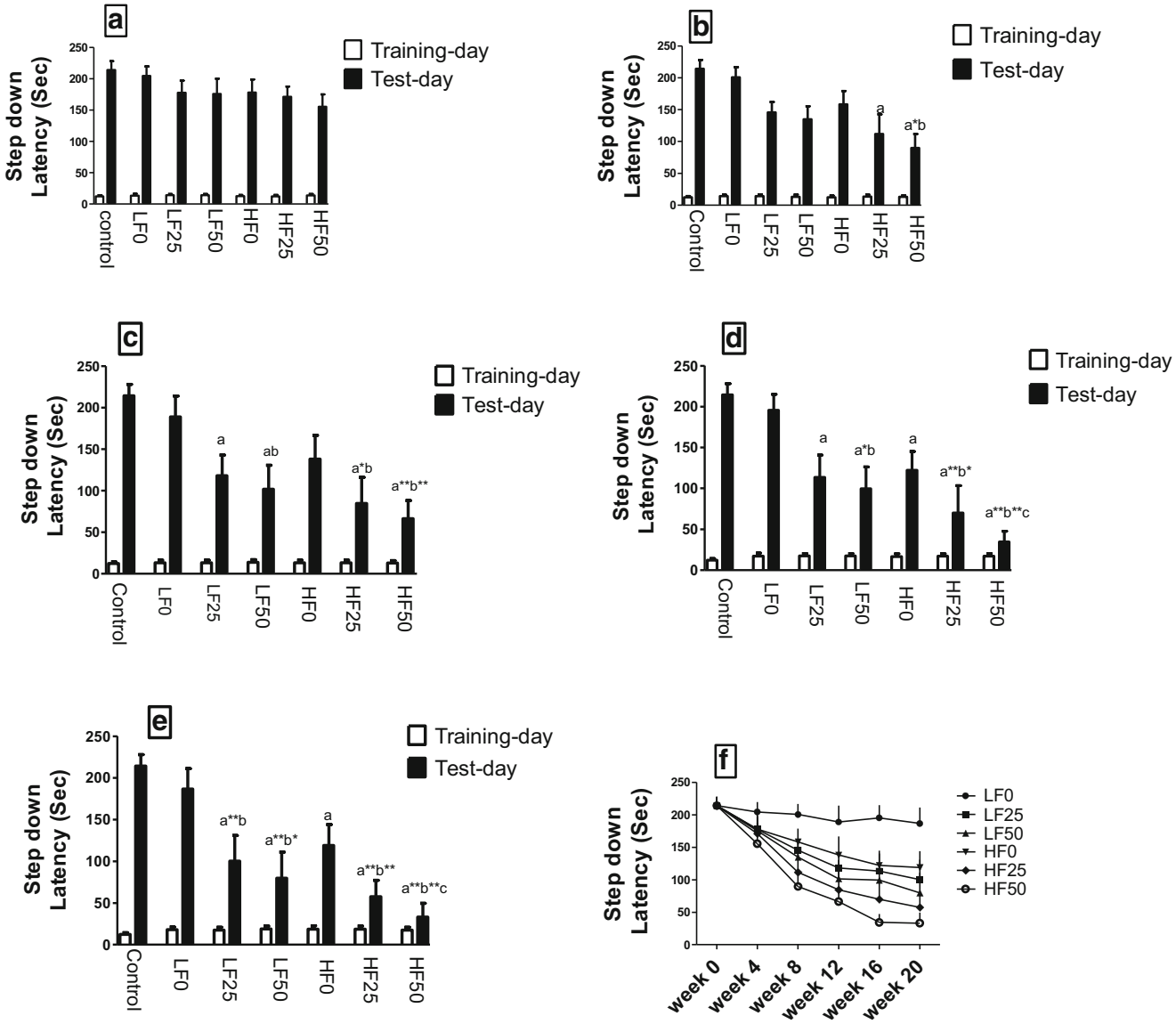

Fig. 3 Effects of arsenic and diet on memory retention in control, OD or HFD fed and As 25 or 50 ppm treated OD or HFD mice. Each value was presented as means ± SEM ($n = 8$). a: Significantly different from control group ($p < 0.05$), b: Significantly different from control OD group ($p < 0.05$), c: Significantly different from HFD group, a* and b*: $p < 0.01$, a**: $p < 0.001$. p values were from one-way ANOVA, followed by Tukey's test for multiple comparisons

