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RESEARCH ARTICLE

NEUROBEHAVIORAL ALTERATIONS IN CADMIUM EXPOSED RATS

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ABSTRACT

A complex network of different interrelated functions working together to manage information is known as memory. Learning and memory engage several processes, including acquisition, consolidation, retention, and recall of information which are mediated by multiple anatomical and neurochemical mechanism systems. This present study was undertaken to examine whether cadmium administration can induce behavioural alterations in male albino rat. Two months old rats were exposed to Cadmium subcutaneously at a concentration of low (2mg/kg bw) and high doses (5mglkg bw) for a period of three weeks. Open field revealed marked impairment in habituation such as rearings, crossings and sniffings in rat exposed to higher doses of Cadmium. Additionally learning and memory assessment during water maze test showed retention in latency, swim speed and swim distance in cadmium exposed rats when compared to the controls. Overall, these results submit that treatment with Cadmium altered behavioural dysfunctions, exploratory behaviour such as head dip duration and head dip counts, locomotor activity and a retention in learning and memory.

INTRODUCTION

Cd can increase BBB(Blood Brain Barrier) permeability, consequently penetrating and accumulating in the brain of developing and adult rats (Gonçalves *et al*., 2010; Méndez-Armenta and Ríos, 2007; Pari and Murugavel, 2007) leading to brain intracellular accumulation, cellular dysfunction, and cerebral edema. There are several reports stating that exposure to Cd can produce impairment in neurobehavioral status in humans and animals, such as alterations in attention and memory as well as in the psychomotor, and visuomotor functioning and speed in workers (Hart *et al*., 1989; Viaene *et al*, 2000). Aggressive and anxiety-like behaviours, impaired learning and memory processes, and changes in the development of the visual system were observed in rat studies (Desi*et al*, 1998; Gonçalves *et al*, 2010;Terçariol*et al*, 2011; Yargiçoglu *et al*, 1997).

The open field test provides measures of locomotor activity. Horizontally directed activity (or locomotion) is measured by the number of line crossing and vertically directed activity (or exploration) is measured by the frequency of rearings. An increase in both activity measures when aggregated over consecutive open field sessions is assumed to reflect a lower level of anxiety (Vanderstaay and Blokland, 1996). The open field test also provides occupancy measurers of which an increase in the aggregated time spent in the corner squares is considered as reflecting a higher level of anxiety (Vanderstaay *et al*., 1990).

The water maze was originally designed to test the ability of rodents to learn and memorize the location of a hidden platform in a pool of opaque water by its position relative to distal extra maze cues (Morris *et al*, 1982). A great deal of knowledge has been obtained on the neurochemical, neuroanatomical and neurophysiological basis for the behaviour associated with this paradigm. For example, several neurotransmitter receptor antagonists have been shown to cause deficits in swim task performance when administered to rats (Mc Namera and Skelton, 1993).

In view of conflicting results reported in the behavioural studies made in Cd-exposed rats, the present work was focused on the effect of Cd intoxication on cognitive, non-cognitive performance and extent of Cd toxicity was compared with the effect of Vitamin-C. Open field behaviour, exploratory behaviour and total locomotory activity was observed in non-cognitive performance. Acquisition phase, reversal phase, working memory tasks were observed in cognitive performance.

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MATERIALS AND METHODS

Chemicals

Cd chloride and Vitamin-C were selected as test chemicals. The chemicals used in this study were obtained from Sigma, USA.

Animal exposure to Cd and Vitamin-C

The young albino rats (2months) were exposed to Cd and vitamin-C through subcutaneous injections. Rats were randomly divided in to five groups, first group served as a control, Second and third group rats were treated with low dose of Cd(2mg/kg),and high dose of Cd for a period of 4 weeks, whereas fourth and fifth groups of rats were treated with both Cd and vitamin-C(50mg/kg).