task after 12 weeks, which is consistent with the above mentioned studies. These results suggest that As exposure impaired state-dependent learning and memory abilities in mice (Chin-Chan et al. 2015). However, the behind mechanism for the neurotoxicity is unclear. As neurotoxic effects could be due to its interaction with GSH contents and related enzymes. Some studies have connected changes in the GSH contents with neurodegenerative conditions such as Alzheimer's disease, amyotrophic lateral sclerosis, schizophrenia, and Parkinson's disease (Bharath et al. 2002; Rodrıguez et al. 2002).

Brain cells may be at particular risk for oxidative stress. The brain derives its energy almost exclusively from oxidative metabolism throughout the mitochondrial respiratory chain, and is relatively deficient in protective mechanisms compared to other tissues, such as liver and kidney. It contains reduced quantities of catalase, glutathione peroxidase, GSH and Vitamin E than liver or kidney. In our study, GSH contents were measured in the mitochondria isolated from rat's brain based on Ellman's method. During the processing or handling of samples, oxidation of thiols may occur. Given that all steps of the experiment were also performed in the control mitochondria, the same way as in the tests, it can be assumed that the oxidation of GSH during the procedure and stress caused by the method were of equal extent in all experiments. However, with the above explanation, this may result in underestimation of the

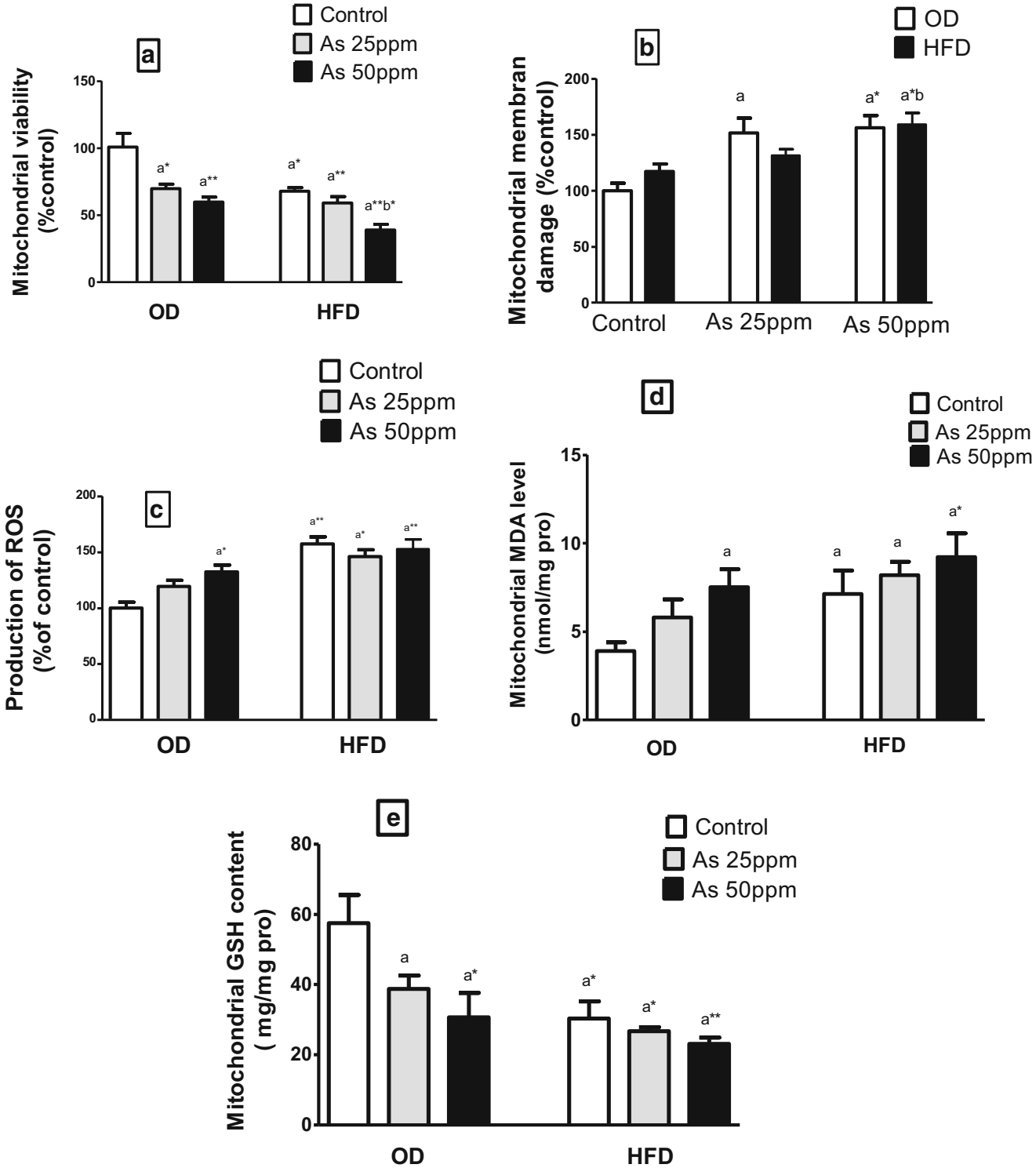

Fig. 4 Effects of arsenic and diet on the mitochondrial oxidative stress and damage in control OD or HFD fed and As 25 or 50 ppm treated OD or HFD mice. **a** Mitochondrial viability; (**b**) Mitochondrial membrane damage; (**c**) Mitochondrial ROS formation; (**d**) Mitochondrial MDA level; (**e**) Mitochondrial GSH level. Each value was presented as means ± SEM ($n = 8$). a: significant difference from control OD ($p < 0.05$), b: significant difference from control HFD ($p < 0.05$). a* and b* $p < 0.01$, a** and b** $p < 0.001$. p values were from one-way ANOVA, followed by Tukey's test for multiple comparisons

real amount of GSH in our work. Thereby to provide a better presentation for GSH contents, the values were expressed as percentage relative to the control (Fig. 3). In cellular researches where all enzymes for de novo synthesis of GSH and recycling