Open Field test

The open field test has been widely used to assess emotional reactivity/anxiety. It provides measures of locomotor activity. The horizontally directed activity (or locomotion) was measured by the number of line crossings, and vertically directed activity (or exploration) was measured by the frequency of rearings (Prickaerts *et al*, 1998). The open-field behaviour of two months and four months old rats was assessed in a wooden box measuring 90 x 90 x 30 cm high. The floor of the arena was divided into 36 equal squares by black lines. Immediately after a rat was placed in the centre of the open field, the movement of the animal was scored. The number of squares crossed with all paws (crossings), the standings on the hind legs (rearings), standing on hind legs and placing forelimbs on the wall of arena (wall rearing), placing the nose against wall or floor (sniffing), wiping, licking, combing or scratching of any part of the body (grooming) were counted in all sessions. All the activities measured were combined together to assess the mean total behaviour in each session. Testing was carried out on five consecutive days in five minute sessions in control, Cd-exposed and Vitamin-C injected animals. The number of crossings indicated locomotor activity (Walsh and Cummins, 1976; Netto *et al*, 1986).

Locomotor activity

Locomotor activity of the rats was studied with Opto-Varimex mini Columbus Instruments (USA). The data was taken as total duration of 15 minutes to each animal during the 5 minutes session interval.

Exploratory behavior

Exploratory behaviour was evaluated in the hole board. The apparatus was an open-field arena with four equally spaced holes (3 cm in diameter) in the floor. Each rat was placed individually in the centre of the arena for 5 minutes, during which we recorded head-dip count and head-dipping duration, in seconds. A head dip was scored if both eyes disappeared in to the hole. Head-dipping duration data were expressed as total duration during the 5 min session. The results for head dip were expressed as number of counts, and head-dipping duration in seconds.

Morris Water Maze

Spatial discrimination learning not only involves place learning, which is learning a position in space which in this case is the position of the hidden platform in the Morris water escape task, but also involves non-spatial components like procedural learning (such as learning to search for an escape platform) and visual or other sensorimotor processes together with possible motivational/emotional processes necessary for executing the task. After acquisition of the spatial water escape task, a probe trial can reveal whether the rats have actually learned the position of the platform. Furthermore, a spatial discrimination reversal task after the acquisition of the spatial task, measures mainly place learning because the rats are already familiar with the procedural component.

The water maze is a circular water tank measuring 1.85 m in diameter and 0.7 m deep constructed according to a basic design similar to that of Morris (Morris, 1984). Four points along the circumference of the water tank are designated arbitrarily North (N), South (S), East (E), and West (W), thus dividing the maze into four quadrants.The pool was filled to a depth of 30 cm with water made opaque with white, nontoxic water-based paint. A circular submerged platform (diameter 12.5 cm) remained below the surface of water. All parameters involving time and distance are measured in seconds. Testing was carried out on five consecutive days. Control and treated rats were subjected to water maze learning tasks for 2 months old rats. Control, Cd treated and Vitamin-C supplemented rats were subjected to water maze learning tasks.

RESULTS

Open field behavior

Fig. 1 Data on open-field behaviour in animals exposed to Cd followed by Vit-C chelation therapy. In our study control animals showed higher frequency of all the open field responses such as crossings, rearing, wall rearings, sniffings, wall sniffings, grooming where as significant decrease was observed in open field responses in Cd-exposed rats when compared to controls. Cd treated rats showed a significant decrease in total open feildbehavior both at low and high concentrations. Chelation therapy with Vit-C was effective in reversing total open field behaviour.

Total locomotor activity

Fig. 2. Total locomotor activity was measured by the number of movements in activity recorder chamber. Cd treated rats show decreased locomotor activity than the control rats. Addition of Vit-C along with Cd, increased the locomotor activity partially. However, the high dose of Cd treated rats showed decreased behaviour in locomotor activity when compared to low dose of Cd treated rats.

Exploratory behavior

Fig. 3. Our results revealed that animals exposed to Cd exhibited reduced head dip counts and head-dipping duration in the hole board as compared with the control animals. However administration with Vit-C along with Cd was effective in reversing the exploratory behaviour of animals; both in cases of head dip counts as well as head-dipping duration.

Water maze

Water maze was designed to test the ability of rodents to learn and memorize the location of a hidden platform in a pool of opaque water by its position relative to distal extra maze cues. Behavioural assessments on water maze confirmed the impairment in performance of the water maze acquisition, and reversal phases in Cd exposed rats. On the first day of training session, no specific alterations were found between control and Cd treated rats in both phases. Control rats fastly proceeded to the north quadrant in acquisition phase and south quadrant in reversal phase. Cd exposed rats exhibited the tendency of peripheral swimming, thereby took longer time to reach the platform. The escape latency however greatly reduced in Cd treated rats administrated with Vit-C.

Working memory

In working memory task platform was changed to different quadrants, escape latencies were longer than acquisition and reversal phases. All the rats easily learned to find the submerged platform except for the first day of training when all subjects performed at chance level. The Cd exposed rats took significantly longer time than control animals to find the hidden platform.

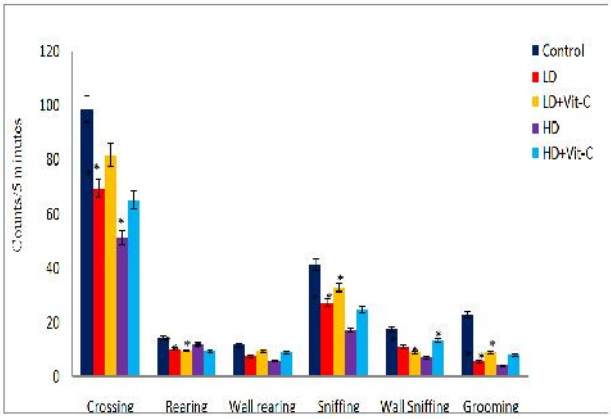

Fig 1: Open field behaviour-Effect of Cadmium on open-field behaviour and its chelation by Vitamin-C. Control rats were treated with normal saline, remaining rats were treated with Cd at Low dose(LD,2mg/kg/bw) and Highdose(HD,5mg/kg/BW) through subcutaneous injections for a period of 3 weeks and chelated with the Vitamin-C(50mg/kg subcutaneously) for last one week. All values are mean values of six albino rats and values marked with (*) are significantat P< 0.05-0.001.

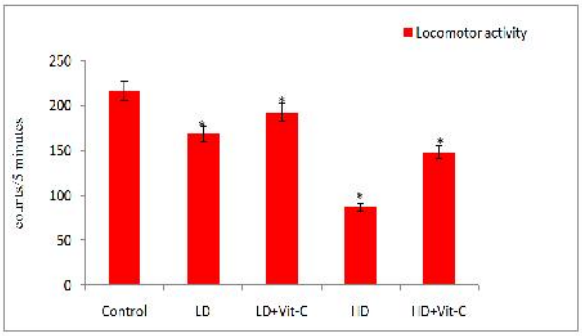

Fig 2: locomotory behaviour-Effect of Cadmium on Locomotor activity and its chelation by Vitamin-C. Control rats were treated with normal saline, remaining rats were treated with Cd at Low dose(LD,2mg/kg/bw) and Highdose(HD,5mg/kg/BW) through subcutaneous injections for a period of 3 weeks and chelated with the Vitamin-C(50mg/kg subcutaneously) for last one week. All values are mean values of six albino rats and values marked with (*) are significantat P< 0.05-0.001

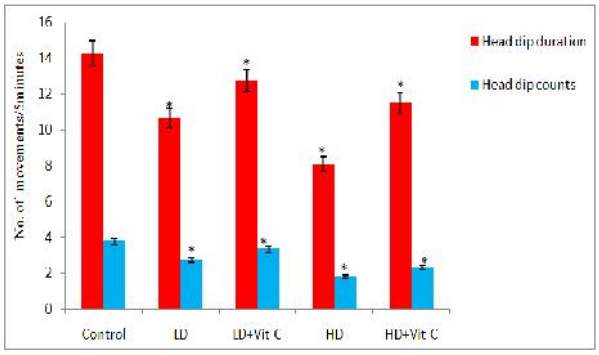

Fig 3: Exploratory behaviour-Effect of Cadmium on Exploratory behaviour and its chelation by Vitamin-C. Control rats were treated with normal saline, remaining rats were treated with Cd at Low dose(LD,2mg/kg/bw) and High dose(HD,5mg/kg/BW) through subcutaneous injections for a period of 3 weeks and chelated with the Vitamin-C(50mg/kg subcutaneously) for last one week. All values are mean values of six albino rats and values marked with (*) are significantat P< 0.05-0.001