of oxidized form are present, GSH/GSSG ratio is used to evaluate the oxidative/reductive states, however de novo synthesis of GSH in mitochondria is not possible due to the absence of relevant enzymes, so that their GSH contents originate from cytosol transferring by specific mitochondrial carriers (Marí et al. 2013). On the other hand, the formed GSSG in mitochondria would not easily transported out of mitochondria (Ribas et al. 2014). Therefore, it seems that the GSH measurement gives good estimation for mitochondrial oxidative stress although determination of the ratio would also be helpful. Polyunsaturated fatty acids are a major constituent of neural cell membranes and are substrates for free radicals and lipid peroxidation (Coyle and Puttfarcken 1993). It has been reported that chronically administered arsenic via drinking water induced oxidative stress in the brain of rats (Chaudhuri et al. 1999; Lynn et al. 1998). (Kalyanaraman et al. 2012) concluded that intracellular H_2O_2 cannot be reliably measured using DCFH-DA because of the intricate redox chemistry of DCFH and for that the yielding oxidized product (DCF) is not directly related to the actual level of H_2O_2. Some of the most important interfering factors are certainly present when the assay runs on the whole cell (e.g. cytochrome c which releases in the cytosol upon the exposure to an apoptotic inducer) not on the isolated mitochondria as we conducted the assay. Moreover, many studies have shown that arsenic disturbed mitochondrial function and produced extra levels of reactive oxygen species (Hei et al. 1998; Rezaei et al. 2018; Sumedha and Miltonprabu 2015; Valko et al.; Yen et al. 2012). In fact, the aim of the present study was not to mechanistically identify the exact levels of H_2O_2 in rat's brain mitochondria, instead it is intended to investigate the redox changing upon the long duration co exposure to arsenic and high fat diet. The obtained results via the total ROS experiment confirmed by other assays performed including MDA and GSH contents. Furthermore it was reported that arsenic exposure increased oxidized DNA and diminished antioxidant capacity of rodents' brains, induced lipid peroxidation in the rat brains and decreased brain levels of enzymes involved in the protection against oxidative states (Gong and O'Bryant 2010). Consistent with these results, we found that As at 50 ppm impaired state-dependent learning and memory abilities by induction of oxidative stress, increased lipid peroxidation and GSH depletion that resulted in decreased brain mitochondrial dehydrogenase activity and membrane potential.

Appropriate nutrition is a major factor in preserving neural and cognitive function during the lifetime of individuals. HFD contributed to cognitive failure in aging and accelerated the development of dementia (Thirumangalakudi et al. 2008). HFD also aggravates the impairment of cognitive functions resulting from traumatic brain damage (Wu et al. 2003), cerebral ischemia/reperfusion injury (Li et al. 2007) and intermittent hypoxia (Goldbart et al. 2006). Even in the healthy animals, HFD debilitated learning and memory (Pathan et al. 2008) in both males and females (Greenwood and Winocur 2005). In contrast, diets rich in monounsaturated fatty acids, fruits and fibers protected cognitive performance and improved memory scores in the elderly (Alzoubi et al. 2013; Cole et al. 2005). The precise mechanism for HFD related cognitive deficiency has not been fully understood. Although fatty diet may have some direct effects on the neuronal function but at the same time can be a main contributor to other chronic diseases, such as cardiovascular disease, hypertension, type 2 diabetes mellitus and depression, all of which are considered risk factors for cognitive decline and dementia (Luchsinger et al. 2002).

Several studies have reported that diet rich in fat is associated with heightened oxidative status and lipid peroxidation (Ding et al. 2013; Ribeiro et al. 2009). Recent studies showed that chronic consumption of HFD is associated with cognitive impairment in rats through impaired antioxidative mechanisms and increased oxidative stress in the hippocampus (Park et al. 2010). In addition HFD are known to increase inflammation, which may adversely affect cognition. Chronic inflammation in adipose tissue caused by HFD or obesity is believed to contribute to insulin sensitivity which, may influence learning and memory. Results of the above mentioned reports are consistent with our study in which long term consumption of HFD (for 16 weeks) impaired normal memory. In the present study chronic HFD feeding induced oxidative stress and imbalance of ROS and antioxidant enzyme activities, as well as increased level of MDA and decreased GSH level in the mice brain which may be responsible for cognitive impairment. The significant increase in brain MDA and decreased the GSH levels in concomitant with HFD and As administration compared to HFD or As alone treated mice and their higher deleterious effects on memory are in agreement with results of step-down passive avoidance task that assesses the ability of the animals to retain and recall information.

In summary, findings of the present study demonstrated that the ingested arsenic entered and accumulated in the brain which together with HFD more impaired state-dependent memory. The neurotoxicity of arsenic and HFD may perhaps be due to their adverse effects on the brain mitochondria and oxidative stress implementation which can then be responsible for the behavioral changes in animal models. More studies are required to clarify the exact toxic mechanisms of inorganic arsenic and HFD on the brain and behavior.

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Compliance with ethical standards

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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