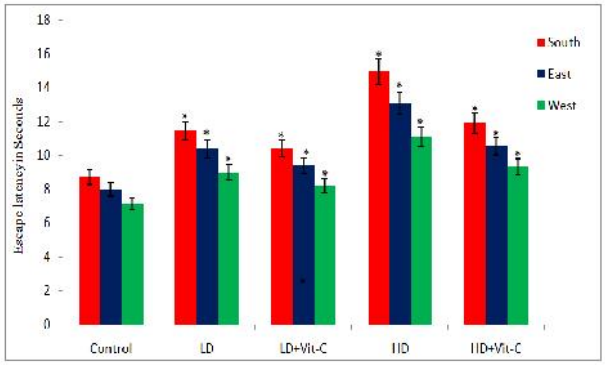

Fig 4: Acqusisition phase-Influence of Vitamin-C on Cadmium induced alterations in water maze of acquisition phase of rats.Control rats were treated with normal saline, remaining rats were treated with Cd at Low dose(LD, 2mg/kg/bw) and Highdose(HD,5mg/kg/BW) through subcutaneous injections

for a period of 3 weeks and chelated with the Vitamin-C(50mg/kg subcutaneously) for last one week. All values are mean values of six albino rats and values marked with (*) are significantat P< 0.05-0.001.

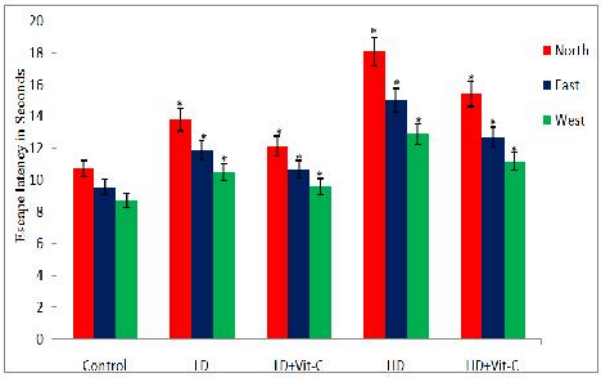

Fig 5: Reversal phase- Influence of Vitamin-C on Cadmium induced alterations in water maze of reversal phase of rats.Control rats were treated with normal saline, remaining rats were treated with Cd at Low dose(LD,2mg/kg/bw) and Highdose(HD,5mg/kg/BW) through subcutaneous injections for a period of 3 weeks and chelated with the Vitamin-C(50mg/kg subcutaneously) for last one week. All values are mean values of six albino rats and values marked with (*) are significantat P< 0.05-0.001.

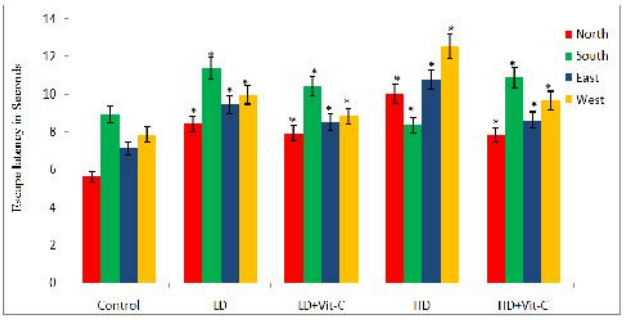

Fig 6: Working memory-Exploratory behaviour Influence of Vitamin-C on Cadmium induced alterations in water maze of working memory of rats.Control rats were treated with normal saline, remaining rats were treated with Cd at Low dose(LD,2mg/kg/bw) and Highdose(HD,5mg/kg/BW) through subcutaneous injections for a period of 3 weeks and chelated with the Vitamin-C(50mg/kg subcutaneously) for last one week. All values are mean values of six albino rats and values marked with (*) are significantat P< 0.05-0.001.

DISCUSSION

Cd is a trace element in the blood, known to cross BBB and produce neurotoxic effects. The present study has revealed that treatment with the graded doses of Cd resulted in significant accumulation of Cd in brain compared to controls leading to possible neurobehavioral alterations such as cognitive(water maze) and non-cognitive(open field) activities. According to Cahill& al., 2001; Cain, 1997 learning and memory cannot be measured directly but only via measuring from behaviour. However, "Behaviour is affected by many processesother than learning and memory(Cahill and al., 2001). Chronic stress has been reported to alter a number of cellular and molecular parameters in the hippocampus (Conrad & al., 2010; Jayatissa& al., 2008) and to impair hippocampus dependent learning (Conrad, 2010 and Joëls and al., 2007) in rats and mice.

Most frequently reported behavioural changes in humans and rodent models areweight loss, anxiety, depression, and motor dysfunction (Stanton 2013, jones 2013, Raupach 2012). Cholinergic system is responsible for the behavioural manifestations in animals and any alterations in the cholinergic system would be reflected in behaviour. Since hippocampus is implicated in memory and cognitive function, cortex in sensory perceptions (Martin, 1996) and cerebellum is critical for locomotor and coordination movements controlled by the Purkinje cells (Schreur*set al.,* 1998).Several experimental studies have suggested that exposure to Cd can enter into the brain parenchyma and neurons during the critical point of development (Nishimura *et al* 2006) which results in neurological alterations(Lukawski 2005) affects the learning, morphological development, sensory motor reflexes, memory in rodents (Lere*tet al*., 2003, Barannski 2007, Bull, 2010).

Our data revealed that exposure of Cd at all the groups significantly decreased open field behavior, locomotor activity and exploratory behaviour with concomitant increase in the escape latency of all the three phases as observed in water maze test. In central nervous system neurotransmitters play a vital role in functioning and behaviour of an individual. Acetylcholine plays an central role in interacting with each other through complex networks in the process of learning and memory(Decker and Mc Gaugh,1991). Acetylcholinestrase (AChE) is an enzyme which is responsible for hydrolyzing and so deactivating acetylcholine in the body and it is a good indicator of sublethal toxicity by heavy metals (Forget *et al.* 1999*)*. So these abnormalities in neurobehaviour can be interrelated with altered cholinergic system by Cd by inhibiting AChE enzyme levels, which play a vital role in modulating synaptic plasticity thought to be important for storing memory and long term potentiation in brain regions (Santoyo*et al.*, 2007). Our results allude that the presence of an association between the cholinergic alterations and behavioural perturbations. Our results are also parallel with data reported by Flicker *et al.*, (1983), where impairment of learning was evinced by decreased cholinergic activity in brain.

Hippocampus and the cerebral cortex are the decisive structures of memory formation (Shirai and Suzuki; 2004), because hippocampus is especially crucial in the integration of spatial information. There are several parameters used to characterize motor performance of open field seems to be able to provide a good measure of the approach response towards novelty (exploration) and describe influences of chemicals exposure (Ehman and Moster, 2006). Behavioral tests, such as the Open-field task, permit the evaluation of primary motor activity. In the present study, the open field test provides simultaneous measures of both habituation and anxiety, in open field behaviour control animals showed higher frequency of all the open field responses as (crossings, rearings, wall rearings, sniffings, wall sniffings, grooming) where as significant decrease was observed in open field responses of Cd-exposed

rats compared to controls. Our results are consistent with animal records that showed diminishing in memory and habituation of cadmium intoxication (Lehotzky*et al.,* 1990).

The decrease in locomotor activity observed in the Cd exposed rats in the testing sessions of the open field suggests impaired locomotion. Salinas and Huff (2002) also reported reduced performance latencies of an open field food motivated place learning task in rats. A significant reduction in head dip counts and head dip duration of exploratory behaviour was observed in high dose of Cd exposed rats than low dose when compared to controls. The alterations in exploratory behaviour may be due to altered cholinergic and monoamnergicsystems(Delgado *et al.,* 2000; Kannan *et al.,* 2001). Our results are also consistent with the results of (Desi*et al*. 1999,Kaoudi *et al* 2010) related the decrease of exploratory activity and a significantly lower exploration frequency of the open field centre in rats, to cadmium, which affects the bioelectrical and higher order functions of the nervous system.

Memory is not a static or isolated brain function; it can be best described as a complex network of different interrelated functions working together to manage information. Spatial memory can be defined as that brain function responsible for recognizing, codifying, storing and recovering spatial information about the arrangement of objects or specific routes (Paul *et al.,* 2009). Mazes are the experimental devices more often employed for overall evaluation of spatial memory in rodents, although they are not the only tools used for this purpose.

The alterations of cognitive functions observed (i.e exploration and learning and memory) seem to be in agreement with the earlier reports on both animals and children, which argue for an association between low levels of Cd exposure and cognitive dysfunction. A general agreement is that exposure to Cd may lead to fatigue and disturbance of sensory and motor functions in humans (Murphy 1997) and a significant decrease in distance travelled, stereotypic time and movements, ambulatory time and vertical movements in Cd-exposed rats (Ali *et al*. 1990), both in experimental animals and humans.A worker suffered from peripheral neuropathy and complains about equilibrium in chronic occupational exposure to cadmium (Viaene*et al,* 2000).

Morris water maze. Performance in the swim task was originally shown to be highly sensitive to hippocampal lesions (Morris *et al,* 1982) an area known to undergo morphological changes in rats exposed to heavy metals(Alfano and Petit, 1982; Kiraly and Jones, 1982).The present study showed that exposure to Cd to young rats causes long term changes that affect learning and memory in adult rats In addition, associative learning in water maze, declared that, rats treated with high doses of cadmium, demonstrated higher latency with increased numbers of errors in the maze reflecting poorer memory retention relative to other treatments. Where groups of animals exposed to high concentrations of cadmium, showed higher frequency for entering arms. A proof that there was impairment in working spatial memory. These results confirmed that cadmium intoxication impair learning and memory. (Kaoud*et al* 2010). Study from Baranski*et al*, (1983), also showed a decreased acquisition of avoidance behaviour and alterations in behaviour in open field in Cd exposed rats. Our findings of toxicity of Cd effects on spatial learning are in good agreement with the above findings.

From our results it is evident that Cd exposure significantly impaired the Water maze acquisition and reversal performance. In the first day of training session no specific alterations were found between control and treated rats. Later control rats quickly proceeded to the south and north quadrants of both phases and where the platform is located and identified the hidden platform, where as low and high dose of Cd treated rats took longer time to reach the hidden platform. Cd exposed rats exhibited the tendency of peripheral swimming, there by took longer time to reach the platform. Unlike the rats exposed to high doses of cadmium showed shorter escape latencies during acquisition and reversal phases of the spatial discrimination task .Our studies on the behavioural assessment in water maze confirmed the previously reported (Jett *et al*., 1997; Kuhlman, 1997) impairments in performance of the water maze reference and working memory tasks.

In conclusion our studies suggest that cadmium can induce neurobehavioral alterations in rats. Furthermore, impaired performance of hidden platform test by Cd exposed rats can be attributed to motor impairments because there were significant difference between swimming speed in control and Cd exposed groups. These results demonstrate that chronic exposure to low level and high level Cd cause learning impairment by way of deficits in both working memory and reference memory. Thus the results of our behavioural investigations indicate that the memory ability needed to solve a complex task is affected by low and high level exposure to Cd. We have shown that Cdexposure impairs the open field test, exploratory, locomotory, reference and the working memory component of the water maze and these deficits were seen in both high dose and low dose of young rats.

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